

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208711Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

**NDA/BLA Multi-Disciplinary Review and Evaluation**

|                                                       |                                                                      |
|-------------------------------------------------------|----------------------------------------------------------------------|
| <b>Application Type</b>                               | NDA                                                                  |
| <b>Application Number(s)</b>                          | 208711                                                               |
| <b>Priority or Standard</b>                           | Priority                                                             |
| <b>Submit Date(s)</b>                                 | 6/14/18                                                              |
| <b>Received Date(s)</b>                               | Rolling Review: 9/21/17; 6/14/18                                     |
| <b>PDUFA Goal Date</b>                                | February 14, 2019                                                    |
| <b>Division/Office</b>                                | Division of Anti-Infective Products/Office of Antimicrobial Products |
| <b>Review Completion Date</b>                         | February 11, 2019                                                    |
| <b>Established Name</b>                               | Triclabendazole                                                      |
| <b>(Proposed) Trade Name</b>                          | Egaten                                                               |
| <b>Pharmacologic Class</b>                            | Anthelmintic Drug                                                    |
| <b>Applicant</b>                                      | Novartis Pharmaceuticals Corporation                                 |
| <b>Formulation(s)</b>                                 | Oral                                                                 |
| <b>Dosing Regimen</b>                                 | 10 mg/kg q12h x 2                                                    |
| <b>Applicant Proposed Indication(s)/Population(s)</b> | Treatment of Fascioliasis                                            |
| <b>Regulatory Action</b>                              | Approval                                                             |
| <b>Indication(s)/Population(s)</b>                    | Patients with fascioliasis ≥6 years of age                           |

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| DISCIPLINE                     | REVIEWER                                                                                                                                                                                                                                                                                                    | OFFICE/DIVISION | SECTIONS AUTHORED/ACKNOWLEDGED/APPROVED | AUTHORED/ACKNOWLEDGED/APPROVED                                                                                                                   |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Product Quality Team Lead      | Andrei Ponta, Ph.D.                                                                                                                                                                                                                                                                                         | OPQ/ONDP        | Section 4.2                             | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
|                                | <b>Signature: Andrei Ponta -S</b><br><small>Digitally signed by Andrei Ponta -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrei Ponta -S, 0.9.2342.19200300.100.1.1=2001460476<br/>                     Date: 2019.02.13 12:39:51 -05'00'</small>                |                 |                                         |                                                                                                                                                  |
| Nonclinical Reviewer           | Tessie Alapatt, Ph.D.                                                                                                                                                                                                                                                                                       | OAP/DAIP        | Section 5                               | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved |
|                                | <b>Signature: Tessie P. Alapatt -S</b><br><small>Digitally signed by Tessie P. Alapatt -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001626066, cn=Tessie P. Alapatt -S<br/>                     Date: 2019.02.13 12:27:58 -05'00'</small> |                 |                                         |                                                                                                                                                  |
| Nonclinical Supervisor         | Terry Miller, Ph.D.                                                                                                                                                                                                                                                                                         | OAP/DAIP        | Section 5                               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
|                                | <b>Signature: Terry J. Miller -S</b><br><small>Digitally signed by Terry J. Miller -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S<br/>                     Date: 2019.02.13 12:34:25 -05'00'</small>       |                 |                                         |                                                                                                                                                  |
| Clinical Pharmacology Reviewer | Jason Moore, Pharm. D.                                                                                                                                                                                                                                                                                      | OCP/DCPIV       | Sections: 6, 15.3                       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved |
|                                | <b>Signature: Jason N. Moore Jr -S</b><br><small>Digitally signed by Jason N. Moore Jr -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001404935, cn=Jason N. Moore Jr -S<br/>                     Date: 2019.02.13 13:46:26 -05'00'</small> |                 |                                         |                                                                                                                                                  |

NDA Multi-Disciplinary Review and Evaluation – NDA

| DISCIPLINE                                                                                                                                                                                                                                                                                                         | REVIEWER                                                                                                                                                                                                                                                                                                                                      | OFFICE/DIVISION | SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED                             | AUTHORED/ ACKNOWLEDGED/ APPROVED                                                                                                                 |
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| Pharmacometric Reviewer                                                                                                                                                                                                                                                                                            | Yuching Yang, Ph.D.                                                                                                                                                                                                                                                                                                                           | OCP/DCPIV       | Sections: 6, 15.3                                                     | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input type="checkbox"/> Approved |
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| Pharmacometric Secondary Reviewer                                                                                                                                                                                                                                                                                  | Xinyuan Zhang, Ph.D.                                                                                                                                                                                                                                                                                                                          | OCP/DCPIV       | Sections: 6, 15.3                                                     | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
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| Clinical Team Leader                                                                                                                                                                                                                                                                                               | Yuliya Yasinskaya, M.D.                                                                                                                                                                                                                                                                                                                       | OAP/DAIP        | Sections: 1, 1.1, 1.2, 2, 3, 4.1, 7.3, 7.4, 9, 10, 11, 12, 13, 14, 15 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
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| Microbiology Team Leader | Avery Goodwin, Ph.D.                                                                                                                                                                                                                                                                            | OAP/DAIP        | Section 8                                 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input type="checkbox"/> Acknowledged<br><input checked="" type="checkbox"/> Approved |
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| <b>OSE/DEPI</b>    | LCDC James Trinidad, MPH, MS |
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| <b>OSE/DRISK</b>   | Mei-Yean Chen, PharmD        |
| <b>Other: DMPP</b> |                              |

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

DMPP= Division of Medical Policy

## Glossary

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|        |                                                        |
|--------|--------------------------------------------------------|
| AC     | advisory committee                                     |
| ADME   | absorption, distribution, metabolism, excretion        |
| ADR    | adverse drug reaction                                  |
| AE     | adverse event                                          |
| AESI   | adverse events of special interest                     |
| AIDS   | acquired immunodeficiency syndrome                     |
| BL     | baseline                                               |
| BMD    | bone mineral density                                   |
| BPCA   | Best Pharmaceuticals for Children Act                  |
| CDC    | Centers for Disease Control and Prevention             |
| CDER   | Center for Drug Evaluation and Research                |
| CDRH   | Center for Devices and Radiological Health             |
| CDTL   | Cross-Discipline Team Leader                           |
| CFR    | Code of Federal Regulations                            |
| CIBA   | CIBA-Geigy Pharmaceutical Company                      |
| CMC    | chemistry, manufacturing, and controls                 |
| CRF    | case report form                                       |
| CRO    | contract research organization                         |
| CRT    | clinical review template                               |
| CSR    | clinical study report                                  |
| DAIP   | Division of Anti-Infective Products, FDA               |
| DMC    | data monitoring committee                              |
| DPV    | Division of Pharmacovigilance                          |
| ECG    | electrocardiogram                                      |
| eCTD   | electronic common technical document                   |
| EPG    | eggs per gram of stool                                 |
| FDA    | Food and Drug Administration                           |
| FDAAA  | Food and Drug Administration Amendments Act of 2007    |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| FDC    | fixed dose combination                                 |
| GCP    | good clinical practice                                 |
| GLP    | good laboratory practice                               |
| GRMP   | good review management practice                        |
| ICH    | International Conference on Harmonization              |
| IIT    | Investigator-initiated trial                           |
| IND    | Investigational New Drug                               |
| IR     | Information Request                                    |
| ISE    | integrated summary of effectiveness                    |
| ISS    | integrated summary of safety                           |

## NDA Multi-Disciplinary Review and Evaluation – NDA

|                      |                                                     |
|----------------------|-----------------------------------------------------|
| ITT                  | intent-to-treat                                     |
| MedDRA               | Medical Dictionary for Regulatory Activities        |
| mITT                 | modified intent to treat                            |
| NDA                  | new drug application                                |
| NME                  | new molecular entity                                |
| OPQ                  | Office of Pharmaceutical Quality                    |
| OSE                  | Office of Surveillance and Epidemiology             |
| OSI                  | Office of Scientific Investigation                  |
| PBRER                | Periodic Benefit-Risk Evaluation Report             |
| PD                   | pharmacodynamics                                    |
| PK                   | pharmacokinetics                                    |
| PMC                  | postmarketing commitment                            |
| PMR                  | postmarketing requirement                           |
| PP                   | per protocol                                        |
| PPI                  | patient package insert                              |
| PREA                 | Pediatric Research Equity Act                       |
| PRO                  | patient reported outcome                            |
| PSUR                 | Periodic Safety Update report                       |
| REMS                 | risk evaluation and mitigation strategy             |
| RST                  | Rapid Sedimentation Technique                       |
| RUQ                  | right upper quadrant                                |
| SAE                  | serious adverse event                               |
| SAP                  | statistical analysis plan                           |
| SCRIHS               | Scientific Committee for Research in Human Subjects |
| TCBZ                 | triclabendazole                                     |
| TCBZ-SO              | triclabendazole sulfoxide                           |
| TCBZ-SO <sub>2</sub> | triclabendazole sulfone                             |
| TEAE                 | treatment emergent adverse event                    |
| TEADR                | treatment emergent adverse reaction                 |
| TN                   | treatment-naive                                     |
| USPI                 | US prescribing information                          |
| WHO                  | World Health Organization                           |

## **1 Executive Summary Office Level Concurrence**

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### **1.1. Product Introduction**

Triclabendazole (TCBZ) is a benzimidazole derivative developed as both veterinary and human formulations by CIBA-Geigy (predecessor to the current Applicant, Novartis) for the treatment of fascioliasis caused by *Fasciola hepatica* and *gigantica*. TCBZ is recommended as first-line therapy by the CDC and WHO for the treatment of fascioliasis; it is also approved in France and Egypt for the treatment of fascioliasis and has been used for mass drug administration (MDA) in Egypt and Bolivia [1].

### **1.2. Conclusions on the Substantial Evidence of Effectiveness**

Evidence for effectiveness of TCBZ for the treatment of fascioliasis in adults and children  $\geq 6$  years of age is provided by the analyses and results from patient-level data from published trials (Hien, Maco and Keiser), 6 non-randomized studies conducted by CIBA-Geigy and WHO, and supportive evidence from the literature.

The Hien study is a randomized controlled trial for which patient-level data were submitted in the NDA. This study evaluated TCBZ at 10 mg/kg q12h x 2 (N=50) vs. artesunate (N=50) for treatment of acute fascioliasis in adults and children in Vietnam. Findings from this study showed that 92% and 76% of patients with acute fascioliasis in the TCBZ and artesunate arms respectively, reported no clinical symptoms at 3 months, with a risk difference of 16% (95% CI 1.7%, 30.8%;  $p=0.035$ ). Findings on normalization of eosinophil count and ultrasound readings at 3 months also favored TCBZ over artesunate providing supportive evidence in support of TCBZ treatment for acute fascioliasis at a dose of 10 mg/kg q12h x two doses.

Given the limited comparative data available evaluating TCBZ for the treatment of fascioliasis, the FDA utilized patient-level data from the Keiser study to estimate a 22% historical estimate of cure (defined as no *Fasciola* eggs in stool) in adults and adolescents with chronic fascioliasis who failed a treatment regimen of oral artemether. When using patient-level data from Keiser and published data from studies including placebo and inadequate treatment for fascioliasis, an estimate for historical control of approximately 40% was established based on the upper bound around the observed cure rate for placebo/inadequate treatment in patients with chronic fascioliasis.

The CIBA/WHO dose-finding, open-label, non-randomized studies enrolled a total of 245 subjects with chronic fascioliasis, ranging in age from 5 to 75 years. Although dosing regimens varied (5-20 mg/kg of TCBZ in single or divided doses administered on Days 1 and 2 or 1 and 3), the majority of patients ( $n=186$ ) were treated with 10 mg/kg either as a single dose or two doses of 5 mg/kg, while 22 subjects received TCBZ 20 mg/kg in two divided doses on Days 1 and 3. In the CIBA/WHO studies, pooled, unweighted analyses yielded cure rates of 72.2%, 82.4% and 95.5% at day 30 in the 10 mg/kg, 15 mg/kg, and 20 mg/kg dose groups, respectively. At day

60, cure rates were 80.1%, 88.2% and 95.5% in the 10 mg/kg, 15 mg/kg, and 20 mg/kg dose groups, respectively. A logistic regression analyses using dose as a continuous predictor and study demonstrated a dose response where the odds of cure were increased by 1.5 for each increase in dose [model estimate for dose of 0.42 ( $p=0.0002$ )]. In addition, treatment difference and 95% CI for the day 30 pooled estimates from the CIBA/WHO studies compared to the inadequately treated control estimate of 22% from the Keiser study, were 50.6% (33.4%, 63.3%), 60.7% (33.2%, 77.9%), and 73.9% (52.4%, 85.9%) in the 10, 15, and 20 mg/kg dose groups, respectively. These findings strongly support a treatment effect of TCBZ at a dose of 20 mg/kg in divided doses.

The open-label Maco study which randomized 84 Peruvian children, ages 2-15 years, with chronic fascioliasis to TCBZ dosing arms of 10 mg/kg x 1 and 7.5 mg/kg x 2, provided supportive evidence for TCBZ efficacy. The day 30 and 60 cure rates in the 10 mg/kg single dose and 7.5 mg/kg BID TCBZ groups, were comparable to the cure rates seen in the CIBA/WHO studies.

The randomized controlled Hien trial with patient level data in patients with acute fascioliasis, the Keiser and Maco studies, and data from published studies and patient-level data from non-randomized unpublished studies, provide substantial evidence for the effectiveness of TCBZ at a dose of 10 mg/kg x 2 for treatment of fascioliasis in adult and pediatric patients.

### 1.3. Benefit-Risk Assessment

#### **Benefit-Risk Summary and Assessment**

In NDA 208711, the Applicant is seeking approval of TCBZ for the treatment of fascioliasis in adults and children  $\geq 6$  years of age. There are no therapies approved for the treatment of fascioliasis in the US.

TCBZ is a benzimidazole derivative initially developed for treatment of veterinary fascioliasis and has been used in humans for over three decades. TCBZ is recommended as first-line treatment for fascioliasis by CDC and WHO. The mechanism of action of TCBZ is incompletely understood but studies suggest that the drug and its metabolites penetrate through the tegument of immature and adult *Fasciola* flukes leading to an alteration of the resting tegumental membrane potential, interference with microtubule structure and function, and inhibition of protein and enzyme synthesis resulting in death of the fluke.

Fascioliasis, is a zoonotic disease of the human hepatobiliary system caused by two species of the genus *Fasciola* – *hepatica* and *gigantica* and affects humans in many parts of the world as well as many species of animals. Fascioliasis in the U.S. is rare. Most cases in the U.S. occur in travelers or immigrants from endemic countries, although domestically-acquired infection has been reported (28 cases in California, Hawaii, and Florida from 1950 through 2011).[2] Human fascioliasis occurs through ingestion of vegetation (e.g. watercress) or water contaminated with metacercariae; these pass through the duodenal wall, peritoneal cavity and liver to reach the biliary tree where the flukes grow to adulthood and complete the cycle by releasing eggs in stool. Diagnosis primarily depends on detection of *Fasciola* eggs in stool; detection of *Fasciola* antibodies in blood, excretory/secretory antigen in serum and stool, peripheral blood eosinophilia, and characteristic abnormalities on CT scan or ultrasound are supportive.

Patient-level data from three published trials (Hein, Maco, and Keiser) [3-5] and 6 historical unpublished studies conducted by WHO/CIBA, were submitted to support the safety and efficacy of TCBZ. The Hien study was a randomized controlled trial comparing TCBZ at 10 mg/kg q12h x 2 (N=50) vs. artesunate (N=50) for the treatment of patients with acute fascioliasis. The Maco study was an open-label, randomized, dose-ranging trial in 84 Peruvian children with chronic fascioliasis and evaluated TCBZ doses of 10 mg/kg x 1 and 7.5 mg/kg x 2. In the Keiser study, TCBZ 10 mg/kg was administered as a single-dose or two doses as rescue therapy in 16 patients who failed oral artemether for chronic fascioliasis. The CIBA/WHO trials were open-label, non-randomized, and dose-finding in a total of 245 subjects with fascioliasis, ranging in age from 5-75 years. The doses studied ranged from 5-20 mg/kg received on Day 1 or over Days 1, 2 and 3.

The Hien study showed that 92% and 76% of patients in the TCBZ and artesunate arms, respectively, reported no clinical symptoms at 3 months, with a risk difference of 16% (95% CI 1.7%, 30.8%;  $p=0.035$ ). Using patient-level data in the Keiser trial, a treatment effect of 22% for no treatment/ineffective treatment control was established in patients with chronic fascioliasis. The Maco study provided supportive evidence of a TCBZ treatment effect compared to the no treatment/ineffective treatment control. In the CIBA/WHO trials, combined unweighted analyses yielded cure rates of 72.2%, 82.4% and 95.5% at

day 30 and cure rates of 80.1%, 88.2% and 95.5% at day 60 in the 10 mg/kg, 15 mg/kg and 20 mg/kg dose regimens, respectively. A logistic regression analyses using dose as a continuous predictor and study demonstrated a dose response where the odds of cure were increased by 1.5 for each increase in dose [model estimate for dose of 0.42 (p=0.0002)]. In addition, compared against the no treatment/ineffective treatment control, the treatment effect at day 30 in the CIBA/WHO studies is 73.9% (95% CI: 52.4%, 85.9%) strongly favoring 20 mg/kg TCBZ. Overall, both the Hien trial for acute fascioliasis, the Keiser and Maco studies, and data from published studies and patient-level data from non-randomized unpublished studies, provide substantial evidence for the effectiveness of TCBZ at a dose of 10 mg/kg x 2 for treatment of fascioliasis in adult and pediatric patients.

No deaths related to TCBZ were reported in any of the studies. In the Keiser and Maco studies, limited safety data were available on 100 patients who received TCBZ, while no safety data was available from the Hien study. In the CIBA/WHO studies, the overall safety database included 245 patients; 186 were treated with a single dose of TCBZ 10 mg/kg, 28 received TCBZ 20 mg/kg dose in two divided doses either q6-8h or q48h (22 assigned to 20 mg/kg + 6 failed subjects retreated with 20 mg/kg), and 37 received lower doses. Adverse events occurring in more than 5% of subjects who received 10 mg/kg included abdominal pain (56.5%), hyperhidrosis (22.6%), nausea (8.1%), urticaria (6.5%), headache (5.9%), and vomiting (5.9%). Although a direct comparison cannot be made, a higher frequency of these AEs was seen in the 28 patients who received a 20 mg/kg dose – abdominal pain occurred in 92.9%, nausea in 17.9%, urticaria in 10.7%, headache in 14.3% and vomiting in 7.1%. Additional safety information for the 20 mg/kg dose came from 4/16 subjects from the Keiser study who received the 20 mg/kg dose, 104 subjects from the CIBA/WHO studies of TCBZ for paragonimiasis and 208 subjects from supportive literature studies. In contrast to the fascioliasis studies, the rates of abdominal pain were much lower in the paragonimiasis studies ( $\leq 5\%$ ), without a dose-response, suggesting that post-treatment abdominal pain in fascioliasis is likely related to the expulsion of the fluke through the biliary duct rather than to the drug. Transient prolongation of the mean QTc interval was noted on the electrocardiographic recordings in some animals at week 5 in a 13-week dog study. The potential for QT prolongation with TCBZ was not evaluated in clinical trials. The Applicant will conduct a thorough QT study as a postmarketing requirement. No other serious safety concerns have been reported thus far with use of TCBZ for the treatment of fascioliasis but given the limited safety data for the 20 mg/kg dose, the Applicant will also conduct a <sup>(b) (4)</sup> study of approximately <sup>(b) (4)</sup> to collect additional information on the safety of the 20 mg/kg dose of TCBZ for treatment of fascioliasis.

| Dimension                               | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Conclusions and Reasons                                                                                                                              |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><u>Analysis of Condition</u></p>     | <ul style="list-style-type: none"> <li>• Fascioliasis, a zoonotic disease of the human hepatobiliary system caused by <i>F. hepatica</i> and <i>gigantica</i>, affects an estimated 2.4 to 17 million people, including young children, in 70 countries worldwide as well as many animal species.</li> <li>• U.S. cases occur primarily in travelers to or immigrants from endemic countries, although domestically-acquired infection has been reported.</li> <li>• Humans are infected through ingestion of vegetation or water contaminated with <i>Fasciola</i> metacercariae; these migrate through the duodenal wall, peritoneal cavity and liver to reach the biliary tree where the flukes grow to adulthood and start releasing eggs.</li> <li>• The acute phase associated with fluke migration is characterized by fever, abdominal pain, urticaria, dizziness, hepatosplenomegaly, anemia, jaundice, and eosinophilia; the chronic phase can last for the 9-13-year life span of the adult fluke and can be asymptomatic or marked by intermittent biliary obstruction with consequent cholangitis, cholecystitis, cholestatic hepatitis and pancreatitis.</li> <li>• Diagnosis is made by detection of <i>Fasciola</i> eggs in stool, although detection of <i>Fasciola</i> antibodies in blood, excretory/secretory antigen in serum and stool, peripheral blood eosinophilia and abnormalities on CT scan or ultrasound is also used.</li> </ul> | <p>Fascioliasis is a zoonotic parasitic infection associated with significant morbidity that affects up to 17 million people worldwide.</p>          |
| <p><u>Current Treatment Options</u></p> | <ul style="list-style-type: none"> <li>• There are no FDA-approved products for the treatment of fascioliasis. TCBZ has been used worldwide for human fascioliasis for decades and is recommended by CDC and WHO as first-line treatment. Currently, TCBZ is available in the US under the expanded access program.</li> <li>• Historically, bithionol, emetine, dehydroemetine, and praziquantel were used for fascioliasis treatment but are associated with significant adverse reactions and require long durations of therapy.</li> <li>• Mebendazole in combination with metronidazole and nitazoxanide, nitazoxanide alone, and artemisin derivatives have been tried but are variably effective. Resistance to TCBZ has been reported, especially from Peru, but prevalence of resistance is undefined.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>There are no approved therapies for fascioliasis in the USA. There is an unmet need for approved therapies for the treatment of fascioliasis.</p> |

| Dimension             | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Conclusions and Reasons                                                                                                                                                   |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><u>Benefit</u></p> | <ul style="list-style-type: none"> <li>• Evidence for benefit of TCBZ comes from patient-level data from 3 published studies, 6 CIBA/WHO trials, and published studies in the literature.</li> <li>• The Hien study was an RCT that evaluated TCBZ at 10 mg/kg q12h x 2 (N=50) vs. artesunate (N=50) for the treatment of patients with acute fascioliasis; 92% and 76% of patients in the TCBZ and artesunate arms respectively reported no clinical symptoms at 3 months, with a risk difference of 16% (95% CI 1.7%, 30.8%; p=0.035).</li> <li>• In the Keiser study, TCBZ 10 mg/kg administered once or twice was used as rescue therapy in 16 patients who failed oral artemether for chronic fascioliasis. An approximately 22% historical control estimate in patients with chronic fascioliasis was determined using patient-level data in this study. When using patient-level data from Keiser along with data from published studies including placebo and inadequate treatment for fascioliasis, an estimate for historical control of approximately 40% was established based on the upper bound around the cure rate.</li> <li>• The CIBA/WHO studies were open-label and dose-finding in a total of 245 subjects, ages 6-75 years, with chronic fascioliasis. Inclusion criteria included the presence of eggs in stool, no intercurrent illness, and no treatment for fascioliasis within the past month. Although dosing regimens varied (5-20 mg/kg received on Day 1, Days 1 and 3 or on Days 1, 2 and 3), the majority of patients (N=186) were treated with 10 mg/kg x 1.</li> <li>• Combined, unweighted analyses of these studies yielded cure rates of 72.2%, 82.4% and 95.5% at day 30 and cure rates of 80.1%, 88.2% and 95.5% at day 60 in the 10 mg/kg, 15 mg/kg and 20 mg/kg dose regimens, respectively. A logistic regression analyses using dose as a continuous predictor and study demonstrated a dose response where the odds of cure were increased by 1.5 for each increase in dose [model estimate for dose of 0.42 (p=0.0002)]. In addition, a large treatment effect of 73.9% (95% CI: 52.4%, 85.9%) at Day 30 was seen compared with the historical control estimate of 22% derived from the Keiser study.</li> <li>• The Maco study was open-label and randomized 84 Peruvian children with chronic fascioliasis to TCBZ dosing arms of 10 mg/kg x 1 and 7.5 mg/kg x 2. As the 20 mg/kg dose was not studied, results of this study provide supportive evidence for efficacy of TCBZ at doses less than 20 mg/kg dose.</li> </ul> | <p>Patient-level data, and evidence from the literature support a large treatment effect for TCBZ in both acute and chronic fascioliasis at a total dose of 20 mg/kg.</p> |

| Dimension                     | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><u>Risk</u></p>            | <ul style="list-style-type: none"> <li>No deaths or safety-related discontinuations were reported in any of the studies submitted in the NDA.</li> <li>No safety data were collected in the Hien trial, and were limited in the Maco and Keiser trials; AEs were uncommon in the latter two studies and consisted primarily of abdominal pain, headache, nausea, and vomiting.</li> <li>In the CIBA/WHO trials, adverse events occurring in more than 5% of subjects who received 10 mg/kg included abdominal pain (56.5%), hyperhidrosis (22.6%), nausea (8.1%), urticaria (6.5%), headache (5.9%), and vomiting (5.9%). A higher frequency of these AEs was seen in the 28 subjects who received a 20 mg/kg dose – abdominal pain in 92.9% of subjects, nausea in 17.9%, urticaria in 10.7%, headache in 14.3% and vomiting in 7.1%.</li> <li>Additional safety data for the 20 mg/kg dose was obtained from study reports of TCBZ administered for treatment of paragonimiasis in addition to published literature. In the paragonimiasis studies, post-treatment abdominal pain occurred in ≤5% of patients; this supports the idea that post-treatment abdominal pain in fascioliasis is likely related to expulsion of the adult fluke(s) rather than to the drug itself.</li> <li>The Applicant’s Periodic Safety Update from 2012-2017, literature evidence and other postmarketing information have not identified major safety concerns after extensive worldwide use of Egaten for fascioliasis.</li> </ul> | <p>Safety data from the studies were limited. Review of data for TCBZ 20 mg/kg and the use of TCBZ worldwide have not identified any major safety concerns. Although the safety profile of the 20 mg/kg dose appears similar to that of the 10 mg/kg dose for fascioliasis treatment, some AEs such as abdominal pain occurred more frequently with the higher dose.</p> |
| <p><u>Risk Management</u></p> | <ul style="list-style-type: none"> <li>Based on the findings of QT prolongation in nonclinical studies, a Warning about the potential for QT prolongation with TCBZ is included in the labeling.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p>The Applicant will conduct a TQT study as a PMR and an observational study as a PMC to assess the safety of TCBZ 20 mg/kg dose.</p>                                                                                                                                                                                                                                   |

### 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

|                          |                                                                                                                                    |                                        |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| <input type="checkbox"/> | The patient experience data that was submitted as part of the application include:                                                 | Section where discussed, if applicable |
| <input type="checkbox"/> | Clinical outcome assessment (COA) data, such as                                                                                    | [e.g., Sec 6.1 Study endpoints]        |
| <input type="checkbox"/> | Patient reported outcome (PRO)                                                                                                     |                                        |
| <input type="checkbox"/> | Observer reported outcome (ObsRO)                                                                                                  |                                        |
| <input type="checkbox"/> | Clinician reported outcome (ClinRO)                                                                                                |                                        |
| <input type="checkbox"/> | Performance outcome (PerfO)                                                                                                        |                                        |
| <input type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                        |
| <input type="checkbox"/> | Patient-focused drug development or other stakeholder meeting summary reports                                                      | [e.g., Sec 2.1 Analysis of Condition]  |
| <input type="checkbox"/> | Observational survey studies designed to capture patient experience data                                                           |                                        |

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Fascioliasis is a zoonotic disease caused by two species of the genus *Fasciola* – *hepatica* and *gigantica*. It is estimated that between 2.4 and 17 million people are infected worldwide in more than 70 countries [6]. Although fascioliasis affects many species of domesticated animals: cattle, sheep, pigs, buffaloes, donkeys, camels, horses, goats, as well as rabbits and rodents, high prevalences in humans do not seem to be necessarily related to areas where veterinary fascioliasis is most common – some of these differences appear related to differences in human diet as well as to economic and hygiene and sanitation [7]. Most human infections occur in Bolivia, Peru, Chile, Puerto Rico, Ecuador, Cuba, Egypt, Iran, Vietnam, Turkey, Spain, France, and Portugal, but cases have been reported in virtually every part of the globe [8, 9]. *F. hepatica* is the only species transmitted in Europe, the Americas, and Oceania, while the two species overlap in Africa and Asia.

In surveys developed during the 1990's, 3 types of human endemic situations have been described – hypoendemic, with prevalence < 1% and mean egg intensities <50 eggs per gram (epg); mesoendemic, with prevalences between 1 and 10% with potentially higher prevalence in children ages 5-15 and egg intensities between 50 and 300 epg; and hyperendemic, with prevalences >10% and mean egg intensities >300 epg [7]. Distribution of infection within populations varies – in Egypt and South American countries such as Bolivia and Peru, most infections occur in school-aged children with a peak in the 9-11 age group in hyperendemic areas [7]; in Vietnam, cases occur mainly in women aged 20-50 years, and outbreaks in Cuba have affected mainly adults [8]. In the hyperendemic area of the Northern Bolivian Altiplano, prevalence of fascioliasis in some communities by coprological and serological surveys were 72% and 100% respectively, with intensities of up to >5000 epg in children [7]. Prevalence and intensity of infection appear higher in females compared with males in certain human hyperendemic areas like Egypt [10]. The intermediate hosts of the parasite, lymnaeid snails, are endemic to the US, and endemic life cycles involving herbivores do occur. Locally acquired infections have been reported mostly from Hawaii, but there is at least one report from the continental US [11]. The parasite targets the human hepatobiliary system and can cause a range of symptoms during acute disease, and results in chronic disease years after infection.

*Fasciola spp* have a complex life-cycle (see diagram below), and fascioliasis can be transmitted through both food and water. Eggs hatch to release miracidia which infect lymnaeid snails, their intermediate hosts. Cercariae released from snails encyst on water plants and develop into metacercariae. Infections in humans occur when the host swallows metacercarial cysts attached to contaminated vegetation. Watercress is the classic vehicle, but many other plants can be infected with the cercariae of *F. hepatica*. Acquisition of the infection may also occur through contaminated drinking water with free-floating cysts, or by ingestion of metacercariae attached to the surface of food or kitchen utensils washed with contaminated water [8].

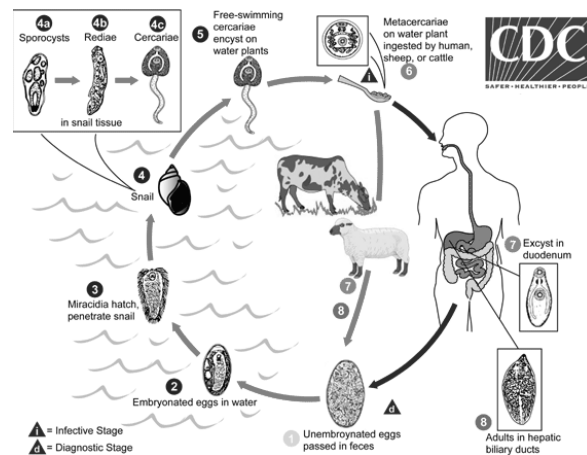


**Figure 2-1 Fasciola lifecycle**

Source: <https://www.cdc.gov/parasites/fasciola/biology.html>

Once ingested, metacercarial cysts excyst in the small intestine, penetrate the intestinal wall, migrate through the peritoneal cavity, penetrate Glisson’s capsule, travel through hepatic parenchyma, and finally enter the biliary system. Infection and inflammation in the hepatobiliary system caused by mechanical disruption along with the excretory/secretory products by the immature flukes result in the symptoms of acute fascioliasis. The hermaphroditic young flukes reach sexual maturity in the biliary tree, and produce eggs which pass into the intestine via the bile ducts, and then out in stool. The incubation period, from ingestion of metacercariae to onset of symptoms, is usually between 4 and 6 weeks, but can range from several days to a few months.

The acute phase associated with fluke migration and destruction of liver parenchyma is often characterized by fever, right upper quadrant and generalized abdominal pain, urticaria, respiratory symptoms, dizziness, hepatomegaly, splenomegaly, anemia, and jaundice. Subcapsular hematomata in the liver and intra-abdominal hemorrhage may also occur as the immature fluke migrates. High eosinophil counts and high IgE levels are characteristic at this stage. Symptoms usually ameliorate when the fluke reaches the bile ducts; this chronic phase can last for months or years and is the period when the parasite matures and starts laying eggs. Egg production can number in the hundreds each day; the adult usually lives for 9-13.5 years [8]. The parasitic prepatent period between the ingestion of metacercariae and passage of ova is usually about 4 months, but can range between 3 and 18 months [9]. The chronic phase is marked by intermittent or constant obstruction of the biliary tree with consequent cholecystitis, hemobilia, pancreatitis, cholangitis, or cholestatic hepatitis. Symptoms range in severity and are associated with the underlying pathogenesis. Anemia is frequent and likely multifactorial in etiology. Hepatic lesions, sometimes mistaken for malignant mass lesions, fibrosis, and chronic inflammation are important pathological features. Erratic migration of juvenile flukes could result in ectopic fascioliasis in subcutaneous tissues, lung, heart, brain, muscle and genitourinary tract [12].

The oldest and previously standard diagnostic test was the detection of *Fasciola* eggs in stool. However, eggs are not released for the first 3-4 months after infection, and can be intermittent. There are now multiple immunological tests available for detection of both antigen and antibodies to *Fasciola*, including PCR; however, none are FDA-approved. The most commonly-used specific diagnostic tests in the published literature are coprology, measurement of IgG antibodies to *F. hepatica* antigen, and testing for excretory/secretory (E/S) antigen in serum and stool. Marked eosinophilia, though non-specific, is a consistent marker of acute fascioliasis but less so of chronic disease. Eosinophilia reliably declines with treatment and is therefore considered an useful surrogate marker for response to treatment. Radiological abnormalities commonly seen on ultrasound (US) or computerized tomography (CT) are nodular lesions, tubular branching lesions, subcapsular low density areas, solitary nodules, and perihepatic fluid accumulation [13]. Live flukes have sometimes been extracted during ERCP [13].

Cure is determined by a variety of factors including improvement in clinical symptoms over a period of weeks to months, disappearance of eggs in stool [14], decrease in eosinophils and IgE followed by a decrease in anti-*Fasciola* antibodies, disappearance of Fas E/S antigens (FES-Ag) in serum or stool, and improvement in hepatic ultrasound or CT appearance [15].

In the acute phase, the primary criteria for response to treatment and cure are:

- a) Resolution of fever and abdominal pain
- b) Decline of liver enzymes
- c) Decline/normalization of eosinophilia
- d) Decline in antibody levels

In the chronic (often asymptomatic) phase, the major clinical criterion of cure is clearance of parasite eggs from stool (3 stool samples). Biliary colic, and transient increases in GGT and ALP may be seen soon after therapy, presumably related to expulsion of the adult fluke(s). Additional suggestive markers of cure are decrease in serum anti-*Fasciola* antibodies and resolution of IgE and eosinophilia [8], although the latter may be affected by the presence of concurrent parasitic infections.

TCBZ was first developed by Novartis' predecessor CIBA-Geigy, as Fasinex, for veterinary treatment of *Fasciola* spp infection. Given as a single dose in animals, it was found effective against adult parasites as well as immature flukes. In 1986, it was first used to treat human infection in 2 patients – at a dose equivalent to that used in animals - and in 1989, after its use in an epidemic of fascioliasis in Iran, the WHO worked with CIBA to develop a human formulation of TCBZ [16]. The initial human formulation, CGP23030, was used in 6 CIBA/WHO studies and 3 Egyptian government-sponsored studies, but was found to be 20% less bioavailable than Fasinex; the current formulation, Egaten was subsequently developed and has

been commercially available for human use since 1997<sup>1</sup>. Since then, Egaten has become the mainstay of treatment for human fascioliasis - the CDC has recommended Egaten as first-line therapy for human fascioliasis since 1998 due to its ease of administration and tolerability as a single 10 mg/kg dose, and in severe infections, as two 10 mg/kg doses administered 12 hours apart [14].

## 2.2. Analysis of Current Treatment Options

There are no FDA-approved products for the treatment of fascioliasis. In endemic areas, historically, bithionol was the drug of choice but the need for multiple daily doses for 20-30 days, frequent adverse effects and cure rates of around 50% [17] made it sub-optimal. Praziquantel, the drug of choice for other food-borne trematode infections, is ineffective for fascioliasis with cure rates ranging from 0-71% [18]. Emetime and dehydroemetine achieved higher cure rates but had to be given parenterally for 10 days, and also caused severe adverse effects [8, 19], including cardio- and hepatotoxicity. Other medications such as mebendazole in combination with metronidazole and nitazoxanide have been tried but required prolonged courses [3 weeks for mebendazole and metronidazole [18] and 6-7 days of nitazoxanide [18] [20] with inconsistent cure rates. However, recent studies [21, 22] indicate much higher cure rates for nitazoxanide (60% and 94%, respectively). Artemisinin derivatives have also been studied as possible treatment options for fascioliasis though the efficacy outcomes vary [3, 4].

TCBZ has been routinely used for *Fasciola spp* infection in veterinary practice since 1983. Since 1986, TCBZ has become the mainstay of treatment worldwide [18]. It is active against adult parasites as well as immature flukes migrating through the liver and is thought to irreversibly damage the tegument of the fluke by tubulin inhibition. Cure rates of 79-83% have been reported with a single dose, and about 93% with two doses [23, 24].

Resistance to TCBZ in livestock with fascioliasis is increasingly reported and resistant human infections have been reported in Peru and the Netherlands [25, 26].

## 3 Regulatory Background

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### 3.1. U.S. Regulatory Actions and Marketing History

Egaten is not approved for marketing in the U.S. It is available under expanded access and dispensed by the CDC.

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<sup>1</sup> Mull R. Named patient use of triclabendazole (CGP 23030) in the treatment of human infection with *Fasciola hepatica*. Novartis Clinical Study Report 1999, page 14. Submitted as part of NDA 208711, June 14, 2018

### 3.2. Summary of Presubmission/Submission Regulatory Activity

- Pre-Investigational New Drug (PIND) 127946 was established September 30, 2015.
- Type C meeting on January 20, 2016, to discuss a marketing application for the treatment of fascioliasis due to *Fasciola hepatica* and *gigantica*.
- Type C meetings were held on July 13, 2016, and June 13, 2017
- No pre-NDA meeting was held.
- Orphan Drug Designation was granted on April 17, 2017.
- The proprietary name “Egaten” was approved on May 4, 2017.
- After multiple conversations with FDA, Novartis obtained right of reference to three investigator-initiated trials (IITs) and submitted a right of reference statement. CRFs from the Keiser study [4] were submitted to FDA under PIND (b) (4) on September 18, 2017.
- NDA was submitted as a rolling review with the first part submitted on September 22, 2017.
- Rolling review of the NDA was granted September 29, 2017.
- Fast Track designation was granted September 29, 2017.
- The final component of the rolling submission was submitted on June 14, 2018.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Because Novartis had not performed any of the investigator-initiated trials, the source material available was requested and is summarized below:

- **Hien:** Original and translated blank CRFs were available. Paper CRFs and source documents were no longer available due to expiration of institutional document retrieval policy (>10 years since study completion). The protocol was not available.

*Reviewer comment: No inspections could be carried out for the Hien study owing to the lack of availability of study material and source documents.*

- **Maco:** The following documents were available: Original informed consent for all 84 subjects, original data collection forms and adverse event questionnaires for the 59 patients from a single site (Asillo), data collection forms for the remaining 25 patients in Excel format, a copy of 2 notebooks from the lab technicians with stool count results. The primary efficacy endpoint of mean egg counts was only assessed in the 59 Asillo patients.

*Reviewer comment: The Maco site audit by the OSI team during the review revealed gaps in the available source data at the study site. Specifically, while data on all 84 enrolled patients were maintained in an Excel spreadsheet, data collection forms (source data) were unavailable for 26 of these patients and incomplete for the remaining 58 patients. In addition, original laboratory reports (paper format) for stool tests were not available. These findings have been summarized in the Clinical Inspection Summary by Dr. John Lee; the Maco study is viewed as supportive for purposes of this review.*

- **Keiser:** The protocol, blank CRF and paper CRFs for individual patients were available. The latter were shared with the Division, in anonymized format, directly by the PI under PIND (b) (4). The PI confirmed that study information was collected directly on paper CRFs (except for parasitology stool survey and hematology and biochemistry results). Source documents for parasitology stool survey and hematology and biochemistry results were not available, but this data was available in CRFs and electronic format.

*Reviewer comment: No issues were identified by OSI on inspection of documents related to the Keiser study.*

- Drs. Keiser and Maco indicated their availability for interview. Dr. Hien was not available, but the Division was referred to the Head of the Clinical Trials Unit, Ms. Evelyne Kestelyn, at the Oxford University Clinical Research Unit, U.K. which collaborated on the Hien trial.

- Novartis could not provide a GCP statement for any of the submitted trials as they were not the Sponsor for any of them.
- Keiser has provided a full GCP statement but noted their shortcoming regarding storage of clinical trial records.

#### 4.2. Product Quality

The proposed drug product, Egaten, is an immediate release tablet containing 250 mg TCBZ.

The TCBZ drug substance is a new molecular entity (NME). The Applicant considers TCBZ as a BCS Class II/IV drug substance. It is a white to almost white crystalline powder and is known to exhibit polymorphism. The drug substance manufacturing process only produces the polymorph (b) (4)

The drug product is an immediate release tablet containing TCBZ and the following compendial excipients: lactose monohydrate, corn starch, methyl hydroxyethyl cellulose, magnesium stearate, silicon dioxide, and red iron oxide. The Applicant has manufactured numerous drug product batches to date and provided release results for eight clinical, production, and/or commercial batches. All drug product batches manufactured to date met the proposed release specifications, included below.

NDA Multi-Disciplinary Review and Evaluation – NDA

| Test Code                                              | Title of Test, Principle                                                                                                                                                                                                                                | Requirements                                                                                                                                                                     |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Description</b>                                     |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 10001.01                                               | Appearance by visual examination                                                                                                                                                                                                                        | Shape: (b) (4)<br>Color: pale red, speckled<br>Imprint and score: one side with score and imprint "EG EG" and score on other side                                                |
| <b>Properties</b>                                      |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 10901.01                                               | Mean mass                                                                                                                                                                                                                                               | (b) (4) mg                                                                                                                                                                       |
| <b>Identification</b>                                  |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 20101.01                                               | Identification by TLC <ul style="list-style-type: none"> <li>• Triclabendazole</li> </ul>                                                                                                                                                               | Triclabendazole spot corresponds to the reference                                                                                                                                |
| 53501.01                                               | Identification by HPLC <ul style="list-style-type: none"> <li>• Triclabendazole</li> </ul>                                                                                                                                                              | Retention time of Triclabendazole peak corresponds to the reference                                                                                                              |
| <b>Performance</b>                                     |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 50111.01                                               | Dissolution by UV <ul style="list-style-type: none"> <li>• Triclabendazole</li> </ul>                                                                                                                                                                   | Not less than (b) (4) % (Q-value) of the declared content in 30 minutes according to acceptance table of Ph. Eur or USP, JP (level 1 and 2 only, up to 3 for stability testing). |
| <b>Impurities</b>                                      |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 53501.01                                               | Degradation products, based on the declared content of Triclabendazole, by HPLC<br>Specified degradation products<br>(b) (4)                                                                                                                            | Not more than (b) (4) %                                                                                                                                                          |
|                                                        | Other degradation products <ul style="list-style-type: none"> <li>• Individually</li> </ul>                                                                                                                                                             | Not more than (b) (4) %                                                                                                                                                          |
|                                                        | Total degradation products                                                                                                                                                                                                                              | Not more than (b) (4) %                                                                                                                                                          |
| <b>Uniformity of dosage units</b>                      |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 50431.01                                               | Uniformity of dosage units by weight variation                                                                                                                                                                                                          | Meets the requirements of Ph. Eur. JP and USP                                                                                                                                    |
| <b>Test Code Title of Test, Principle Requirements</b> |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 70161.01                                               | Microbial enumeration tests (Plate-count method) <ul style="list-style-type: none"> <li>• Total aerobic microbial count (TAMC)</li> <li>• Total combined yeasts and moulds count (TYMC)</li> <li>• Specified micro-organism Escherichia coli</li> </ul> | Not more than (b) (4) CFU/g<br>Not more than (b) (4) CFU/g<br>Absence in 1 g                                                                                                     |
| <b>Assay</b>                                           |                                                                                                                                                                                                                                                         |                                                                                                                                                                                  |
| 53501.01                                               | Assay by HPLC <ul style="list-style-type: none"> <li>• Triclabendazole</li> </ul>                                                                                                                                                                       | (b) (4) % of the declared content                                                                                                                                                |

The dissolution method has been evaluated and was shown to have discriminating power for changes in critical quality attributes of the drug product (e.g. drug substance particle size). The drug product has a score on both sides of the tablet to facilitate splitting into two equal halves. Comparative dissolution profiles of the whole versus split tablets have demonstrated that

splitting of the tablets do not significantly impact the dissolution profile. Additional studies performed on split tablets (e.g. assay, degradation products, content uniformity, friability, weight variation) provided further support that the drug product has a functional score. Both manual and mechanical splitting of tablets is recommended as an acceptable means for ease of administering divided dose to patients. An additional dissolution study demonstrated that crushing the drug product with and without applesauce does not impact in vitro dissolution. Additional stability studies (e.g. assay, degradation products) confirmed that the crushed drug product is stable in applesauce up to four hours.

The drug product is packaged in (b) (4) blister packs commonly used for solid oral dosage forms, contained in a cardboard box. Each blister pack contains four tablets. Evaluation of the stability results indicates that drug product is stable at long-term storage conditions and that no significant change occurs at accelerated conditions. Based on the stability data, the proposed shelf life of 24 months is acceptable when stored below 30°C.

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All sites are found acceptable upon completion of this review. The Overall Manufacturing Facility Status in Panorama is Approval. For details, see the Facility evaluation within this review.

Novel excipients: No

Any impurity of concern: No

Sufficient controls to insure safety and efficacy of the commercial product: Yes

#### 4.3. **Devices and Companion Diagnostic Issues**

Not relevant to this product.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

TCBZ was originally developed to treat fascioliasis in domestic livestock, with a comprehensive animal health development program undertaken in the 1970s by Ciba-Geigy (a legacy Novartis company).

The majority of the nonclinical testing with TCBZ was conducted prior to the implementation of Good Laboratory Practice (GLP) in 1978. However, all studies were reported to be performed according to internationally accepted guidelines and standards applicable at the time of conduct and were certified to be of reputable scientific quality. The preclinical investigations with TCBZ were conducted to support the veterinary product for treatment of fluke diseases. However, the data from these studies are considered valid to support the safety of clinical formulation of TCBZ for the treatment of fascioliasis. The test drug has been referred to as CGA 89317 (in previously conducted study reports by Ciba-Geigy), and NVP-EGA230 (by Novartis in recent study reports). For the sake of simplicity, the proposed drug is referred to as TCBZ throughout the review. The nonclinical studies submitted in this NDA included safety pharmacology studies, general and reproductive toxicology studies, genotoxicity as well as pharmacokinetic and metabolism studies. The proposed dose and duration of TCBZ to treat fascioliasis are two doses of 10 mg/kg, 12 hours apart.

To evaluate potential secondary effects of TCBZ treatment, an *in vitro* study was conducted on 72 potential off-target sites for binding (Study 2017-00272) including the hERG channel. TCBZ had no relevant affinities in any of the secondary-target binding assays. As part of the Safety Pharmacology assessments, a stand-alone hERG channel inhibition assay was not conducted with TCBZ. However, in a series of other non-GLP Safety Pharmacology studies, no adverse effects were observed in studies that evaluated the effects of TCBZ on the central nervous, cardiovascular, digestive and urinary systems, blood, and smooth muscle in mice, rats and rabbits. A GLP-compliant single-dose cardiovascular study in dogs indicated transient QTc interval prolongation in dogs after dosing with TCBZ at 100 mg/kg which is about 2.5 times the proposed clinical dose based on body surface area comparison. QTc interval effects in the dog correlated with peak sulfone metabolite concentrations and hence, it is likely that the sulfone metabolite may be playing a role in the observed QTc interval prolongation. *In vitro* studies done on rabbit Purkinje fibers showed that the sulfoxide and sulfone metabolites had greater inhibitory effects on cardiac action potential duration at high concentrations of 30 and 100  $\mu\text{M}$  than TCBZ. The Table 5.1 below compares the plasma levels of the TCBZ and its metabolites in human (healthy human volunteers and fed or fasted patients (Study B2212) treated with 12.5 mg/kg and 10 mg/kg TCBZ, respectively) with plasma levels of the drug and its metabolites in dogs treated with 100 mg/kg TCBZ (study details can be found in Safety Pharmacology in Section 5.3 below). In this study, at the 100 mg/kg dose, transient QT prolongation as well as minimal heart rate alterations was seen in dogs. The numbers in parentheses indicate the safety margin based on exposure levels in human and dogs. The data show that in dogs, the

sulfone metabolite of TCBZ tends to accumulate more than the sulfoxide metabolite. However, the accumulation of the sulfone metabolite in dogs is about 100-fold higher than that measured in healthy human volunteers and about 100-500-fold higher in fed or fasted patients in the clinic (Table 5.1).

**Table 5.1 Comparative AUC exposure for triclabendazole and its sulfoxide and sulfone metabolites**

|           | AUC <sub>0-96</sub> in Dog treated to 100 mg/kg TCBZ (umol.h/L) | AUC <sub>0-72</sub> in healthy human volunteers treated to 12.5 mg/kg TCBZ (umol.h/L) | AUC <sub>0-48</sub> in fed patients (Study B2212) treated to 10 mg/kg TCBZ (umol.h/L) | AUC <sub>0-48</sub> in fasted patients (Study B2212) treated to 10 mg/kg TCBZ (umol.h/L) |
|-----------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| TCBZ      | 20                                                              | 10 (2X)*                                                                              | 10 (2X)*                                                                              | 2 (10X)*                                                                                 |
| Sulfone   | 7300                                                            | 70 (100X)*                                                                            | 30 (250X)*                                                                            | 15 (500X)*                                                                               |
| Sulfoxide | 3500                                                            | 780 (5X)*                                                                             | 400 (10X)*                                                                            | 200 (20X)*                                                                               |

\* indicates safety margin (AUC<sub>Dog</sub>/AUC<sub>Human</sub>); All values are approximate and rounded to the nearest multiple of 5, 10 or 100. Sources: NDA 208711; Clinical Overview and Nonclinical Overview

TCBZ was administered as a diet admixture to rats and beagle dogs at doses of 10, 100 and 1000 ppm daily, for 13 weeks. The rat study showed no evidence of dose-related mortality or any other major toxicologically relevant effects. The no observed adverse effect level (NOAEL) was 0.7 to 0.8 mg/kg/day dose in rats (10 ppm) and 0.35 mg/kg/day dose in dogs (10 ppm). In the dog study (n = 12 per dose group), weight loss was found at the highest dose of 1000 ppm (equivalent to a dose of 39 mg/kg body weight). In addition, at the highest dose, an increase in the QT interval was reported in the ECG recordings (QT of 0.24 s in 4 dogs and 0.26 s in 1 dog at weeks 5 and 9; QT normal range: 0.19–0.23 s). Slight elevation of reticulocytes and minimal decreases of red blood cell counts and hemoglobin levels were observed in dogs predominantly, and to a lesser extent in rats, at the highest dose, which may suggest a slight effect of drug-induced anemia in the animals. Effects on the liver included liver enzyme increases and increased liver weights in mice and dogs after repeat dosing. In rats, liver enzymes were also increased at the highest doses. The highest dose in rats is almost equivalent to the proposed clinical dose, whereas the highest dose in dogs is about twice the proposed clinical dose based on a body surface area comparison. No TK analyses were conducted in the 13-week repeat-dose toxicology studies in the rat or dog.

TCBZ had no genotoxic potential in a battery of in vitro and in vivo assays. Orally administered TCBZ did not have effects on fertility in rats. Oral administration of TCBZ was not embryotoxic in rats and rabbits up to 200 and 20 mg/kg/day, which is 1.6 and 0.3 times the clinical dose respectively, based on a body surface area comparison. In a 2-generation, combined fertility and pre- and postnatal developmental toxicity study in rats, decreases in body weight gain of second generation pups (F2) were observed at the highest dose, and hence, the NOAEL was determined to be the mid-dose of 1.3 mg/kg/day (below the proposed clinical dose). No effects on fertility were attributable to drug administration at doses up to 6.4 mg/kg. However, since the highest dose failed to manifest any maternal toxicity in F0 and F1 dams, the doses used in

the study are likely inadequate to indicate whether the drug causes postnatal developmental toxicity apart from the observed body weight loss in F2 offspring. No TK analyses were conducted in any of the reproductive toxicology studies in rats or rabbits. However, a PK study done in pregnant rabbits treated with a single dose of C14 radiolabeled TCBZ on day 13 and day 18 of pregnancy showed that the drug did cross the placental barrier and was present in fetuses.

In sum, from a Pharmacology/Toxicology perspective, the clinical relevance of the transient QT prolongation seen in the repeat-dose study as well as in the single dose safety Pharmacology study in dogs is unclear, particularly in the absence of cardiac monitoring in the clinical trials, and hence a post-marketing thorough QT study in the clinic will be conducted as recommended by the clinical review team. Additionally, there were inadequacies in the nonclinical studies, including the study design of the repeat dose toxicity study in rats, doses used in the 2-generation reproductive toxicology study, as well as lack of TK analyses in the rat and dog repeat-dose studies (see Reviewer's comments in 5.5.1). However, it should be noted that the proposed clinical treatment regimen of TCBZ is a single day of dosing with 2 doses of 10 mg/kg, 12 hours apart, whereas dogs and rats were treated with TCBZ for 13 weeks continually in the repeat-dose studies. Furthermore, the TK study from the single-dose safety Pharmacology study in dogs indicate that plasma level of the metabolite TCBZ sulfone, which is thought to mediate the transient QT prolongation in dogs, is more than 100 times the amount found in the clinic (Table 5.1). Therefore, from a Pharmacology/Toxicology standpoint, TCBZ is recommended for approval, taking into account the nonclinical study findings, past clinical experience of the drug, and the short duration (single day) of the proposed clinical treatment.

## 5.2. Referenced NDAs, BLAs, DMFs

IND 127946, DMFs (b) (4)

## 5.3. Pharmacology

### Primary pharmacology

TCBZ has been reported to have specific activity against flukes infecting animals and humans including *F. hepatica* and *F. gigantica*. Although the mechanism of action has been extensively investigated, it is not fully understood. TCBZ and two of its metabolites have been shown to affect the structural integrity of flukes by interference with the microtubular structure and inhibition of protein synthesis. Additionally, mechanisms of resistance to TCBZ remain unclear, but possibly include changes in the target molecule, beta-tubulin, changes in drug uptake and/or efflux mechanisms and altered drug metabolism.

### Secondary Pharmacology

**NVP-EGA230: Secondary Pharmacology Profile (Study RD-2017-00272):** The proposed drug, TCBZ was tested in secondary pharmacology profiling assays comprising 72 assays (48 GPCRs, 3

transporters, 8 ion channels, 8 nuclear hormone receptors, 5 enzymes). TCBZ had no relevant off-target affinities in any of the assays.

### Safety Pharmacology

#### **Cardiovascular Effects in dogs (Study 001004):**

In this GLP study, 10 male Beagle dogs were administered a single dose of gelatin capsules containing TCBZ. Each dog received both doses i.e. 40 and 100 mg of the drug, once with a 13-day washout period between both doses. Electrocardiographic (ECG) measurements were done during the pretest period i.e. 2, 4 and 8 hours after administration of an empty gelatin capsule, and just before dosing and approximately 2, 4, 8, 24, 48 and 96 hours after each administration. Standard parameters including P, PQ (named PR on ECG recordings), QRS, QT, heart rate as well as heart rate corrected QT intervals (QTc) was calculated. QTc, QT and R-R were calculated or measured in milliseconds (msec). The normal range of variation for QTc interval in males is  $212 \pm 19$  msec (average  $\pm 2$  SD).

ECG examinations following administration of 40 mg/kg revealed marginal prolongation of QT and QTc intervals in 24-48 hour recordings of 2 animals, QTc values ranging from 219 – 220 msec compared to pretest values at 216 - 218 msec. Moderate prolongation of QT and QTc intervals in 1 animal after administration of 40 mg/kg was noted at 230 msec. At 100 mg/kg, QT and/or QTc intervals were moderately prolonged in the 24-hour and 48-hour recordings of 2 animals (232-247 msec) and marginally prolonged in 2 animals (222-226 msec). In the prematurely sacrificed animal, a tachycardia of 186 beats per minute was observed, which was reported to be related to an endogenous infection as determined by clinical signs and pathology. Other changes including slight decrease in heart rate in 2- and/or 4-hour recordings or slight increase in heart rate in mainly 8-hour recordings of some animals, respectively, were seen at a similar incidence also in the pretest recordings of the animals. Although the intensity was slightly more pronounced in some animals after treatment, there was no dose-dependency seen.

Toxicokinetic (TK) analysis was done on blood samples collected from the dogs at 2, 4, 8, 24, 48 and 96 hours after dosing to determine the amount of TCBZ and its sulfoxide and sulfone metabolites in dog plasma. TK data is available in Table 5.10 in Section 5.4 below

#### **Safety Pharmacology Electrophysiology Purkinje Fibers (Study 001410/ 001411/001412)**

The aim of this non-GLP study was to evaluate the cardiovascular safety of the proposed drug, TCBZ by evaluating the electrophysiologic effects of the drug and two of its major metabolites (sulfone and sulfoxide TCBZ) on the action potential parameters recorded from rabbit Purkinje fibers. New Zealand white rabbits of either sex were sacrificed and running Purkinje fibers with ventricular muscle were dissected from the left ventricle and mounted in a tissue bath. The concentrations of drug and metabolites used in the experiment were 0.1, 0.3, 1, 3, 10, 30 and

100 uM. At 100 uM, TCBZ precipitated in the vehicle, DMSO, and hence this concentration was not tested for the drug.

The results showed that the parent drug TCBZ (0.1-30 uM) did not exert any effect on the action potentials recorded from rabbit Purkinje fibers (Table 5.2). The sulfone and sulfoxide metabolites did modify the action potential parameters in the range of 0.1 to 3 uM. However, at higher concentrations (10-100 uM), the sulfone metabolite exerted potent class IV antiarrhythmic effects, i.e. it decreased the plateau height in a concentration-dependent manner, resulting in a reduction of the action potential duration (APD). These effects were so severe that the cells did not respond (cellular death) to the stimulation after 10 minutes of superfusion with this compound. The sulfoxide metabolite exerted similar class IV antiarrhythmic effects but to a lesser extent. Such decreases in the plateau height and in the dome amplitude characterize the effects of L-type calcium current inhibitors including nifedipine, cadmium or verapamil.

**Table 5.2 Effects of EGA230, sulfone TCB and sulfoxide TCB on action potential duration**

|                       |       | Control  | 0.1 uM   | 0.3 uM   | 1 uM     | 3 uM     | 10 uM     | 30 uM     | 100 uM     |
|-----------------------|-------|----------|----------|----------|----------|----------|-----------|-----------|------------|
| <b>TCBZ</b>           | APD50 | 208 ± 12 | 218 ± 11 | 221 ± 10 | 220 ± 9  | 212 ± 10 | 189 ± 13* | 181 ± 13* | not tested |
|                       | APD90 | 268 ± 10 | 278 ± 9  | 280 ± 7  | 278 ± 7  | 276 ± 8  | 269 ± 9   | 263 ± 12  | not tested |
| <b>Sulfone TCBZ</b>   | APD50 | 227 ± 15 | 228 ± 16 | 234 ± 14 | 227 ± 15 | 221 ± 13 | 184 ± 16* | 89 ± 16*  | cytotoxic  |
|                       | APD90 | 292 ± 14 | 294 ± 15 | 300 ± 14 | 299 ± 13 | 297 ± 12 | 276 ± 13  | 218 ± 16* | cytotoxic  |
| <b>Sulfoxide TCBZ</b> | APD50 | 234 ± 7  | 237 ± 7  | 239 ± 6  | 239 ± 7  | 225 ± 10 | 194 ± 16* | 150 ± 24* | 116 ± 18*  |
|                       | APD90 | 298 ± 7  | 304 ± 7  | 306 ± 6  | 308 ± 6  | 300 ± 6  | 282 ± 9   | 269 ± 11* | 250 ± 13*  |

\*p < 0.05 versus control values.

APD50, APD90: Action Potential Duration at 50% and 90%

Source: NDA 208711 Safety Pharmacology study report

**Non-GLP Safety Pharmacology studies conducted by**

(b) (4)

\_\_\_\_\_ :

5 male mice of ddY strain given a single oral dose of 300 mg/kg TCBZ were evaluated for the following:

Effects on the central nervous system:

The effects of thiopental-induced anesthesia, inhibitory effects on bemegride-induced convulsions, muscle-relaxant effects and inhibitory effects on reserpine-induced ptosis in mice were evaluated. There were no significant effects noted in any of these tests.

Effects on the cardiovascular system:

A slight, slow-onset and continuous fall in blood pressure was seen (-10%), which returned to the baseline within 24 hr. The heart rate was not affected.

Effects on the smooth muscle:

TCBZ showed no effects on the spontaneous movement of isolated rabbit ileum and no anti-histamine effects in the isolated guinea pig ileum.

Effects on the urinary system:

Urine volume was slightly reduced during 0 - 2 hr after administration of the drug, but restored to normal by 24 hr.

Effects on the digestive system:

TCBZ showed no significant effects on the intestinal propulsion in mice.

Effects on the blood:

TCBZ caused neither aggregation of platelets nor significant inhibition of collagen-induced aggregation.

5.4. **ADME/PK**

| Type of Study                                                                                                                                                                                                                                            | Major Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Absorption</b>                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p><b>Study no. R25/1991 Kinetics of unchanged TCBZ and its sulphoxide and sulphone metabolites in plasma and urine of dogs, and in urine of rats, following intravenous and oral administration of single doses of C<sup>14</sup>-labelled TCBZ</b></p> | <p><b>Study no. R25/1991: Dog:</b> A single dose of 0.5 mg/kg of C<sup>14</sup>-labelled TCBZ was administered IV via a cephalic vein as a solution in PEG 400/0.9 % saline (1:1) and orally as crystalline substance in a gelatin capsule to two animals each. For toxicity supplementary studies, single doses of 5 and 40 mg/kg were administered orally in gelatin capsules to one animal each.</p> <p><b>Rat:</b> For toxicity studies, single doses of 10 and 80 mg/kg of C<sup>14</sup>-labelled TCBZ were administered orally by gavage to 2 animals each as a suspension in 0.5 % aqueous carboxymethyl cellulose.</p> <p>In dogs, TCBZ was rapidly cleared from plasma and converted to the sulphoxide and sulphone metabolites. The sulphone metabolite accounted for about 80% of the circulating radioactivity in plasma. It was slowly formed and eliminated and is likely to accumulate upon repeated administration of TCBZ. Altogether the two metabolites represented virtually the total radioactivity measured in plasma and therefore no significant amounts of other possible metabolites were circulating.</p> <p>In rats, negligible amount of unchanged drug and of the measured metabolites were renally excreted. Renal excretion of total radioactivity amounted to 3-8 % of the dose.</p> |

**Table 5.3 Kinetics of unchanged CGP 23030 and its sulphoxide and sulphone metabolites in plasma of dogs (R25/1991)**

| PK parameters:                         | Route of administration (Dose) | TCBZ | Sulphoxide | Sulphone                               | Total C <sup>14</sup> |
|----------------------------------------|--------------------------------|------|------------|----------------------------------------|-----------------------|
| <b>C<sub>max</sub> (umol/L)</b>        | IV(0.5 mg/kg)                  | 0.7  | 2.9        | 3.2                                    | 5.0                   |
|                                        | PO(0.5 mg/kg)                  | n.d. | 1.1        | 1.2                                    | 1.9                   |
|                                        | PO(5 mg/kg)                    | n.d. | 11.7       | 11.1                                   | 18.9                  |
|                                        | PO(40 mg/kg)                   | #    | 42.6       | 84.6                                   | 96.1                  |
| <b>T<sub>max</sub> (h)</b>             | IV(0.5 mg/kg)                  | 0.08 | 1 & 8      | 12                                     | 8                     |
|                                        | PO(0.5 mg/kg)                  | n.a. | 6          | 36                                     | 8 & 24                |
|                                        | PO(5 mg/kg)                    | n.a. | 8          | 24                                     | 8                     |
|                                        | PO(40 mg/kg)                   | n.a. | 24         | 48                                     | 24                    |
| <b>AUC<sub>0-168</sub> (umol.h /L)</b> | IV(0.5 mg/kg)                  | 0.27 | 59         | 290                                    | 392                   |
|                                        | PO(0.5 mg/kg)                  | n.a. | 27         | 126                                    | 164                   |
|                                        | PO(5 mg/kg)                    | n.a. | 196        | 1060                                   | 1260                  |
|                                        | PO(40 mg/kg)                   | n.a. | 1370       | 7420                                   | 8500                  |
| <b>T<sub>1/2</sub> (h)</b>             | IV(0.5 mg/kg)                  | 0.4  | 17         | 64                                     | n.a.                  |
|                                        | PO(0.5 mg/kg)                  |      | 21         | 60                                     | n.a.                  |
|                                        | PO(5 mg/kg)                    |      | 13         | 43                                     | n.a.                  |
|                                        | PO(40 mg/kg)                   |      |            | α= 8 and β = 48 (biphasic elimination) | 53                    |

#: detected in 2 samples only; n.d.:Not detected; n.a.: Not applicable; PO: Oral; IV intravenous

Source: NDA 208711 Pharmacokinetic Tabulated Summary

**Study no. (R22/1991) Kinetics of unchanged CGP TCBZ and its sulphoxide and sulphone metabolites in female rabbits following intravenous and oral administration of single doses of C<sup>14</sup>-labelled TCBZ**

**Study no. (R22/1991):** 2 female rabbits (chinchilla) were administered TCBZ via IV as a solution in polyethylene glycol 400/0.9% saline (2:1.1 w/w) and orally as aqueous suspension in 0.5% Klucel. Doses used were 3 mg/kg IV; 3 and 26 mg/kg oral. Plasma was analyzed.

In rabbits, TCBZ was rapidly cleared from plasma and converted to the sulphoxide and sulphone metabolites. The sulphoxide metabolite accounted for about 40-50% of the circulating radioactivity in plasma. During the first 8 hours after administration, the two metabolites represented virtually the total radioactivity measured in plasma. The systemic exposure to the sulphoxide and sulphone metabolites increased more than proportionally to the oral dose.

**Table 5.4 Pharmacokinetics: Absorption after a single dose in rabbits - Unchanged TCBZ and its major metabolites (sulphoxide and sulphone) in plasma (Study R22/1991)**

| PK parameters:                  | Route of administration (Dose) | TCBZ       | Sulphoxide | Sulphone | Total C <sup>14</sup> |
|---------------------------------|--------------------------------|------------|------------|----------|-----------------------|
| C <sub>max</sub> (umol/L)       | IV (3 mg/kg)                   | 6.6        | 25.4       | 7.3      | 33.4                  |
|                                 | PO (3 mg/kg)                   | n.d.       | 9.6        | 6.9      | 19.4                  |
|                                 | PO (26 mg/kg)                  | 0.3        | 90.5       | 62.9     | 160                   |
| T <sub>max</sub> (h)            | IV (3 mg/kg)                   | 0.08       | 0.3        | 5        | 0.5-1                 |
|                                 | PO (3 mg/kg)                   | n.a.       | 4          | 8        | 8                     |
|                                 | PO (26 mg/kg)                  | 4          | 8          | 12       | 8-12                  |
| AUC <sub>0-168</sub> (umol.h/L) | IV (3 mg/kg)                   | 4.5        | 214        | 119      | 445                   |
|                                 | PO (3 mg/kg)                   | n.d.       | 167        | 155      | 441                   |
|                                 | PO (26 mg/kg)                  | 5.4        | 3160       | 2390     | 6120                  |
| T <sub>1/2</sub> (h)            | IV (3 mg/kg)                   | 2.3        | 4.3        | 5.5      | n.a.                  |
|                                 | PO (3 mg/kg)                   | n.d.       | 6.7        | 8.5      | n.a.                  |
|                                 | PO (26 mg/kg)                  | 6.8 (n =1) | 9.2        | 11.4     | n.a.                  |

n.d.:Not detected; n.a.: Not applicable; PO: Oral; IV intravenous  
Source: NDA 208711 Pharmacokinetic Tabulated Summary

**Study DM12/1991 Absorption and Disposition Studies in Female Rabbits**

**Study DM12/1991:** 2 female rabbits were administered TCBZ via IV as solution in polyethylene glycol 400/0.9% saline (2:1.1 w/w); and orally as an aqueous suspension in 0.5% Klucel. Doses used were 3 mg/kg IV; 3 and 26 mg/kg oral. Blood, plasma and urine were analyzed.

**Table 5.5 Absorption and disposition studies in blood plasma of female rabbits. Study DM12/1991**

| PK parameters:                     | Route of administration (Dose) | Total C <sup>14</sup> in Plasma | Total C <sup>14</sup> in Blood |
|------------------------------------|--------------------------------|---------------------------------|--------------------------------|
| C <sub>max</sub> (µmol/L)          | IV (3 mg/kg)                   | 33.2                            | 20.1                           |
|                                    | PO (3 mg/kg)                   | 19.4                            | 12.5                           |
|                                    | PO (26 mg/kg)                  | 154                             | 102                            |
| T <sub>max</sub> (h)               | IV (3 mg/kg)                   | 1                               | 1                              |
|                                    | PO (3 mg/kg)                   | 8                               | 4-8                            |
|                                    | PO (26 mg/kg)                  | 8-12                            | 8-24                           |
| AUC <sub>0.08-168</sub> (µmol.h/L) | IV (3 mg/kg)                   | 443                             | 289                            |
|                                    | PO (3 mg/kg)                   | 441                             | 312                            |
|                                    | PO (26 mg/kg)                  | 6109                            | 4166                           |

PO: Oral; IV intravenous  
Source: NDA 208711 Pharmacokinetic Tabulated Summary

| <p><b>Study DM23/1991 C<sup>14</sup>-labelled TCBZ: Absorption and disposition studies in rats and dogs</b></p> | <p><b>Study DM23/1991:</b> Rats: 3 male rats were fasted 15-20 hours before and at least 6 hours after administration of the TCBZ. The drug was administered 1 mg/kg (IV) as a solution in polyethylene glycol 400/0.9% saline (1:1); and 1, 10 and 80 (orally) as a suspension in carboxymethyl cellulose. Blood, plasma and urine were analyzed.</p> <p>Dogs: 2 male Beagle dogs were administered TCBZ IV (0.5 mg/kg) and PO (0.5, 5 and 40 mg/kg/day). Blood, plasma and urine were analyzed by radiometry.</p> <p><b>Table 5.6 Pharmacokinetic Parameters of Total C14 Radioactivity in Blood and Plasma (Study DM23/1991)</b></p> <table border="1"> <thead> <tr> <th></th> <th>Dose mg/kg</th> <th>C<sub>max</sub> blood (umol/L )</th> <th>T<sub>max</sub> (h)</th> <th>AUC blood (umol.h/L )</th> <th>AUC plasma (umol.h/L )</th> <th>Specific AUC blood (umol.h/L) / mg/kg</th> <th>Specific AUC plasma (umol.h/L) / mg/kg</th> </tr> </thead> <tbody> <tr> <td colspan="8" style="text-align: center;"><b>Rat</b></td> </tr> <tr> <td><b>IV</b></td> <td>1</td> <td>3.3</td> <td>2</td> <td>55</td> <td>61</td> <td>55</td> <td>61</td> </tr> <tr> <td rowspan="2"><b>PO</b></td> <td>1</td> <td>2.7</td> <td>8</td> <td>57</td> <td>60</td> <td>57</td> <td>60</td> </tr> <tr> <td>10</td> <td>20</td> <td>8</td> <td>413</td> <td>n.d.</td> <td>41</td> <td>n.d.</td> </tr> <tr> <td></td> <td>80</td> <td>81.5</td> <td>8</td> <td>2104</td> <td>n.d.</td> <td>26</td> <td>n.d.</td> </tr> <tr> <td colspan="8" style="text-align: center;"><b>Dog</b></td> </tr> <tr> <td><b>IV</b></td> <td>0.5</td> <td>2.8</td> <td>8</td> <td>227</td> <td>392</td> <td>454</td> <td>784</td> </tr> <tr> <td rowspan="2"><b>PO</b></td> <td>0.5</td> <td>1.1</td> <td>24</td> <td>97</td> <td>164</td> <td>195</td> <td>328</td> </tr> <tr> <td>5</td> <td>10.8</td> <td>8</td> <td>708</td> <td>1260</td> <td>142</td> <td>252</td> </tr> <tr> <td></td> <td>40</td> <td>45.9</td> <td>24</td> <td>4251</td> <td>8503</td> <td>106</td> <td>213</td> </tr> </tbody> </table> <p>n.d.: not detected; Source: NDA 208711 Study Report 23/1991</p> |                                  | Dose mg/kg           | C <sub>max</sub> blood (umol/L ) | T <sub>max</sub> (h)   | AUC blood (umol.h/L )                 | AUC plasma (umol.h/L )                 | Specific AUC blood (umol.h/L) / mg/kg | Specific AUC plasma (umol.h/L) / mg/kg | <b>Rat</b> |  |  |  |  |  |  |  | <b>IV</b> | 1 | 3.3 | 2 | 55 | 61 | 55 | 61 | <b>PO</b> | 1 | 2.7 | 8 | 57 | 60 | 57 | 60 | 10 | 20 | 8 | 413 | n.d. | 41 | n.d. |  | 80 | 81.5 | 8 | 2104 | n.d. | 26 | n.d. | <b>Dog</b> |  |  |  |  |  |  |  | <b>IV</b> | 0.5 | 2.8 | 8 | 227 | 392 | 454 | 784 | <b>PO</b> | 0.5 | 1.1 | 24 | 97 | 164 | 195 | 328 | 5 | 10.8 | 8 | 708 | 1260 | 142 | 252 |  | 40 | 45.9 | 24 | 4251 | 8503 | 106 | 213 |
|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------|----------------------------------|------------------------|---------------------------------------|----------------------------------------|---------------------------------------|----------------------------------------|------------|--|--|--|--|--|--|--|-----------|---|-----|---|----|----|----|----|-----------|---|-----|---|----|----|----|----|----|----|---|-----|------|----|------|--|----|------|---|------|------|----|------|------------|--|--|--|--|--|--|--|-----------|-----|-----|---|-----|-----|-----|-----|-----------|-----|-----|----|----|-----|-----|-----|---|------|---|-----|------|-----|-----|--|----|------|----|------|------|-----|-----|
|                                                                                                                 | Dose mg/kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | C <sub>max</sub> blood (umol/L ) | T <sub>max</sub> (h) | AUC blood (umol.h/L )            | AUC plasma (umol.h/L ) | Specific AUC blood (umol.h/L) / mg/kg | Specific AUC plasma (umol.h/L) / mg/kg |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>Rat</b>                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  |                      |                                  |                        |                                       |                                        |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>IV</b>                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3.3                              | 2                    | 55                               | 61                     | 55                                    | 61                                     |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>PO</b>                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 2.7                              | 8                    | 57                               | 60                     | 57                                    | 60                                     |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
|                                                                                                                 | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 20                               | 8                    | 413                              | n.d.                   | 41                                    | n.d.                                   |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
|                                                                                                                 | 80                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 81.5                             | 8                    | 2104                             | n.d.                   | 26                                    | n.d.                                   |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>Dog</b>                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  |                      |                                  |                        |                                       |                                        |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>IV</b>                                                                                                       | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2.8                              | 8                    | 227                              | 392                    | 454                                   | 784                                    |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <b>PO</b>                                                                                                       | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.1                              | 24                   | 97                               | 164                    | 195                                   | 328                                    |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
|                                                                                                                 | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 10.8                             | 8                    | 708                              | 1260                   | 142                                   | 252                                    |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
|                                                                                                                 | 40                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 45.9                             | 24                   | 4251                             | 8503                   | 106                                   | 213                                    |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |
| <p><b>Distribution</b></p>                                                                                      | <p><b>Study no. DM23/1991 Absorption and disposition studies in rats and dogs</b></p> <p><b>Study DM23/1991:</b> Distribution of the drug was determined by measuring radioactivity of C<sup>14</sup>-labelled TCBZ in various organ and tissues. Drug distribution was extensive in rats with only a slight accumulation in most organs and tissues investigated after 10 daily oral doses of 1 mg/kg. The accumulation of radioactivity was between 2-fold (thyroid and skin) and 6-fold (brain), with concentrations found 24 hours after a single oral dose of 1 mg/kg being taken as reference values. Distribution patterns indicated a first pass metabolism, with a redistribution of radioactivity between 5 minutes and 4 hours after intravenous dosing. Eight hours after oral administration, the only organs containing substantially higher levels of radioactivity than the blood were liver (4-fold higher than in blood) and kidney (2-fold higher than in blood) whereas other organs and tissues had drug levels similar to plasma levels. Distribution was extensive in rats with only a slight accumulation in most organs and tissues investigated after 10 daily oral doses of 1 mg/kg.</p> <p><b>Table 5.7 Concentrations of radioactive substances (nmol/g) in in organs and tissues after single 1 mg/kg IV administration of C14TCBZ (Study DM</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                  |                      |                                  |                        |                                       |                                        |                                       |                                        |            |  |  |  |  |  |  |  |           |   |     |   |    |    |    |    |           |   |     |   |    |    |    |    |    |    |   |     |      |    |      |  |    |      |   |      |      |    |      |            |  |  |  |  |  |  |  |           |     |     |   |     |     |     |     |           |     |     |    |    |     |     |     |   |      |   |     |      |     |     |  |    |      |    |      |      |     |     |

**23/1991)**

| Tissues / organs: | C <sub>5min</sub> | C <sub>4h</sub> | C <sub>168h</sub> |
|-------------------|-------------------|-----------------|-------------------|
| Blood             | 2.23              | 2.92            | 0.15              |
| Plasma            | 3.13              | 4.97            | 0                 |
| Salivary          | 6.51              | 3.48            | 0.1               |
| Thyroid           | 6.18              | 2.85            | 0.19              |
| Thymus            | 2.01              | 1.48            | 0.02              |
| Lung              | 5.73              | 3.61            | 0.08              |
| Heart             | 8.43              | 3.43            | 0.27              |
| Aorta             | 3.57              | 2.01            | 0.05              |
| Liver             | 10.38             | 8.58            | 0.11              |
| Pancreas          | 7.55              | 3.35            | 0.09              |
| Spleen            | 3.07              | 1.71            | 0.06              |
| Adrenal           | 17.42             | 6.06            | 0.16              |
| Kidney            | 7.36              | 5.48            | 0.15              |
| White fat         | 1.67              | 7.5             | 0.02              |
| Testis            | 0.86              | 1.9             | 0.21              |
| Muscle            | 2.71              | 1.13            | 0.04              |
| Sciatic nerve     | 1.58              | 3.87            | 0.11              |
| Bone marrow       | 3.52              | 2.06            | 0.02              |
| Stomach           | 5.78              | 2.23            | 0.08              |
| Small intestine   | 4.61              | 4.98            | 0.07              |
| Skin              | 1.4               | 1.94            | 0.06              |
| Brown fat         | 16.67             | 4.41            | 0.12              |
| Eye               | 0.9               | 0.68            | 0.04              |
| Brain             | 4.01              | 2.1             | 0.23              |

Source: NDA 208711 Pharmacokinetic Tabulated Summary

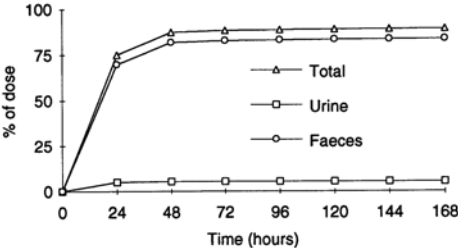
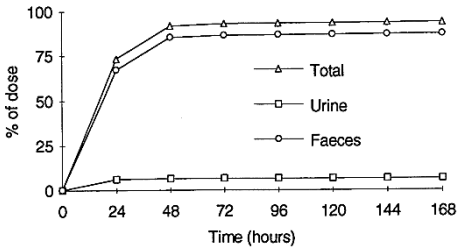
**Table 5.8 Concentrations of radioactive substances [nmol/g] in in organs and tissues after single and repeated (once daily for 10 days) 1 mg/kg oral administration of C14 TCBZ (Study DM 23/1991)**

| Tissues/organs | Conc. <sub>.8h</sub> after single dose | Conc. <sub>.24h</sub> after single dose | Conc. <sub>.168h</sub> after single dose | Conc. <sub>.24h</sub> after repeat dose |
|----------------|----------------------------------------|-----------------------------------------|------------------------------------------|-----------------------------------------|
| Blood          | 2.14                                   | 0.25                                    | 0.1                                      | 1.12                                    |
| Plasma         | 3.6                                    | 0.21                                    | <0.01                                    | 0.31                                    |
| Salivary       | 2.43                                   | 0.32                                    | 0.09                                     | 1.24                                    |
| Thyroid        | 3.36                                   | 2.02                                    | 0.15                                     | 3.54                                    |
| Thymus         | 1.06                                   | 0.15                                    | 0.01                                     | 0.32                                    |
| Lung           | 2.28                                   | 0.36                                    | 0.08                                     | 1.03                                    |
| Heart          | 2.64                                   | 0.39                                    | 0.19                                     | 2.01                                    |
| Aorta          | 1.35                                   | 0.31                                    | 0.03                                     | 0.55                                    |
| Liver          | 8.69                                   | 0.86                                    | 0.09                                     | 1.79                                    |
| Pancreas       | 2.32                                   | 0.3                                     | 0.08                                     | 0.89                                    |
| Spleen         | 1.2                                    | 0.2                                     | 0.04                                     | 0.63                                    |
| Adrenal        | 3.64                                   | 0.56                                    | 0.11                                     | 1.52                                    |
| Kidney         | 4.2                                    | 0.74                                    | 0.13                                     | 1.79                                    |
| White fat      | 2.36                                   | 0.15                                    | 0.01                                     | 0.27                                    |
| Testis         | 1.5                                    | 0.36                                    | 0.15                                     | 1.49                                    |
| Muscle         | 0.74                                   | 0.13                                    | 0.05                                     | 0.39                                    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Sciatic nerve</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2.38                                             | 0.26                  | 0.06                                             | 1.02 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------|--------------------------------------------------|------|---------------|-----------------------|--|-----------------------|--|----------------|--------------------------------------------------|----------------|--------------------------------------------------|--------------|------|--|------|--|---------------|------|-----|-----|-----|-------------|------|---|------|-----|--------------|----|-----|------|-----|--------------|----|-----|------|-----|---------------|------|-----|----|-----|------------------|------|-----|------|-----|------------------|------|-----|------|-----|--------------|------|-----|------|-----|----------------------|------|-----|------|-----|-----------------|------|---|-----|-----|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Bone marrow</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1.42                                             | 0.16                  | 0.01                                             | 0.33 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Stomach</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1.98                                             | 0.22                  | 0.06                                             | 0.85 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Small intestine</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1.98                                             | 0.33                  | 0.03                                             | 0.73 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Skin</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.29                                             | 0.48                  | 0.11                                             | 0.84 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Brown fat</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 2.57                                             | 0.39                  | 0.09                                             | 1.24 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Eye</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.48                                             | 0.08                  | 0.03                                             | 0.31 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Brain</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.33                                             | 0.28                  | 0.19                                             | 1.64 |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Source: NDA 208711 Pharmacokinetic Tabulated Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                  |                       |                                                  |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p><b>Study no. R99-1751</b><br/> <b>Distribution in the dam and transfer of radioactive substance(s) to the embryo fetal compartment of rats after single oral administration of 10 mg/kg C<sup>14</sup> TCBZ on Day 13 or Day 18 of gestation.</b></p> <p><b>Study R99-1751:</b> Pregnant rats were administered radioactive TCBZ 10 mg/kg as a single dose on Day 13 and Day 18 of the pregnancy by oral gavage. The uptake of radioactivity into the fetuses after administration on Day 13 was extensive. At 24 hours postdose, radioactivity levels in fetuses were higher than those in blood and most of the investigated organs and tissues. After administration on Day 18, the uptake of radioactivity was more pronounced. At 8 and 24 hours postdose the absolute concentrations of radioactivity in the fetuses were about 3-fold higher after administration on Day 18 than those in fetuses on Day 13, and the ratio Conc.<sub>fetus</sub>/Conc.<sub>blood</sub> at 24 hours postdose was 6-fold (Day 18) versus 1.6-fold (Day 13). Highest C<sup>14</sup> concentrations were at 8 hours postdose (in the dam and the fetuses). Extensive distribution was seen throughout the body of the dam. Highest C<sup>14</sup> concentrations (higher than in blood) were observed in the gastro-intestinal tract, liver, kidneys, and glandular tissues (adrenal, lachrymal, salivary, clitoral and thyroid glands). The lowest levels of radioactivity (lower than in blood) were seen in the muscles, cartilage and eyes. Distinct uptake into mammary glands was recorded. Extensive transfer/uptake in the fetuses was seen. At 0.5 and 8 h postdose, the C<sup>14</sup> concentration in fetuses were roughly comparable to those in maternal organs and tissues, and at 24 and 48 h postdose, they were higher than those in the tissues of the dam.</p> |                                                  |                       |                                                  |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <p><b>Table 5.9 Distribution into tissues and organs in time dependency: After administration on Day 13 (Study R99-1751)</b></p> <table border="1"> <thead> <tr> <th rowspan="2">Tissue/organs</th> <th colspan="2">First time point (8h)</th> <th colspan="2">Last time-point (24h)</th> </tr> <tr> <th>Conc. (nmol/g)</th> <th>Conc.<sub>Tissue</sub> / Conc.<sub>blood</sub></th> <th>Conc. (nmol/g)</th> <th>Conc.<sub>Tissue</sub> / Conc.<sub>blood</sub></th> </tr> </thead> <tbody> <tr> <td><b>Blood</b></td> <td>17.1</td> <td></td> <td>4.18</td> <td></td> </tr> <tr> <td><b>Plasma</b></td> <td>25.9</td> <td>1.5</td> <td>4.9</td> <td>1.2</td> </tr> <tr> <td><b>Lung</b></td> <td>17.4</td> <td>1</td> <td>4.65</td> <td>1.1</td> </tr> <tr> <td><b>Heart</b></td> <td>18</td> <td>1.1</td> <td>5.81</td> <td>1.4</td> </tr> <tr> <td><b>Liver</b></td> <td>39</td> <td>2.3</td> <td>14.3</td> <td>3.4</td> </tr> <tr> <td><b>Kidney</b></td> <td>33.1</td> <td>1.9</td> <td>11</td> <td>2.6</td> </tr> <tr> <td><b>White fat</b></td> <td>16.2</td> <td>0.9</td> <td>3.93</td> <td>0.9</td> </tr> <tr> <td><b>Brown fat</b></td> <td>15.5</td> <td>0.9</td> <td>2.48</td> <td>0.6</td> </tr> <tr> <td><b>Brain</b></td> <td>9.48</td> <td>0.6</td> <td>3.45</td> <td>0.8</td> </tr> <tr> <td><b>Mammary gland</b></td> <td>16.2</td> <td>0.9</td> <td>3.65</td> <td>0.9</td> </tr> <tr> <td><b>Placenta</b></td> <td>16.9</td> <td>1</td> <td>5.3</td> <td>1.3</td> </tr> </tbody> </table> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                  |                       |                                                  |      | Tissue/organs | First time point (8h) |  | Last time-point (24h) |  | Conc. (nmol/g) | Conc. <sub>Tissue</sub> / Conc. <sub>blood</sub> | Conc. (nmol/g) | Conc. <sub>Tissue</sub> / Conc. <sub>blood</sub> | <b>Blood</b> | 17.1 |  | 4.18 |  | <b>Plasma</b> | 25.9 | 1.5 | 4.9 | 1.2 | <b>Lung</b> | 17.4 | 1 | 4.65 | 1.1 | <b>Heart</b> | 18 | 1.1 | 5.81 | 1.4 | <b>Liver</b> | 39 | 2.3 | 14.3 | 3.4 | <b>Kidney</b> | 33.1 | 1.9 | 11 | 2.6 | <b>White fat</b> | 16.2 | 0.9 | 3.93 | 0.9 | <b>Brown fat</b> | 15.5 | 0.9 | 2.48 | 0.6 | <b>Brain</b> | 9.48 | 0.6 | 3.45 | 0.8 | <b>Mammary gland</b> | 16.2 | 0.9 | 3.65 | 0.9 | <b>Placenta</b> | 16.9 | 1 | 5.3 | 1.3 |
| Tissue/organs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | First time point (8h)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                  | Last time-point (24h) |                                                  |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Conc. (nmol/g)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Conc. <sub>Tissue</sub> / Conc. <sub>blood</sub> | Conc. (nmol/g)        | Conc. <sub>Tissue</sub> / Conc. <sub>blood</sub> |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Blood</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 17.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                  | 4.18                  |                                                  |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Plasma</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 25.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1.5                                              | 4.9                   | 1.2                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Lung</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 17.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1                                                | 4.65                  | 1.1                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Heart</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1.1                                              | 5.81                  | 1.4                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Liver</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 39                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 2.3                                              | 14.3                  | 3.4                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Kidney</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 33.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1.9                                              | 11                    | 2.6                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>White fat</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 16.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.9                                              | 3.93                  | 0.9                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Brown fat</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 15.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.9                                              | 2.48                  | 0.6                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Brain</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 9.48                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.6                                              | 3.45                  | 0.8                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Mammary gland</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 16.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.9                                              | 3.65                  | 0.9                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |
| <b>Placenta</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 16.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1                                                | 5.3                   | 1.3                                              |      |               |                       |  |                       |  |                |                                                  |                |                                                  |              |      |  |      |  |               |      |     |     |     |             |      |   |      |     |              |    |     |      |     |              |    |     |      |     |               |      |     |    |     |                  |      |     |      |     |                  |      |     |      |     |              |      |     |      |     |                      |      |     |      |     |                 |      |   |     |     |

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |      |     |      |     |
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|                   | <b>Fetus</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 11.6 | 0.7 | 6.84 | 1.6 |
|                   | <b>Distribution into tissues and organs in time dependency: After administration on Day 18</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |      |     |      |     |
|                   | <b>Blood</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 15.2 |     | 3.69 |     |
|                   | <b>Fetus</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 31.3 | 2.1 | 22.2 | 6   |
|                   | Source: NDA 208711 Pharmacokinetic Tabulated Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |      |     |      |     |
| <b>Metabolism</b> | <p>TCBZ is metabolized to sulfoxide metabolite (TCBZ-SO), in which the thio part in the parent chemical structure is oxidized to the sulfone and sulfoxide metabolite is further metabolized to sulfoxide (TCBZ-SO<sub>2</sub>); both these metabolites are also pharmacologically active against liverfluke and the sulfoxide is recognized to be more pharmacologically active than TCBZ itself and the sulfone metabolite. Orally administered TCBZ was rapidly metabolized (within 5 minutes) in dogs and rabbits with unchanged parent drug only detected at very low levels (Table 5.3 and Table 5.4) as a result of extensive presystemic first pass metabolism. The sulfoxide and sulfone metabolites were identified systemically in rabbits after either oral or intravenous administration. The sulfone metabolite was the major metabolite in dogs after oral administration of TCBZ, and accounted for about 80% of the circulating radioactivity and, due to its long half-life (43h), suggested a potential for accumulation after repeated administration (Table 5.3). Radioactivity present in rat urine after an oral dose of either 10 or 80 mg/kg C<sup>14</sup> triclabendazole represented 0.1% of dose as sulfoxide metabolite. In dogs 6.3 % of the urinary radioactivity was TCBZ while the remainder represented unidentified polar metabolites. Finally, in female rabbits after IV (3 mg/kg) and PO doses (3 or 26 mg/kg) urinary radioactivity consisted of polar metabolites. These polar metabolites were most likely conjugates of the two primary metabolites. As the predominant part of the dose was excreted in the feces, and the feces were not specifically analyzed for metabolites, understanding of metabolic fate of TCBZ is difficult.</p> <p>Metabolism of TCBZ has been investigated in vitro in animal and human liver microsomes and hepatocytes. No human ADME studies were performed with radiolabeled TCBZ.</p> <p>Metabolism of TCBZ in Sheep liver microsomes: In vitro studies using sheep liver microsomes suggested the involvement of both Flavin monooxygenase (FMOs) and cytochrome P450 (CYP450s) in metabolism of TCBZ to its sulfoxide and sulfone metabolites (Virkel et al 2006<sup>2</sup>). The in vitro data suggest that the FMO is the main enzymatic pathway involved in TCBZ sulphoxidation, although both enzymatic systems participate in a similar proportion in the sulphonation</p> |      |     |      |     |

<sup>2</sup> Virkel G, Lifschitz A, Sallovitz J, et al (2006) Assessment of the main metabolism pathways for the flukicidal compound triclabendazole in sheep. J Vet Pharmacol Therap; 29:213–223.

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  | to form the sulfone metabolite.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Excretion</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                  | <p>Excretion in Rats: After intravenous and oral administration of 1 mg/kg radiolabeled dose to rats, drug and/or metabolites (radioactive dose) were rapidly excreted with urine and feces, about 82-85% being recovered within 48 hours and levels of 84-94% within a period of 7 days. The majority of the dose was excreted with the feces (&gt;80% of the dose) while urinary C<sup>14</sup> excretion levels accounted for at most 8% of the dose. Excretion was not complete after 7 days as indicated by the low but detectable level of radioactivity recovered in both urine and feces on Day 7. This indicates the slow terminal elimination of <sup>14</sup>C from blood and tissues. Less than 5% of the administered radioactivity was excreted in the urine within 7 days after higher oral doses of 10 or 80 mg/kg and excretion in feces was not investigated at these doses (Study DM23/1991).</p> <p>Excretion in Dogs: Recovery of total radioactivity in urine and feces of dogs after intravenous or oral administration of drug at 0.5 mg/kg was 80% (IV) and 55% (PO) of the dose within 7 days (Study 23/1991). In both cases, fecal recovery was predominant (54 % of the dose after oral administration, 79 % of the dose after IV administration) and only a low level of 1-2% excreted with the urine. Excretion was continuing on Day 7 after both routes of dosing. Following higher oral doses of 5 and 40 mg/kg, feces excretion levels rose to 69 and 89% of the dose, respectively.</p> <div style="display: flex; justify-content: space-around;">   </div> <p><b>Figure 5-1 Cumulative excretion of radioactivity in urine and feces of rats after intravenous (left) and oral (right) administration of 1 mg/kg C<sup>14</sup> triclabendazole (means of 3 rats for both routes of administration).</b></p> |

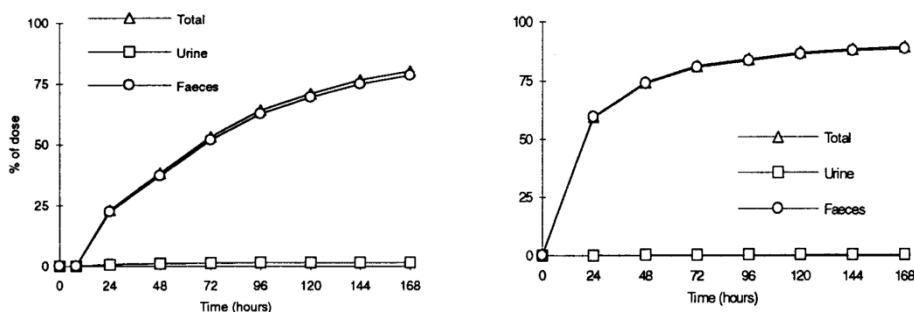


**Figure 5-2 Cumulative excretion of radioactivity in urine and feces of dogs after intravenous (left) administration of 0.5 mg/kg and oral (right) administration of 40 mg/kg C14 triclabendazole (means of 2 dogs for 0.5 mg/kg doses and 1 dog for 5 mg/kg and 40 mg/kg)**

Source for both figures: NDA 208711 Study Report DM23/1991

Excretion in Female rabbits: After intravenous and peroral administration to female rabbits, the kinetics of radioactive substance(s) in blood and plasma were characterized by a biphasic decline. Most of the radioactivity was cleared from the circulation within 72 h predominantly via the bile, thereafter the blood/plasma <sup>14</sup>C concentrations declined slowly. Excretion of radioactivity was not complete within 7 days (amounted to 80 - 93% of the dose). After oral administration, the proportion of the dose excreted renally increased dose-dependently from about 7% after 3 mg/kg to 17-30% after 26 mg/kg (DM 12/1991).

Excretion in Pregnant rats: After oral administration to pregnant rats at a dose of 10mg/kg, elimination of radioactivity from the fetuses proceeded slower than from maternal blood, tissues and organs. As a result of the uptake of radioactivity into the mammary glands observed in pregnant rats, the compound may be excreted with the milk in lactating animals (R99-1751). Excretion into the milk of lactating rats was not specifically investigated. In conclusion, the major excretory route was clearly the bile and subsequently with the feces in all three animal species in which excretion was investigated.

**TK data from Study 001004 Cardiovascular effects in dogs**

**Study 001004:** Toxicokinetic investigations revealed that TCBZ levels were low after both doses and near the limit of quantitation after the 40 mg/kg dose. The maximum concentrations ( $C_{max}$ ) were reached between 2 and 24 hours. The sulfoxide metabolite was rapidly formed and represented the major part of the circulating compounds during the first 8 hours at both dose levels with a  $C_{max}$  between 8 and 24 hours and a rapid decrease thereafter. The sulfone metabolite was slowly formed and reached its  $C_{max}$  between 24 and 48 hours post-dosing. Its concentrations were still high at 96 hours.

**Table 5.10 Mean toxicokinetic parameters in dog (Study 001004)**

| <b>TCBZ (40 mg/kg)</b>                                     |                                |                                     |                                                |                                          |                                                     |
|------------------------------------------------------------|--------------------------------|-------------------------------------|------------------------------------------------|------------------------------------------|-----------------------------------------------------|
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 2 to 24                        | 0.33                                | 0.008                                          | 4.32                                     | 0.11                                                |
| SD                                                         | *                              | 0.32                                | 0.008                                          | 5.46                                     | 0.14                                                |
| CV (%)                                                     | *                              | 98                                  | 98                                             | 126                                      | 126                                                 |
| <b>TCBZ (100 mg/kg)</b>                                    |                                |                                     |                                                |                                          |                                                     |
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 2 to 24                        | 1.05                                | 0.01                                           | 19.2                                     | 0.19                                                |
| SD                                                         | *                              | 0.8                                 | 0.008                                          | 22.1                                     | 0.22                                                |
| CV (%)                                                     | *                              | 76                                  | 76                                             | 115                                      | 115                                                 |
| <b>Sulfoxide (40 mg/kg)</b>                                |                                |                                     |                                                |                                          |                                                     |
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 2 to 24                        | 62.2                                | 1.55                                           | 1623                                     | 40.58                                               |
| SD                                                         | *                              | 52.2                                | 1.30                                           | 1341                                     | 33.54                                               |
| CV (%)                                                     | *                              | 84                                  | 84                                             | 83                                       | 83                                                  |
| <b>Sulfoxide (100 mg/kg)</b>                               |                                |                                     |                                                |                                          |                                                     |
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 8 to 24                        | 128.8                               | 1.29                                           | 3433                                     | 34.33                                               |
| SD                                                         | *                              | 88.4                                | 0.88                                           | 2672                                     | 26.72                                               |
| CV (%)                                                     | *                              | 69                                  | 69                                             | 78                                       | 78                                                  |
| <b>Sulfone (40 mg/kg)</b>                                  |                                |                                     |                                                |                                          |                                                     |
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 24 to 48                       | 67.5                                | 1.69                                           | 4132                                     | 103.3                                               |
| SD                                                         | *                              | 68.3                                | 1.707                                          | 4190                                     | 104.7                                               |
| CV (%)                                                     | *                              | 101                                 | 101                                            | 101                                      | 101                                                 |
| <b>Sulfone (100 mg/kg)</b>                                 |                                |                                     |                                                |                                          |                                                     |
| <b>Parameter</b>                                           | <b>t<sub>max</sub><br/>(h)</b> | <b>C<sub>max</sub><br/>(µmol/L)</b> | <b>C<sub>max</sub>/dose<br/>(µmol/L/mg/kg)</b> | <b>AUC<sub>0-96</sub><br/>(µmol*h/L)</b> | <b>AUC<sub>0-96</sub>/dose<br/>(µmol*h/L/mg/kg)</b> |
| Mean or range                                              | 24 to 48                       | 129                                 | 1.29                                           | 7325                                     | 73.25                                               |
| SD                                                         | *                              | 102                                 | 1.02                                           | 5931                                     | 59.31                                               |
| CV (%)                                                     | *                              | 79                                  | 79                                             | 81                                       | 81                                                  |
| * : not applicable; Source: NDA 208711 Study Report 001004 |                                |                                     |                                                |                                          |                                                     |

## 5.5. Toxicology

### 5.5.1. General Toxicology

**Study title: A 13-Week Toxicity Study in Rats by Incorporation in the Diet**

**Study number: 79-1817; Year study was conducted: 1980**

**Key Study Findings:**

- At the highest dose (HD) of 1000 ppm or a mean intake of 78 mg/kg/day dose (which is below the clinical dose based on a body surface area comparison), food intake and body weight gain was lower than controls
- At the HD white blood cells and red blood cell parameters (week 12) were slightly lower than controls.
- Alkaline phosphatase (ALP) levels and cholesterol were higher at HD.
- The HD in rats is almost equivalent to the proposed clinical dose based on a body surface area comparison. No TK assessments were done.
- The NOAEL was determined to be 10 ppm (corresponding to a mean of 0.75 mg/kg/day dose) which is below the proposed clinical dose based on a body surface area comparison.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose:

0, 10, 100 and 1000 ppm;  
 Mean daily intake of drug calculated as [(weekly food consumption in gm)/body weight in gm) X (dose in ppm)/7]] in the 10, 100 and 1000 ppm groups were 0.7, 6.6 and 68.5 mg/kg/day in males and 0.8, 7.9 and 87.3 mg/kg/day in females respectively

Route of administration:

Orally via diet

Species/Strain:

Sprague Dawley Rats

Number/Sex/Group:

20/sex/group

Age:

40 days old

Satellite groups/ unique design:

No

Deviation from study protocol

No

affecting interpretation of results:

**Observations and Results:**

| Parameters            | Major findings                                                                                                                |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>Mortality</b>      | Control: 1 rat died on week 12<br>HD: 1 rat died on week 6<br>Deaths were not treatment-related according to necropsy reports |
| <b>Clinical Signs</b> | Unremarkable                                                                                                                  |

| <b>Parameters</b>                                     | <b>Major findings</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Body Weights</b>                                   | <p><u>Week 5:</u><br/>HD: Males: -29.3%; Females -28.3% on week 0 to 5</p> <p><u>Week 5 to 13:</u><br/>HD: Males: -26%; Females -37.5%<br/>MD: Males: -20.7%<br/>Body weight loss correlated with significantly decreased food consumption in the animals</p>                                                                                                                                                                                                   |
| <b>Ophthalmoscopy</b>                                 | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Hearing Test</b>                                   | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Hematology</b>                                     | <p><u>Week 5:</u><br/>MD: Females: -16.5% total white blood cell (WBC) and -16.1% lymphocytes;<br/>Males: -12% lymphocytes<br/>HD: Females: -31% total WBC and -33% lymphocytes;<br/>Males: -23.2% lymphocytes</p> <p><u>Week 12:</u><br/>MD: Females: -20.1% WBC and -22.4% lymphocytes<br/>Males: -25% WBC and -24.1% lymphocytes; -11% Hb; -11% RBC<br/>HD: Females: -31% WBC and -34% lymphocytes; -11% PCV<br/>Males: -18% lymphocytes; -15% platelets</p> |
| <b>Clinical Chemistry</b>                             | <p><u>Week 5:</u><br/>MD: Females: -19% glucose<br/>HD: Females: -12% glucose; +28% alkaline phosphatase (ALP); +61% cholesterol<br/>Males: -14% glucose; +42% ALP; +26% cholesterol; -10% phosphorus</p> <p><u>Week 12:</u><br/>MD: Females: +46% ALP<br/>HD: Females: +77% ALP<br/>Males: -17% glucose; +19% ALP; +22% cholesterol</p>                                                                                                                        |
| <b>Urinalysis</b>                                     | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Gross Pathology</b>                                | MD and HD: Congested lungs and pale liver and kidneys in males and females                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Organ Weights</b>                                  | HD: Males: -18% heart; -13% liver; -10% kidneys<br>Females: -10% heart; -19% ovaries                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Histopathology</b><br><b>Adequate battery: Yes</b> | <p><u>Heart:</u><br/>Occasional or minimal foci of myocarditis in small numbers of the control and treated rats. Occasional foci of mast cells in the myocardium of 1 male rat (LD) and 1 female rat (MD)</p>                                                                                                                                                                                                                                                   |

| Parameters | Major findings                                                                                                                                                                                                                                                                                     |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|            | <p><u>Thymus:</u><br/>Areas of congestion and/or hemorrhages in the medullary portion of 4 male (HD) and a female rat (MD).</p> <p><u>Adrenals:</u><br/>Several vacuolated cortical cells in the adrenal cortex of 3 male rats (HD). Areas of congestion and hemorrhages in a female rat (HD).</p> |

LD: low dose; MD: mid dose; HD: high dose.

:- indicates reduction in parameters compared to control.

*Reviewer’s comments: While, overall the repeat-dose study in rats seems adequate, the study design is, to some extent, flawed, as 5 animals per treatment group were housed together in a cage. Since the drug was admixed in the diet, it is unclear how much drug each animal per cage was exposed to. Furthermore, no TK analysis was done on the animals to determine the plasma concentration of the drug or metabolites in the animals.*

**Study title: A 13-Week Dietary Toxicity Study in the Dog**

**Study Report number: 2588-380/6; Date study was conducted: February 1981**

**Key Study Findings**

- Transient QT prolongation at the highest dose, which was more prominent at 5 and 9 weeks (ranging from 0.32-0.34 secs compared to 0.28-0.3 secs in controls), but not at 13 weeks.
- Minimally decreased hemoglobin and RBC and increased reticulocytes (Weeks 9 and 13 only) were noted in high dose group which may indicate anemia caused by the drug.
- Increased liver enzymes and cholesterol levels in the HD group.
- The high dose in dogs is twice the proposed clinical dose based on a body surface area comparison. No TK assessment was done.
- The NOAEL was determined to be 10 ppm (corresponding to a mean of 0.35 mg/kg/day dose), which is below the proposed clinical dose based on a body surface area comparison.

Conducting laboratory and location:

(b) (4)

GLP compliance:

No

Methods

Dose:

0, 10, 100 and 1000 ppm;  
Mean daily intake of drug calculated as [(weekly food consumption in gm)/body weight in gm) X (dose in ppm)/7]] in the 10, 100 and 1000 ppm

|                                                                    |                                                                                                                 |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
|                                                                    | groups were 0.35, 3.43 and 37.04 mg/kg/day in males and 0.35, 3.53 and 39.04 mg/kg/day in females respectively. |
| Route of administration:                                           | Incorporation in the diet                                                                                       |
| Species/Strain:                                                    | Beagle Dogs                                                                                                     |
| Number/Sex/Group:                                                  | 6/sex/group                                                                                                     |
| Age and Weight:                                                    | 6-8 months; 8.2 – 12.5 kg                                                                                       |
| Satellite groups/ unique design:                                   | No                                                                                                              |
| Deviation from study protocol affecting interpretation of results: | No                                                                                                              |

**Observations and Results:**

| Parameters            | Major findings                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mortality</b>      | None                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical Signs</b> | Unremarkable except for 1 male dog in HD group that developed a mass in the abdomen starting on day 11, along with elevated WBC and ALP levels in the blood and significant weight loss. After the treatment period necropsy revealed it was due to intussusception of the cecum into the colon. However, this was an isolated incident and likely not treatment related.                                                                              |
| <b>Body Weights</b>   | HD: Both sexes: -13% at week 13<br>Body weight loss correlated with decreased food intake intermittently throughout the treatment period                                                                                                                                                                                                                                                                                                               |
| <b>Ophthalmoscopy</b> | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>ECG</b>            | <u>Week 5:</u><br>HD: Males: +14% QT <sub>c</sub> ; Females: +7% QT <sub>c</sub><br><u>Week 9:</u><br>HD: Males: +14% QT <sub>c</sub> ; Females: +27 % QT <sub>c</sub><br><u>Week 13:</u><br>HD: Males: +7% QT <sub>c</sub> ; Females: +6% QT <sub>c</sub>                                                                                                                                                                                             |
| <b>Hematology</b>     | <u>Week 5:</u><br>HD: Males: -11% Hb; -12% RBC; -10% Packed Cell Volume (PCV); -40% Reticulocytes (RET)<br>HD: Females: -14% Hb; -15% RBC; -13% PCV; -40% RET<br><u>Week 9:</u><br>HD: Males: -14% Hb; -20% RBC; -14% PCV; +113% RET<br>HD: Females: -23 % Hb; -24% RBC; -43% PCV; +56% RET<br><u>Week 13:</u><br>HD: Males: -5% Hb; -10% RBC; PCV & RET no change; +12% Mean Cell Volume (MCV)<br>HD: Females: -19% Hb; -23% RBC; -16% PCV; +25% RET; |

| Parameters                                            | Major findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------|---------|--------|---------|--------|-------|------|----|------|----|------|---------|------|------|----|------|------|
|                                                       | +11% MCV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| <b>Clinical Chemistry</b>                             | <p><u>Week 5:</u><br/>                     MD: Males: +273% alkaline phosphatase (ALP);<br/>                     MD: Females: +270% ALP;<br/>                     HD: Males: +544% ALP; +53% cholesterol; +42% Glutamate Pyruvate Transaminase (GPT)<br/>                     HD: Females: +236% ALP; +73% cholesterol; +10% GPT</p> <p><u>Week 9:</u><br/>                     MD: Males: +289% ALP;<br/>                     MD: Females: +241% ALP<br/>                     HD: Males: +655% ALP; +55% cholesterol; +29% GPT<br/>                     HD: Females: +417% ALP; +67% cholesterol; +93% GPT</p> <p><u>Week 13:</u><br/>                     MD: Males: +349% ALP;<br/>                     MD: Females: + 353% ALP<br/>                     HD: Males: +782% ALP; +79% cholesterol; +63% GPT<br/>                     HD: Females: +472% ALP; +44% cholesterol; +170% GPT</p> |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| <b>Urinalysis</b>                                     | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| <b>Gross Pathology</b>                                | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| <b>Organ Weights</b>                                  | <p>HD:</p> <table border="1"> <thead> <tr> <th></th> <th>Liver</th> <th>Lungs</th> <th>Testes</th> <th>Ovaries</th> <th>Thymus</th> </tr> </thead> <tbody> <tr> <td>Males</td> <td>+61%</td> <td>NC</td> <td>-31%</td> <td>NA</td> <td>-29%</td> </tr> <tr> <td>Females</td> <td>+43%</td> <td>+18%</td> <td>NA</td> <td>-41%</td> <td>-48%</td> </tr> </tbody> </table> <p>NC: No Change; NA: Not Applicable</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |       | Liver  | Lungs   | Testes | Ovaries | Thymus | Males | +61% | NC | -31% | NA | -29% | Females | +43% | +18% | NA | -41% | -48% |
|                                                       | Liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Lungs | Testes | Ovaries | Thymus |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| Males                                                 | +61%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | NC    | -31%   | NA      | -29%   |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| Females                                               | +43%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | +18%  | NA     | -41%    | -48%   |         |        |       |      |    |      |    |      |         |      |      |    |      |      |
| <b>Histopathology</b><br><b>Adequate battery: Yes</b> | <p>HD:<br/>                     Liver: Presence of centrilobular hepatocellular pigment granules in all animals<br/>                     Reproductive tract: immature in 3/6 male animals</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |        |         |        |         |        |       |      |    |      |    |      |         |      |      |    |      |      |

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

*Reviewer’s comments: No TK analysis was done in the animals to determine the plasma concentration of the drug or metabolites in the dogs. It is further unclear in this study whether it is the drug itself or the metabolites that cause QT/QTc prolongation as well as liver enzyme alterations.*

**Study title: 28 Days Palatability Study In Mice**

**Study Report number: 79 1174; Date of Study: Nov 16, 1979**

Key Study Findings

## NDA Multi-Disciplinary Review and Evaluation – NDA

- The highest dose of 10,000 ppm or 1060 mg/kg/day caused all mice to become moribund by the 8<sup>th</sup> day. This dose is 9 times higher than the proposed clinical dose based on a body surface area comparison.

Conducting laboratory and location: Ciba-Geigy  
GLP compliance: No

### Methods

Dose: 0, 100, 1000 and 10,000 ppm;  
Achieved mean intake of drug in the 10, 100 and 100 ppm groups were 16, 172.05 and 1059.42 mg/kg/day respectively

Route of administration: Incorporation in the diet

Species/Strain: SPF mice

Number/Sex/Group: 10/sex/group

Age and Weight: 5 weeks; 25-29 gm

Satellite groups/ unique design: No

Deviation from study protocol affecting interpretation of results: No

### **Observations and Results:**

| <b>Parameters</b>     | <b>Major findings</b>                                                                                                                                               |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mortality</b>      | HD: 2 animals died spontaneously and the remaining animals were sacrificed moribund on the 8 <sup>th</sup> day of treatment. No necropsy was done on these animals. |
| <b>Clinical Signs</b> | HD: all animals were moribund by 8 <sup>th</sup> day of treatment.                                                                                                  |
| <b>Body Weights</b>   | HD: -20% weight loss. Significantly reduced food intake by 8 <sup>th</sup> day                                                                                      |
| <b>Ophthalmoscopy</b> | Unremarkable                                                                                                                                                        |

LD: low dose; MD: mid dose; HD: high dose.1059.42 mg/kg/day

-: indicates reduction in parameters compared to control.

### 5.5.2. Genetic Toxicology

#### In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title/ number: Salmonella/Mammalian-Microsome Mutagenicity Test/Study #: 87 1171**

#### Key Study Findings:

- In the experiments performed without and with microsomal activation, none of the tested concentrations of the drug led to an increase in point mutations in comparison with the negative control.

## NDA Multi-Disciplinary Review and Evaluation – NDA

- Cytotoxicity occurred at concentrations of 20 ug/0.1 ml and above without microsomal activation and at 78 ug/0.1 ml and above with microsomal activation.
- Precipitation occurred at 313 ug/0.1 ml and above.

GLP compliance: Yes

Test system: TA 98, TA 100, TA 1535, TA 1537 and TA 1538 up to 1250 ug/plate; +/- S9]

Study is valid: Yes

### In Vitro Assay in Mammalian Cells

**Study title/ number: *In vitro* Point mutation test with V79 Chinese hamster cells/Study #: 87 1170):**

Key Study Findings:

An original and a confirmatory experiment without metabolic activation were performed at concentrations of 0.025 - 0.50 mcg/ml and with metabolic activation at concentrations of 3.50 - 70.0 mcg/ml. Under the experimental conditions, TCBZ and its metabolites induced no mutagenic effects in this assay.

GLP compliance: Yes

Test system: V79 Chinese hamster cells

Study is valid: Yes

### In Vitro Assay in Mammalian Cells

**Study title/ number: Autoradiographic DNA Repair Test on Human Fibroblasts/Study #: 87 1172**

Key Study Findings:

- Comparison of the mean number of silver grains per nucleus in the vehicle control and after treatment with the drug revealed no marked differences.
- The positive control experiments with 4NQO (5 uM) yielded a marked increase in the number of silver grains per nucleus.

GLP compliance: Yes

Test system: Diploid Human Skin Fibroblasts; up to 60 ug/mL

Study is valid: Yes

### In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

**Study title/ number: Nucleus Anomaly Test in Somatic Interphase Nuclei/Study #: 80 1392**

Key Study Findings:

- In the negative control group one male animal died after the second dose.
- In all treatment groups the percentage of cells displaying anomalies of nuclei did not differ significantly from the negative control.
- The positive control (cyclophosphamide, 128 mg/kg) yielded a marked increase of the percentage of cells with anomalies.

GLP compliance: Yes

Test system: Chinese Hamsters (6/group) were orally administered 2 doses (24 hours apart) of the following:

1. TCBZ 172, 344 and 688 mg/kg in 20 ml/kg Polyethylene Glycol 400 (PEG 400).
2. Cyclophosphamide: 128 mg/kg in 20 ml/kg PEG 400 (positive control).
3. 20 ml PEG 400/kg (negative control).

24 h after the second application, the animals were sacrificed and bone marrow was harvested from the shafts of both femurs.

Study is valid: Yes

#### Other GLP Genetic Toxicity Studies

##### ***In vitro* Cytogenetic test on Chinese hamster cells *in vitro* (Study 92 6092).**

TCBZ was tested for clastogenic effects on Chinese hamster ovary (CHO) cells *in vitro*. Concentrations up to 15.63 µg/ml were used in experiments with and without metabolic activation. Under the given experimental conditions, no evidence of clastogenic effects was obtained in CHO cells *in vitro* treated with TCBZ.

##### ***In vitro* Autoradiographic DNA-repair test on rat hepatocytes (Study 87 1173)**

TCBZ was tested for DNA-damaging effects on rat hepatocytes *in vitro* using concentrations up to 40 µg/ml. Under the given experimental conditions, no evidence of induction of DNA damage by TCBZ or by its metabolites was obtained.

##### ***In vivo* Sister chromatid exchange study (Study 82 0209).**

A single dose of varying doses of TCBZ (up to 692 mg/kg) was administered by gavage to male and female Chinese Hamsters (4/sex/treatment group). The animals were sacrificed 24h after the administration of the drug. The experiments were performed in order to detect a possible mutagenic property of the substance, manifested in somatic cells *in vivo* in the form of sister chromatid exchanges (SCE). The number of SCEs in animals treated with the various doses of TCBZ showed no significant increase compared to the negative control group (PEG 400). The positive control experiment with DMBA (100 mg/kg) yielded significantly higher SCE compared to negative controls.

### 5.5.3. Reproductive and Developmental Toxicology

#### Fertility and Early Embryonic Development

A stand-alone FEED study was not conducted. However, fertility was examined in the F<sub>1</sub> generation rats in the peri- and postnatal development study, via dietary administration of the drug (Study No. 81 1540 reviewed below).

#### Embryo-Fetal Development

**Study title/ number: Teratology study in rats; Study number: 80 2099**

Key Study Findings

## NDA Multi-Disciplinary Review and Evaluation – NDA

- The highest dose, which is below the clinical dose, based on a body surface area comparison, was maternotoxic, but did not cause any developmental toxicity in the fetuses.
- No TK analysis was done.

Conducting laboratory and location: Ciba-Geigy Ltd, Reproductive Toxicology, Switzerland

GLP compliance: Yes

### Methods

Dose and frequency of dosing: 0, 10, 30, 100 mg/kg/day once daily

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% aqueous solution of a sodium carboxymethylcellulose

Species/Strain: Sprague Dawley Rats

Number/Sex/Group: 25

Satellite groups: No

Study design: Drug was administered from day 6 to day 16 of pregnancy

Deviation from study protocol affecting interpretation of results: No

### **Observations and Results**

| <b>Parameters</b>                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Major findings</b>                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortality                                                                                                                                                                                                                                                                                                                                                                                                                                    | None                                                                                                                                                                        |
| Clinical Signs                                                                                                                                                                                                                                                                                                                                                                                                                               | None reported                                                                                                                                                               |
| Body Weights                                                                                                                                                                                                                                                                                                                                                                                                                                 | Body weight gain of dams was slightly lower in the LD and MD groups (+18.7 and +18.6% resp.) and to a greater extent in the HD group (+15.3%) compared to controls (+21.7%) |
| Necropsy findings in dams<br>Parameters measured: <ul style="list-style-type: none"> <li>• number of spontaneous deaths,</li> <li>• number of females with corporal lutea (CL)</li> <li>• CL mean</li> <li>• number of females with implantations</li> <li>• implantations mean</li> <li>• number of females with deciduomata</li> <li>• number of females with total abortion</li> <li>• number of females with partial abortion</li> </ul> | Unremarkable                                                                                                                                                                |

| Parameters                                                                                                                                                                          | Major findings |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <ul style="list-style-type: none"> <li>number of aborted embryos</li> <li>embryonal deaths (resorptions)</li> <li>number of dead fetuses</li> <li>number of live fetuses</li> </ul> |                |
| Necropsy findings in offspring                                                                                                                                                      | Unremarkable   |

LD: low dose; MD: mid dose; HD: high dose

### Embryo-Fetal Development

#### **Study title/ number: Teratology study in rabbits; Study number: 80 2090**

##### Key Study Findings

- There was no evidence of developmental toxicity noted in the fetuses at any of the doses. However, the highest dose tested was below the proposed clinical dose, based on a body surface area comparison.
- No TK analysis was done.

Conducting laboratory and location: Ciba-Geigy Ltd, Reproductive Toxicology, Switzerland

GLP compliance: Yes

### Methods

Dose and frequency of dosing: 0, 3, 10, 20 mg/kg/day once daily

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% aqueous solution of a sodium carboxymethylcellulose

Species/Strain: Chinchilla type from a closed breeding colony

Number/Sex/Group: 20

Satellite groups: No

Study design: Drug was administered from day 6 to day 18 of pregnancy

Deviation from study protocol affecting interpretation of results: No

### **Observations and Results**

| Parameters     | Major findings                                                                                                                                                                    |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortality      | LD: 3 animals;                                                                                                                                                                    |
| Clinical Signs | LD: Diarrhea was noted in 2/3 animals before death. In addition 3 more animals developed diarrhea.<br>MD: 1 animal developed diarrhea and no implantation occurred in this animal |

| Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Major findings                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HD: Diarrhea was noted in 3 animals and no implantation occurred in 2/3 animals.                                       |
| Body Weights                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Slight decrease in weight gain in all dose groups compared to controls.                                                |
| Necropsy findings in dams<br><br>Parameters measured: <ul style="list-style-type: none"> <li>• number of spontaneous deaths,</li> <li>• number of females with corporal lutea (CL)</li> <li>• CL mean</li> <li>• number of females with implantations</li> <li>• implantations mean</li> <li>• number of females with deciduomata</li> <li>• number of females with total abortion</li> <li>• number of females with partial abortion</li> <li>• number of aborted embryos</li> <li>• embryonal deaths (repsorptions)</li> <li>• number of dead fetuses</li> <li>• number of live fetuses</li> </ul> | Cause of death was pulurent pleuritis in one of 3 animals whereas 2/3 dead animals had diarrhea 5-7 days before death. |
| Necropsy findings in offspring                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Unremarkable                                                                                                           |

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

**Study title/ number: 2-generation Toxicity Study; Study number: 81 1540**

Key Study Findings:

- No significant effect of TCBZ on fertility indices and peri-/post-natal development in rats.
- F2 generation: mean body weight was slightly reduced in all treatment groups
- NOAEL: Mean daily intake dose of 1.3 mg/kg/day which is below the proposed clinical dose

Conducting laboratory and location: Ciba-Geigy Ltd, Reproductive Toxicology, Switzerland

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 15, 75 ppm

Mean daily intake of drug Calculated as [(weekly food consumption in gm)/body weight in gm) X (dose in ppm)/7]

Route of administration: Orally via diet

Species/Strain: Albino Sprague Dawley (Tif:RAIf)

Number/Sex/Group: 20  
 Satellite groups: No  
 Study design: 1 month old F0 and F1 animals were administered the drug for a period of 110 days beginning when the animals were 28-30 days old, and including a 12-day mating period that started on day 62 of dosing (when they were 3 month old).  
 Deviation from study protocol affecting interpretation of results: No

**Observations and Results**

| Generation    | Major Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| F0            | <ol style="list-style-type: none"> <li>1. Mean daily intake of drug: Males: 0.2, 1 and 5 mg/kg/day Females: 0.29, 1.42 and 7.26 mg/kg/day</li> <li>2. Body weight changes were unremarkable.</li> <li>3. Mean duration of pregnancy was about 21 days for all treatment groups.</li> <li>4. Mating rates and fertility index of treatment groups were not different from controls.</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| F1 Generation | <p>F1 litter necropsied at 28 days:</p> <ol style="list-style-type: none"> <li>1. Body weight changes were slightly lower in LD and MD groups but not different in HD group compared to controls.</li> <li>2. Mating rates and fertility index of treatment groups were not different from controls.</li> <li>3. General development and behavior were unremarkable. However, exploratory locomotion pattern (ELP) or activity index was slightly lower in the LD and MD groups.</li> <li>4. Implantation sites, rate of implantation, number of litter and mean litter size were not different between the groups.</li> <li>5. Number of litters showing postnatal death of at least 1 pup was slightly higher in all the treatment groups compared to controls.</li> </ol> <p>Adults selected for breeding:</p> <ol style="list-style-type: none"> <li>1. Mean daily intake of drug: Males: 0.23, 1.15 and 5.65 mg/kg/day Females: 0.31, 1.49 and 7.54 mg/kg/day.</li> <li>2. No deaths were reported.</li> <li>3. Body weight changes were unremarkable in the treatment groups</li> <li>4. Fertility indices were unremarkable</li> </ol> |
| F2 Generation | <ol style="list-style-type: none"> <li>1. Mean body weight was slightly reduced in all treatment groups</li> <li>2. ELP or activity index was slightly lower in the LD and HD groups</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

*Reviewer’s comments: The highest dose administered to the F0 and F1 animals is much below the proposed clinical dose. There was no maternal toxicity observed at any of the doses tested in*

*the 2-generation study in rat; therefore, the doses used in this study are likely inadequate to indicate whether the drug causes post-natal developmental toxicity in the offspring of F0 and F1 generations. No TK analyses were done.*

Embryo-Fetal Development study from published literature:

**Teratogenic Evaluation of Triclabendazole in Rats:**

In the study by Yoshimura (1987)<sup>3</sup>, TCBZ (10, 25, 50, 100 or 200 mg/kg/day) was administered to pregnant Sprague-Dawley rats throughout the organogenic period (days 8 through 15 of pregnancy). The dams were euthanized on day 21 and the fetuses were examined for skeletal malformations and other developmental effects due to exposure to TCBZ. The drug caused no significant increase in the resorption rate up to 200 mg/kg/day. Body weight gain in the dams was slightly lower, but statistically significant at 100 and 200 mg/kg/day doses, suggesting slight maternal toxicity at the higher doses. Examinations of the fetuses revealed no significant increase in incidences of gross, skeletal and internal malformations at any dose in comparison with the controls. The NOAEL for embryofetal development was 200 mg/kg/day, or approximately 1.6 times the maximum recommended human dose (MRHD) based on body surface area).

**5.5.4. Other Toxicology Studies**

**Skin sensitization in the Guinea Pig (Study 79 1077):**

The test was performed on groups of 10 male and 10 female guinea pigs. The animals received 0.1 % suspension of TCBZ in 70 % propylene glycol in saline administered either intradermally or on shaven skin of the animals. Under the experimental conditions employed, significant differences between the test group and the vehicle treated controls were only seen after intradermal challenge application of TCBZ, i.e. when the skin barrier was intentionally bypassed. No difference between the test and the control group was seen after epidermal challenge application, which suggests that the drug may not produce contact dermatitis.

**Skin irritation in the rabbit (Study 79 0040)**

The test was performed on 3 male and 3 female adult rabbits of the New Zealand White breed weighing 2 to 3 kg. Gauze patches containing 0.5 g of TCBZ were applied to prepared abraded and intact skin. The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The dressings were removed after a 24 hour application and scored for erythema during an observation period of 7 days. Under the conditions of the experiment TCBZ was found to cause a minimal irritation when applied to intact and abraded rabbit skin.

**Eye irritation in the rabbit (Study 79 0041)**

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<sup>3</sup> Teratogenic Evaluation of Triclabendazole In Rats; Haruo Yoshimura; Toxicology 43 (1987) 283-287

The test for eye irritants was performed on 3 male and 3 female adult rabbits of the New Zealand White breed weighing 2 to 3 kg. TCBZ (0.1 g) was inserted into the conjunctival sac of the left eye of the rabbits and the lids were gently closed for a few seconds. The right eye was not treated and served as an untreated control. Under the conditions of this experiment TCBZ was found to cause no irritation when applied to the rabbit eye mucosa.

**Tolerability studies in farm animals**

Possible drug interactions between TCBZ and other anthelmintics such as fenbendazole or levamisole were investigated in farm animals. Tolerability of sheep to TCBZ (Study 80/3/777), when given concurrently in combination with commercial anthelmintics, resulted in reduced body weight gains in treated groups with no remarkable differences between treatments (levamisole, albendazole, oxfendazole, or morantel citrate). Treatment of calves with TCBZ (Study 83/8/964), when given concurrently with oxfendazole, resulted in no signs of toxicity and was well tolerated.

## 6 Clinical Pharmacology

### 6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV and Division of Pharmacometrics) reviewed the information contained in NDA 208,711. The clinical pharmacology information submitted in the application supports the approval of Egaten (TCBZ) tablet for the treatment of fascioliasis in adults and children 6 years of age and older. See **Error! Reference source not found.** for a summary of clinical pharmacology-related recommendations and comments on key review issues.

**Table 6.1. Summary of OCP Recommendations & Comments on Key Review Issues.**

| Review Issue                                                         | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal or supportive evidence of effectiveness</b>               | <p>The pivotal evidence of effectiveness of TCBZ in patients with fascioliasis of 6 years of age and older was provided by 6 studies performed by CIBA/WHO and 2 literature publications.</p> <p>Supportive evidence of effectiveness was provided by 3 unpublished studies performed by the Egyptian government and 5 literature publications.</p>                                                   |
| <b>General dosing instructions</b>                                   | <p>(b) (4)</p> <p>The FDA recommended a dosing regimen of 2 doses of 10 mg/kg given 12 hours apart.</p>                                                                                                                                                                                                                                                                                               |
| <b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b> | <p>No dosing adjustment is recommended based on intrinsic factors (age, sex, ethnicity, hepatic impairment, renal impairment) or extrinsic factors (concomitant use of other medications).</p>                                                                                                                                                                                                        |
| <b>Labeling</b>                                                      | <p>The Applicant’s proposed labeling requires major edits. The content changes include the following sections:</p> <ul style="list-style-type: none"> <li>• 2) Dosage and Administration: Update to the recommended dosage</li> <li>• 5) Warnings and Precautions: Removal of (b) (4)</li> <li>• 7) (b) (4): Update to reflect FDA’s recommendations</li> <li>• 12) Clinical Pharmacology:</li> </ul> |

|                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                          | <ul style="list-style-type: none"> <li>○ Addition of subsection on pharmacodynamics</li> <li>○ Modification of data reporting format to align with the current labeling guidances</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Bridge between the to-be marketed and clinical trial formulations</b> | <p>TCBZ was administered as Fasinex (veterinary formulation) in all PK studies and a majority of efficacy studies and as Egaten (to-be-marketed human formulation) in two efficacy studies. The differences between the formulation are considered minimal, consisting of changes in the <span style="background-color: #cccccc; padding: 0 20px;"> </span> <sup>(b) (4)</sup> <span style="background-color: #cccccc; padding: 0 20px;"> </span> processes. Please see the biopharmaceutics review for more details on the adequacy of bridging between Fasinex and Egaten.</p> |

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 6.2. provides a summary of the clinical pharmacology characteristics of TCBZ.

**Table 6.2. Summary of Clinical Pharmacology Characteristics of Triclabendazole.**

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Absorption   | <p>Absolute bioavailability was not assessed. Following fasted administration of oral TCBZ tablets, TCBZ T<sub>max</sub> is 2 h. When administered with a meal (560 kcal), the AUC of TCBZ is 2.69-fold higher, the C<sub>max</sub> is 2.41-fold higher, and the T<sub>max</sub> is delayed by 1 h. [Studies B2101, B2212]</p>                                                                                                                                                                                   |
| Distribution | <p>TCBZ and its active sulfoxide (TCBZ-SO) and sulfone (TCBZ-SO<sub>2</sub>) metabolites are highly bound to plasma protein, with 96.7%, 98.4%, and 98.8% binding, respectively.</p> <p>The apparent volume of distribution of TCBZ-SO, which is thought to contribute the most to activity, is approximately 1 L/kg. [Studies R200-1279, B2212]</p>                                                                                                                                                             |
| Elimination  | <p>The values of mean terminal half-life of TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> are 7.4, 13.7, and 10.8 h, respectively. [Study B2101]</p> <p><i>Metabolism</i></p> <p>There are 2 major metabolites found in plasma after oral administration of TCBZ—TCBZ-SO and TCBZ-SO<sub>2</sub>—which are both active. The formation of TCBZ-SO is mainly mediated by CYP1A2, and the formation of TCBZ-SO<sub>2</sub> is mainly mediated by CYP2C9 based on the known in vitro data. [Studies R1600737, R1700972]</p> |

|  |                                                                                                                                                                                                              |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p><i>Excretion</i></p> <p>The excretion pathway of TCBZ in humans is unclear as no human mass balance study was performed. However, in animal studies, TCBZ was excreted 90% in feces and 10% in urine.</p> |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The Applicant's proposed dosage regimen of Egaten is [REDACTED] (b) (4)

Based on the efficacy and safety demonstrated in the studies submitted for review, the review team proposes a [REDACTED] (b) (4) dose to ensure efficacy: 2 doses of 10 mg/kg given 12 hours apart.

### Therapeutic Individualization

There are no clinically significant changes in pharmacokinetics or efficacy due to age, sex, or ethnicity. No dedicated mass balance, hepatic impairment, or renal impairment studies were performed. However, the potential for accumulation appears to be low due to the short treatment course and short half-lives of TCBZ and its metabolites. Thus, there is no need to adjust the dose based on these intrinsic factors.

In vitro studies indicate TCBZ is a substrate of CYP1A2, and its active metabolite TCBZ-SO is a substrate of CYP2C9. TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> have also been shown, in vitro, to inhibit CYP enzymes, particularly CYP2C19. Upon careful review of the submitted efficacy, safety and PK data and considering the clinical context of use (short treatment duration), the review team assessed that no dose adjustments are necessary with concomitant use of other medications, regardless of status as a CYP substrate or modulator.

### Outstanding Issues

The potential for TCBZ to prolong the QT interval was not assessed in any of the clinical studies.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Information of general pharmacology and pharmacokinetic characteristics of TCBZ is shown in Table 6.3..

**Table 6.3. General Pharmacology and Pharmacokinetic Characteristics.**

| <b>Pharmacology</b>                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mechanism of Action</b>                                    | The exact mechanism of action for TCBZ in fascioliasis is unknown. TCBZ and its active metabolites have been shown to cause structural damage and impair the motility of <i>Fasciola hepatica</i> and <i>Fasciola gigantica</i> .                                                                                                                                                                                                                                                                         |
| <b>Active Moieties</b>                                        | TCBZ, TCBZ sulfoxide (TCBZ-SO), TCBZ sulfone (TCBZ-SO <sub>2</sub> )                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>QT Prolongation</b>                                        | The QT prolongation liability of TCBZ and its metabolites in humans is unknown. However, QT prolongation was observed in dogs at 40 and 100 mg/kg TCBZ. In dogs, the QT prolongation was associated with high concentrations of the sulfone metabolite, which is lower in humans. [Study 001004]                                                                                                                                                                                                          |
| <b>General Information</b>                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Bioanalysis</b>                                            | Validated HPLC methods were used to determine TCBZ, TCBZ-SO, and TCBZ-SO <sub>2</sub> in human plasma and urine. (See Section 15.4.1)                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Healthy vs. Patients</b>                                   | There does not appear to be a significant difference in PK between TCBZ administered to healthy volunteers and patients with fascioliasis. [Studies B2101 and B2212, [27]]                                                                                                                                                                                                                                                                                                                                |
| <b>Drug exposure following the therapeutic dosing regimen</b> | Because TCBZ is given for a maximum of 2 doses, steady-state exposure was not assessed. After administration of a single dose of 10 mg/kg oral TCBZ with a 560-kcal meal to patients with fascioliasis, the values of AUC of TCBZ, TCBZ-SO, and TCBZ-SO <sub>2</sub> were 5.72, 386, and 30.5 μmol*h/L, respectively. The values of C <sub>max</sub> were 1.16, 38.6, and 2.29 μmol/L, respectively. The exposure following 2 doses of 10 mg/kg oral TCBZ 12 hours apart was not evaluated. [Study B2212] |
| <b>Range of effective dose or exposure</b>                    | Total doses of 5-30 mg/kg TCBZ (given as individual doses of no more than 10 mg/kg, no more frequently than q12h) were shown to be have higher clinical response than the historical control in the submitted clinical studies. (See Section 7)                                                                                                                                                                                                                                                           |
| <b>Maximally tolerated dose (MTD) or exposure</b>             | The maximally tolerated dose was not determined.                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Dose Proportionality</b>                                   | PK data were available only at the 10 mg/kg dose level. Thus, dose proportionality was not assessed.                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Accumulation</b>                                           | Accumulation was not assessed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Variability</b>                                            | After administration of a single dose of 10 mg/kg oral TCBZ with a 560-kcal meal to patients with fascioliasis, the values of inter-subject variability (CV%) in the AUC of TCBZ, TCBZ-SO, and TCBZ-SO <sub>2</sub> were 66%, 41%, and 53%, respectively. The values of inter-subject variability (CV%) in C <sub>max</sub> were 65%, 36%, and 40%, respectively. The exposure following 2 doses                                                                                                          |

|                                                               | of 10 mg/kg oral TCBZ 12 hours apart was not evaluated. [Study B2212]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------|------------------|--------------------------------------------------|------|------|---------|------|----------------------|------|--------------------------------------------------------------|------|------|---------|------|----------------------|------|-------------------------------------------|------|------|---------|------|----------------------|------|
| <b>Bioavailability</b>                                        | Absolute bioavailability of TCBZ was not assessed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>T<sub>max</sub></b>                                        | 2 h (TCBZ) [Study B2101]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Food effect (Fed/fasted)</b>                               | <p>Administration of 10 mg/kg oral TCBZ with a meal (560 kcal) was shown to increase the exposure of TCBZ and its metabolites:</p> <table border="1"> <thead> <tr> <th>PK Parameter</th> <th>Analyte</th> <th>Percent Increase</th> </tr> </thead> <tbody> <tr> <td rowspan="3"><b>AUC</b><br/>(<math>\mu\text{mol}\cdot\text{h/L}</math>)</td> <td>TCBZ</td> <td>269%</td> </tr> <tr> <td>TCBZ-SO</td> <td>118%</td> </tr> <tr> <td>TCBZ-SO<sub>2</sub></td> <td>119%</td> </tr> <tr> <td rowspan="3"><b>C<sub>max</sub></b><br/>(<math>\mu\text{mol}\cdot\text{h/L}</math>)</td> <td>TCBZ</td> <td>241%</td> </tr> <tr> <td>TCBZ-SO</td> <td>144%</td> </tr> <tr> <td>TCBZ-SO<sub>2</sub></td> <td>120%</td> </tr> <tr> <td rowspan="3"><b>T<sub>max</sub><sup>#</sup></b><br/>(h)</td> <td>TCBZ</td> <td>1 hr</td> </tr> <tr> <td>TCBZ-SO</td> <td>2 hr</td> </tr> <tr> <td>TCBZ-SO<sub>2</sub></td> <td>0 hr</td> </tr> </tbody> </table> <p>Source: Study B2212, # delay in T<sub>max</sub></p> | PK Parameter     | Analyte | Percent Increase | <b>AUC</b><br>( $\mu\text{mol}\cdot\text{h/L}$ ) | TCBZ | 269% | TCBZ-SO | 118% | TCBZ-SO <sub>2</sub> | 119% | <b>C<sub>max</sub></b><br>( $\mu\text{mol}\cdot\text{h/L}$ ) | TCBZ | 241% | TCBZ-SO | 144% | TCBZ-SO <sub>2</sub> | 120% | <b>T<sub>max</sub><sup>#</sup></b><br>(h) | TCBZ | 1 hr | TCBZ-SO | 2 hr | TCBZ-SO <sub>2</sub> | 0 hr |
| PK Parameter                                                  | Analyte                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Percent Increase |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>AUC</b><br>( $\mu\text{mol}\cdot\text{h/L}$ )              | TCBZ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 269%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 118%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO <sub>2</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 119%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>C<sub>max</sub></b><br>( $\mu\text{mol}\cdot\text{h/L}$ )  | TCBZ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 241%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 144%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO <sub>2</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 120%             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>T<sub>max</sub><sup>#</sup></b><br>(h)                     | TCBZ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1 hr             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2 hr             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
|                                                               | TCBZ-SO <sub>2</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0 hr             |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Volume of Distribution</b>                                 | The apparent volume of distribution of TCBZ-SO in patients with fascioliasis administered 10 mg/kg TCBZ is approximately 1 L/kg. [Study B2212]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Plasma Protein Binding</b>                                 | TCBZ, TCBZ-SO, and TCBZ-SO <sub>2</sub> are 96.7%, 98.4%, and 98.8% bound to plasma protein, respectively. [DMPK(CH) R00-1279]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Substrate transporter systems [in vitro]</b>               | TCBZ and its metabolites were not characterized as substrates of any major human drug transporters.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Elimination</b>                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Half-life</b>                                              | The values of half-life for TCBZ, TCBZ-SO, and TCBZ-SO <sub>2</sub> are 7.4, 13.7, and 10.8 h, respectively. [Study B2201]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Metabolism</b>                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Fraction metabolized (% dose)</b>                          | No mass balance studies were performed to quantify the fraction metabolized.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Primary metabolic pathway(s) [in vitro]</b>                | TCBZ is metabolized primarily by CYP1A2 to form TCBZ-SO; TCBZ-SO is primarily metabolized by CYP2C9 to form TCBZ-SO <sub>2</sub> based on known in vitro data. [DMPK R1600737, R1700972]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Excretion</b>                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>Primary excretion pathways (% dose) <math>\pm</math>SD</b> | The primary excretion pathways in humans are unknown. In animal studies, 90% of the administered TCBZ dose is excreted in the feces and 10% in the urine. The relevance to excretion in humans is not clear.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |
| <b>In vitro interaction liability (Drug as perpetrator)</b>   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                  |         |                  |                                                  |      |      |         |      |                      |      |                                                              |      |      |         |      |                      |      |                                           |      |      |         |      |                      |      |

|                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Inhibition/Induction of metabolism</b></p>          | <p>Results from in vitro studies suggest that TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> can inhibit CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A at clinically relevant concentrations. TCBZ and its metabolites had the greatest risk to inhibit CYP2C19 with a Ki:Cmax ratio of 20.7. [Studies R160056-01, R1600691, R1700893-01]</p> <p>No in vitro studies were conducted to address the potential for TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> to induce CYP enzymes.</p> <p>No in vivo studies to address drug-drug interaction potential were performed</p> |
| <p><b>Inhibition/Induction of transporter systems</b></p> | <p>No studies were conducted to address the potential for TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> to inhibit or induce human transporters.</p>                                                                                                                                                                                                                                                                                                                                                                                                                    |

Pharmacokinetic parameters are presented as mean (CV%), mean ±standard deviation (SD), or median (minimum, maximum) unless otherwise noted.

### 6.3.2. Clinical Pharmacology Questions

#### 1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The evidence of effectiveness of TCBZ in patients with fascioliasis of 6 years of age and older was provided by 6 studies performed by CIBA/WHO and 2 literature publications. Supportive evidence of effectiveness was provided by 3 studies performed by the Egyptian government and 5 literature publications. Please refer to Section 7.2 “Review of Relevant Individual Trials Used to Support Efficacy” for details on the study designs and endpoint assessments supporting the efficacy of TCBZ.

#### 2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No, the Applicant’s proposed TCBZ dosing regimen (b) (4) is not an optimal dose regimen for the general population in the treatment of fascioliasis. Instead, the review team recommends a dose regimen of 2 doses of 10 mg/kg given 12 hours apart.

#### Chronic Fascioliasis

The statistical reviewer conducted a meta-analysis of the studies submitted in this NDA including the CIBA/WHO studies, Egyptian government studies, and literature publications supporting TCBZ in the treatment of chronic fascioliasis. During these studies, patients with chronic fascioliasis were treated with TCBZ at total doses of 5-30 mg/kg. Total doses above 10 mg/kg were given in divided doses of no more than 10 mg/kg q12-24h. All doses showed higher clinical response relative to the inadequately-treated historical control estimate of 22% (Keiser). The analysis showed a trend where increased total dose resulted in higher overall response.

The combined estimate of cure rate at 10 mg/kg total dose regimen is approximately 83.4% with 95% confidence interval (CI) (76.7, 88.5). Overall, pooled cure rate is 94.5% with 95% CI (84.6, 98.2) from data on the 20 mg/kg total dose regimen. Therefore, the highest efficacy was associated with a total dose of 20 mg/kg, i.e., 10 mg/kg for 2 doses q12-24h.

#### Acute Fascioliasis

Patients with acute fascioliasis were only enrolled in the Hien study and were also administered a total dose of 20 mg/kg, i.e., 10 mg/kg q12h for 2 doses. This dose was also shown to be efficacious.

See Section 7.4 for an in-depth analysis of the efficacy results in both acute and chronic fascioliasis.

As such, considering a better treatment effect of TCBZ with a total dose of 20 mg/kg, the review team proposes a dosing regimen of 20 mg/kg oral TCBZ in 2 divided doses 12 hours apart in adults and children of 6 years of age and older with either acute or chronic fascioliasis.

### **3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No alternative dosing regimens or management strategies are required for subpopulations based on intrinsic patient factors.

#### Hepatic Impairment/ Renal Impairment

No dedicated clinical pharmacokinetic study was performed in patients with hepatic or renal impairment. We agree with the Applicant's proposal that no dose adjustment is necessary in these patient subpopulations due to the short treatment course (two doses). In addition, TCBZ should be used with caution in patients with liver impairment not related to fascioliasis.

#### *Renal Impairment*

Based on animal studies, TCBZ is likely predominantly excreted in the feces via the biliary tract. Although the applicability of the animal data to humans is not known, there are no concerns with administration of the short course of TCBZ in patients with renal impairment.

#### *Hepatic Impairment*

Considering the likely biliary excretion of TCBZ in humans and the involvement of hepatic metabolism in the disposition of TCBZ, it is possible that hepatic impairment will affect the exposure of TCBZ. The ability of the body to biotransform TCBZ to TCBZ-SO and TCBZ-SO<sub>2</sub> may be impaired or delayed, leading to higher concentrations of TCBZ and lower concentrations of TCBZ-SO and TCBZ-SO<sub>2</sub>. Although TCBZ-SO is proposed to be the most active moiety of TCBZ, both TCBZ and TCBZ-SO<sub>2</sub> also have activity against *Fasciola*.

In the submitted clinical studies, some patients had abnormal pre-treatment liver function tests including AST, ALT, ALP, and total bilirubin. These altered lab values were potentially caused by

the pathophysiology of fascioliasis, with the parasite interfering with normal function of the liver and biliary tract. In these patients, there was no significant additional toxicity with administration of TCBZ.

Considering the short treatment duration (two doses within 24 hours), administration of TCBZ to patients with hepatic impairment is unlikely to result in clinically significant toxicity or lack of efficacy. The total exposure and exposure ratio of TCBZ and its metabolites may be altered in patients with hepatic impairment. However, all three moieties possess anti-fluke activity and likely retain the potential for therapeutic success. Additionally, significant accumulation is unlikely given that only two doses of TCBZ will be administered.

#### Other Intrinsic Factors (Age, Sex, Ethnicity)

Age, sex, and ethnicity do not appear to have a clinically significant effect on the efficacy of TCBZ. Data from male and female patients from diverse locations including Cuba, Peru, Egypt, Vietnam, and Iran with a wide age range (2-81 yr) were included in the submitted NDA, with no significant changes in efficacy identified based on these demographic factors. As such, no dose adjustment is needed.

#### **4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

##### Food-Drug Interaction

There is a clinically relevant food-drug interaction. Co-administration of TCBZ with food increases the AUC of TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> by 3.7-, 2.2-, and 2.2-fold, respectively. The review team recommends that TCBZ is administered with food.

Food has been demonstrated to increase the exposure of TCBZ. In Study B2212, patients with fascioliasis were administered 10 mg/kg TCBZ with and without food in a crossover fashion with a washout period of two days. The meal provided for the patients was not the Agency-recommended high-fat meal but a meal consisting of 2 cups of sweetened white coffee, one roll with cheese, and one roll with butter and jam, for a total calorie count of approximately 560 kcal. Administration of TCBZ with this meal as described was shown to increase the AUC and C<sub>max</sub> and to delay the T<sub>max</sub> as shown in Table 6.4.

**Table 6.4. Effect of Food on Exposure of TCBZ and Metabolites.**

| PK Parameter                                      | Analyte              | Percent Increase |
|---------------------------------------------------|----------------------|------------------|
| <b>AUC</b><br>( $\mu\text{mol}\cdot\text{h/L}$ )  | TCBZ                 | 269%             |
|                                                   | TCBZ-SO              | 118%             |
|                                                   | TCBZ-SO <sub>2</sub> | 119%             |
| <b>Cmax</b><br>( $\mu\text{mol}\cdot\text{h/L}$ ) | TCBZ                 | 241%             |
|                                                   | TCBZ-SO              | 144%             |
|                                                   | TCBZ-SO <sub>2</sub> | 120%             |
| <b>Tmax<sup>#</sup></b><br>(h)                    | TCBZ                 | 1 hr             |
|                                                   | TCBZ-SO              | 2 hr             |
|                                                   | TCBZ-SO <sub>2</sub> | 0 hr             |

Source: Study B2212, <sup>#</sup> delay in Tmax

TCBZ is a BCS Class II/IV compound, indicating that the solubility of TCBZ in water is poor and the permeability of TCBZ is unknown. Administration of TCBZ with food likely improves its solubility, leading to higher bioavailability.

While the standard Agency-recommended high fat meal was not used in this study, the composition of the meal likely reflects how TCBZ was administered in many of the clinical trials, in which TCBZ was administered with food with the content of the meal left to the patients' discretion. TCBZ was administered with food in at least 10 studies and fasted in at least 2 studies, but there are also instances where TCBZ was administered in both fed and fasting states and where there are no data on whether food was administered with TCBZ. At the same time, no data are available to assess a difference in clinical response based on the presence or content of food administered with oral TCBZ.

In summary, administration of TCBZ with a meal increases the AUC and Cmax of TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub>. There is no clear effect of administration of TCBZ with a meal on efficacy. However, to maximize the likelihood of efficacious exposure in patients, the clinical pharmacology review team recommends that TCBZ is administered with food.

#### Drug-Drug Interaction (DDI)

There is a potential for drug-drug interactions with TCBZ. However, considering the short treatment duration of TCBZ, TCBZ may be used concomitantly with another medication without regard for status as a CYP substrate, inducer, or inhibitor.

In vitro data suggest that TCBZ and its metabolites have potential to act as victims or perpetrators for CYP mediated DDI. However, no clinical drug-drug interaction studies were performed.

#### *TCBZ and Metabolites as Perpetrators of CYP-Mediated DDIs*

Based on in vitro studies, TCBZ and its metabolites were shown to have the potential to inhibit each major CYP enzyme as shown in Table 6.5. In particular, TCBZ-SO appears to have a strong capacity to inhibit CYP2C19, with an R1 (Ki:Cmax ratio) value of approximately 21.

**Table 6.5. Potential for TCBZ and Its Metabolites to Inhibit CYP Enzymes.**

| Compound             | CYP Enzyme | Probe reaction                     | K <sub>i,u</sub> (μM) | C <sub>max</sub> , (μM) [B2101] | Fraction Unbound | R1           |
|----------------------|------------|------------------------------------|-----------------------|---------------------------------|------------------|--------------|
| TCBZ                 | CYP1A2     | phenacetin <i>O</i> -deethylation  | 0.0180                | 1.7                             | 0.033            | <b>4.08</b>  |
| TCBZ-SO              |            |                                    | 0.760                 | 61.0                            | 0.016            | <b>2.28</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 12.5                  | 4.03                            | 0.0125           | 1.00         |
| TCBZ                 | CYP2A6     | coumarin 7-hydroxylation           | 0.462                 | 1.7                             | 0.033            | <b>1.12</b>  |
| TCBZ-SO              |            |                                    | 3.61                  | 61.0                            | 0.016            | <b>1.27</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 14.1                  | 4.03                            | 0.0125           | 1.00         |
| TCBZ                 | CYP2B6     | bupropion hydroxylation            | 0.0166                | 1.7                             | 0.033            | <b>4.34</b>  |
| TCBZ-SO              |            |                                    | 1.04                  | 61.0                            | 0.016            | <b>1.94</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 1.27                  | 4.03                            | 0.0125           | <b>1.04</b>  |
| TCBZ                 | CYP2C8     | amodiaquine <i>N</i> -deethylation | 0.0564                | 1.7                             | 0.033            | <b>1.98</b>  |
| TCBZ-SO              |            |                                    | 1.79                  | 61.0                            | 0.016            | <b>1.55</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 0.369                 | 4.03                            | 0.0125           | <b>1.14</b>  |
| TCBZ                 | CYP2C9     | diclofenac 4'-hydroxylation        | 0.0660                | 1.7                             | 0.033            | <b>1.84</b>  |
| TCBZ-SO              |            |                                    | 0.553                 | 61.0                            | 0.016            | <b>2.77</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 0.223                 | 4.03                            | 0.0125           | <b>1.23</b>  |
| TCBZ                 | CYP2C19    | 5-mephenytoin 4'-hydroxylation     | 0.0140                | 1.7                             | 0.033            | <b>4.96</b>  |
| TCBZ-SO              |            |                                    | 0.0495                | 61.0                            | 0.016            | <b>20.72</b> |
| TCBZ-SO <sub>2</sub> |            |                                    | 2.79                  | 4.03                            | 0.0125           | <b>1.02</b>  |
| TCBZ                 | CYP2D6     | bufuralol 1'-hydroxylation         | 0.150                 | 1.7                             | 0.033            | <b>1.37</b>  |
| TCBZ-SO              |            |                                    | 4.34                  | 61.0                            | 0.016            | <b>1.23</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 13.0                  | 4.03                            | 0.0125           | 1.00         |
| TCBZ                 | CYP3A      | testosterone 6β-hydroxylation      | 0.162                 | 1.7                             | 0.033            | <b>1.34</b>  |
| TCBZ-SO              |            |                                    | 2.34                  | 61.0                            | 0.016            | <b>1.42</b>  |
| TCBZ-SO <sub>2</sub> |            |                                    | 10.2                  | 4.03                            | 0.0125           | 1.01         |

Source: Reviewer Table. R1 is calculated based on the 2017 FDA guidance.

Values of R1 ≥ 1.02 indicate the potential for a TCBZ or a metabolite to inhibit a CYP enzyme to a significant extent and are bolded.

The Applicant submitted a physiologically-based pharmacokinetic (PBPK) model to further investigate the ability of TCBZ and its metabolites to inhibit relevant CYP enzymes. In this analysis, TCBZ was predicted to increase AUC and C<sub>max</sub> by greater than 2-fold only for omeprazole (substrate of CYP2C19). The PBPK model submitted by the Applicant is adequate to screen the DDI risk for TCBZ to affect concentrations of sensitive CYP substrates. For the full PBPK review, please see Section 15.3.3.

While TCBZ has the potential to increase the exposure of other drugs, especially substrates of CYP2C19, the Applicant proposed that no dose adjustments are necessary due to the short treatment course (two doses) of TCBZ administration. In addition, TCBZ and its metabolites were not evaluated as inducers of CYP enzymes or as modulators (inducers or inhibitors) of human transporters in vitro.

Based on careful review of the available data and the clinical context, the clinical pharmacology review team agrees that TCBZ may be used concomitantly with another medication which is a CYP substrate without a need of dose adjustment. Even though there is a potential of increased plasma concentrations for CYP2C19 substrates with concomitant use of TCBZ, such potential elevation in concentrations of concomitantly used CYP2C19 substrates is expected to be transient based on the short elimination half-life and short treatment duration of TCBZ. The review team recommends to re-check the plasma concentration of the CYP2C19 substrates requiring therapeutic drug monitoring after cessation of TCBZ therapy, if the plasma concentrations of the CYP2C19 substrates are elevated during administration of TCBZ.

#### *TCBZ and Metabolites as Victims of CYP-Mediated DDIs*

TCBZ is metabolized primarily by CYP1A2 to form TCBZ-SO, which is then metabolized primarily by CYP2C9 to form TCBZ-SO<sub>2</sub>. Thus, there is the potential for inhibitors and inducers of CYP1A2 and CYP2C9 to affect the exposure of TCBZ and its metabolites. The Applicant used a PBPK model to assess the potential for CYP1A2 inhibitors to affect the exposure of TCBZ and its metabolites.

The Applicant did not provide a PBPK simulation to predict the exposure of TCBZ and its metabolites when TCBZ is administered concomitantly with a CYP inducer. However, they proposed that there is likely no significant DDI due to the short treatment duration and based on the clinical observation of similar cure rates in a few patients who were co-administered TCBZ with CYP inducers relative to other patients who did not use CYP inducers concomitantly.

The PBPK modeling for TCBZ as a victim of CYP-mediated DDIs was found to be inadequate by the review team. No human mass-balance study was performed to determine and quantify the exact elimination pathway of TCBZ. Additionally, no clinical DDI studies were performed, which would have provided data to verify the *f<sub>m</sub>c<sub>yp</sub>* values for TCBZ and its metabolites determined from in vitro studies. Thus, the review team disagrees with the Applicant's rationale (b) (4)

However, reduced doses of TCBZ down to 5 mg/kg were shown to have greater clinical response than the historical control. Thus, coadministration of a CYP inducer and TCBZ has a higher probability of success than any alternative therapeutic options. Likewise, concomitant use of a CYP inhibitor may increase the exposure of TCBZ, but accumulation is likely to be small due to the use of only two doses. Additionally, no significant safety signal was seen across the range of doses of TCBZ tested in clinical studies: 5 - 30 mg/kg in divided doses of no more than 10 mg/kg each.

Based on the favorable efficacy results and well tolerated safety profiles of TCBZ, the review team proposes that TCBZ may be used concomitantly with CYP inhibitors and inducers without significant clinical concern of lack of efficacy (due to subtherapeutic exposure) or toxicity (due to suprathreshold exposure).

## 7 Statistical and Clinical Evaluation

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### 7.1. Data Source and Review Strategy

This NDA includes patient-level data from the following three published studies.

*Hien TT, Truong NT, Minh Nh, Dat HD, Dung NT, et al. A Randomized Controlled Pilot Study of Artesunate versus Triclabendazole for Human Fascioliasis in Central Vietnam. Am J Trop Med Hyg 78(3),2008: 388-92.[3]*

*Maco V, Marcos L, Delgado J, Herrera J, Terashima A, et al. Efficacy and Tolerability of Two Single-day Regimens of Triclabendazole for Fascioliasis in Peruvian Children. Rev Soc Bras Med Trop. 2015 Jul-Aug;48(4):445-53. doi: 10.1590/0037-8682-0148-2015.[5]*

*Keiser J, Sayed H, El-Ghanam M, Sabry H, Anani S, et al. Efficacy and Safety of Artemether in the Treatment of Chronic Fascioliasis in Egypt: Exploratory Phase-2 Trials. PLoS Negl Trop Dis 5(9), 2011: e1285. doi:10.1371/journal.pntd.0001285.[4]*

The Applicant contacted each publication's primary author to seek access to the patient-level data supporting the respective publication. Upon agreement, the data (in SPSS or Excel format) were transferred electronically to a third-party vendor, (b) (4), who in turn anonymized the data, converted the data into SAS format and then returned the data to the study investigators. The study investigators then transferred the anonymized SAS data files to the Applicant who performed an independent comparison between the patient-level data and the published findings.

Additionally, the NDA includes pooled data from six unpublished, uncontrolled clinical studies that evaluated the veterinary formulation of TCBZ (Fasinex) for the treatment of chronic fascioliasis infection, referred to in the review as the WHO/CIBA studies.

These six WHO/CIBA clinical studies were not performed per GCPs and did not include electronic data collection. Given the absence of electronic datasets, the Applicant created datasets from patient line-listings included in the paper clinical study reports. There are 19 datasets of combined data from the six studies none of which are in standard STDM or ADaM format; however, the AE data are in MedDRA version 20.0.

The links to the study datasets are as follows:

<\\CDSESUB1\evsprod\NDA208711\0000\m5\datasets\hien2008\analysis\legacy\datasets>  
<\\CDSESUB1\evsprod\NDA208711\0000\m5\datasets\keiser2011\analysis\legacy\datasets>  
<\\CDSESUB1\evsprod\NDA208711\0000\m5\datasets\maco2015\analysis\legacy\datasets>  
<\\CDSESUB1\evsprod\NDA208711\0000\m5\datasets\ega230-ciba-pooled-data\analysis\legacy\datasets>

The nine studies for which patient-level data were provided are summarized in Table 7.1. Only the Hien study contains a randomized comparison. The Maco study evaluated two randomized arms of different doses of TCBZ. The Keiser study used TCBZ as a rescue therapy for subjects failing an experimental artemether treatment. This review will use the information from the artemether arm in the Keiser study as a historical control to help understand the efficacy of TCBZ in the Maco and WHO/CIBA studies.

Additionally, the literature studies where patient-level data are unavailable were considered as supportive information.

**Table 7.1: Clinical Studies with Patient-Level Data Supporting the NDA**

| Trial Identity         | Trial Design                                                                                                                                                                                                   | Regimen/<br>schedule/ route                                                                                                                                                                                                      | Study Endpoints                                                                                                                                                                                                         | Treatment<br>Duration/<br>Follow Up | No. of<br>patients<br>enrolled | Study<br>Population                                                                                                                                        | No. of Centers<br>and Countries                                           |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <b>Hien (2008) [3]</b> | Randomized (1:1), open-label, single center (Vietnam) in acute disease<br>3-month f/u                                                                                                                          | Egaten 10 mg/kg x 2d 12 hours apart ( <b>n=50</b> )<br><br>Artesunate 4 mg/kg OD x 10 days ( <b>n=50</b> )                                                                                                                       | Primary endpoint: resolution of abdominal pain at day 10.<br>Secondary: complete response rate at 3 months post-treatment, consisting of a) resolution of symptoms, b) resolution of eosinophilia c) improvement in U/S | Study duration: 3 months            | 100                            | Patients meeting the case definition for fascioliasis > <b>8 years of age</b> . They were hospitalized for 10 days and received directly observed therapy. | Single Center - Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam |
| <b>Maco (2015) [5]</b> | Dose ranging (two TCBZ regimens) study in pediatric patients with chronic infection<br><br><b>Pts in Asillo district received Fasinex (companion animal/livestock formulation); all others received Egaten</b> | Group 1: 7.5 mg/kg BID x 1 day ( <b>n=44</b> )<br>Group 2: 10 mg/kg QD single dose ( <b>n=40</b> )<br><br><b>Asillo site enrolled 70% pts</b><br><b>Group 1: n=31</b><br><b>Group 2: n=28</b><br>Sequential treatment assignment | Primary: Presence of eggs in stool at 60 days post-treatment<br><br>Secondary: Clinical signs and symptoms during the first 7 days post-treatment                                                                       | Study duration: 60 days             | 84                             | <b>2-16 years</b> , presence of eggs in at least 1 stool sample                                                                                            | 6 sites in Peru                                                           |

NDA Multi-Disciplinary Review and Evaluation – NDA

| Trial Identity           | Trial Design                                                              | Regimen/<br>schedule/ route                                                                                                                                                                                                                                                                                                                                           | Study Endpoints                                                              | Treatment<br>Duration/<br>Follow Up | No. of<br>patients<br>enrolled | Study<br>Population                                                                                                        | No. of Centers<br>and Countries                                                |
|--------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                          |                                                                           | based on block randomization (no further details provided)                                                                                                                                                                                                                                                                                                            |                                                                              |                                     |                                |                                                                                                                            |                                                                                |
| <b>Keiser (2011) [4]</b> | Two exploratory, single-arm studies of artemether in chronic fascioliasis | <p>i) Artemether 6 x 80 mg over 3 consecutive days (n=20), ii) 3 x 200 mg artemether in 24 hrs (n=17)</p> <p>TCBZ (Egaten) 10 mg/kg (single dose) (n=16) given to patients who failed on 3 x 200 artemether in 24 hours regimen</p> <p>Note: Patients failing on the 10 mg/kg single dose of TCBZ were re-treated with a 20 mg/kg dose (divided in 2 equal doses)</p> | Primary endpoint: egg excretion in 3 stool samples 28 days after final dose. | Study duration: 2 months            | 37                             | Males and Non-pregnant females aged <b>11-70 years</b> with stool exam positive for <i>F. hepatica</i> or <i>gigantica</i> | <b>Abis village, southwest of Alexandria with 10 sub-villages; pop. 35,000</b> |
| <b>WHO/CIBA</b>          | Single-center, open,                                                      | 2 groups:                                                                                                                                                                                                                                                                                                                                                             | PK, efficacy,                                                                | Inpatient                           | Group a:                       | + <i>F. hepatica</i>                                                                                                       | 1 (Cuzco, Peru)                                                                |

NDA Multi-Disciplinary Review and Evaluation – NDA

| Trial Identity                              | Trial Design                                                      | Regimen/<br>schedule/ route                                                                                                   | Study Endpoints                                                                  | Treatment<br>Duration/<br>Follow Up                               | No. of<br>patients<br>enrolled | Study<br>Population                                                           | No. of Centers<br>and Countries |
|---------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------|---------------------------------|
| <b>B2212 (Peru)</b>                         | sequential, non-randomized, cross-over                            | a. 10 mg/kg fasted on day 1, 10 mg/kg fed on day 3<br><br>b. 10 mg/kg fed on day 1, 10 mg/kg fasted on day 3                  | tolerability, hepatobiliary status                                               | for one week, Outpatient assessment on day 30 and 90              | n=10<br>Group b:<br>n=12       | eggs in stool, Non-pregnant, <b>adult</b> males/females                       |                                 |
| <b>WHO/CIBA B2207 (Bolivia)</b>             | Single center, open label, non-randomized, single arm             | 10 mg/kg PO x 1 fed                                                                                                           | Safety, Efficacy (day 60 egg count)                                              | In-patient for one week, 2 out-patient assessments days 30 and 60 | 22                             | + <i>F. hepatica</i> eggs in stool, Non-pregnant, <b>adult</b> males/females  | 1 (La Paz, Bolivia)             |
| <b>WHO/CIBA B2208 (pediatric) (Bolivia)</b> | Single center, open label, non-randomized, sequential group study | 3 groups<br>a. 5 mg/kg x 1<br>b. 10 mg/kg x1<br>c. 5 mg/kg x 2 6-8 hours apart<br>All fed<br>Treatment failures: 10 mg/kg x 2 | Safety, Efficacy (day 60 egg count), Dose-finding in Children Weighing 27-33 kg. | In-patient for one week, 2 out-patient assessments days 30 and 60 | 20/group                       | + <i>F. hepatica</i> eggs in stool, <b>≤13 years of age</b> , 27-33 kg weight | 1 (La Pa, Bolivia)              |
| <b>WHO/CIBA B2202 (Chile)</b>               | Single center, open label, non-randomized, single arm             | 10 mg/kg x 1, fasted                                                                                                          | Safety, Efficacy (day 60 egg count)                                              | In-patient for one week, 2 out-patient assessments days 30        | 24                             | + <i>F. hepatica</i> eggs in stool, Non-pregnant, <b>adult</b> males/females  | 1 (Santiago, Chile)             |

NDA Multi-Disciplinary Review and Evaluation – NDA

| Trial Identity                   | Trial Design                                          | Regimen/<br>schedule/ route                                                                                                                                                                           | Study Endpoints                                   | Treatment<br>Duration/<br>Follow Up                               | No. of<br>patients<br>enrolled                                                  | Study<br>Population                                                          | No. of Centers<br>and Countries |
|----------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------|
|                                  |                                                       |                                                                                                                                                                                                       |                                                   | and 60                                                            |                                                                                 |                                                                              |                                 |
| <b>WHO/CIBA<br/>B2201 (Iran)</b> | Multi-center, open label, non-randomized              | 4 groups:<br>a. 15 mg/kg in 3 divided doses of 5 mg/kg at 24-hour intervals, fasted<br>b. 10 mg/kg in 2 divided doses at 6-8-hour intervals, fasted<br>c. 10 mg/kg x 1 fasting<br>d. 10 mg/kg x 1 fed | Safety, efficacy (day 60 egg count), dose-finding | In-patient for one week, 2 out-patient assessments days 30 and 60 | Groups:<br>Efficacy/<br>Safety<br>a. 17/17<br>b. 14/14<br>c. 17/17<br>d. 20/54* | + <i>F. hepatica</i> eggs in stool, Non-pregnant, <b>adult</b> males/females | 1 (Tehran, Iran)                |
| <b>WHO/CIBA<br/>B2203 (Cuba)</b> | Single center, open label, non-randomized, single arm | 10 mg/kg x 1 fasted                                                                                                                                                                                   | Safety, Efficacy (day 60 egg count)               | In-patient for one week, 2 out-patient assessments days 30 and 60 | 15                                                                              | + <i>F. hepatica</i> eggs in stool, Non-pregnant, <b>adult</b> males/females | 1 (Havana, Cuba)                |

\*Study B2201, n=20 evaluated for efficacy includes only patients with at least one Kato-Katz/Telemann slide positive for *F. hepatica* eggs at study entry. No explanation was given for the large number of non-efficacy eligible patients who were treated.

Source: Reviewer created

### 7.1.1. Data and Analysis Quality

The three published studies for which patient-level data were supplied, Hien, Keiser, and Maco, were completed and published by researchers independent of the Applicant. The data submitted were obtained retrospectively by the Applicant for purposes of this submission and are only in the legacy format, i.e. there are no ADaM converted data. Given that these studies were neither designed nor conducted for regulatory purposes, the data are not in the standard CDISC format. An audit of the Maco study performed during the NDA reviewed revealed gaps in the available source data at the study site. Specifically, while data on all 84 enrolled patients were maintained in an Excel spreadsheet, data collection forms (source data) were unavailable for 26 of these patients and incomplete for the remaining 58 patients. In addition, original laboratory reports (paper format) for stool tests are no longer available. The Maco study is viewed as supportive for purposes of this review.

Individual randomization codes or algorithms were not provided. Only the Hien study was comparative, but was open-label; therefore, blinding standards do not apply.

Final protocols were supplied for the Maco and the Keiser studies; however, neither protocol outlines the primary and secondary analysis and there are no separate statistical analysis plans (SAP) available. In addition, the protocol for the Maco study is specific to only one site and included Fasinex; however, the results of the study show that there were multiple sites involved and both Egaten and Fasinex formulations were used. Therefore, this protocol does not appear to be the final version. The authors of the Hien study did not supply a protocol or a SAP. Blank copies of the case report forms were provided for all three studies.

Overall, the data and protocols supporting this application are of a lower quality compared to clinical data and documentation often included in an NDA submission. Refer to section 7.2 for specific issues for each study.

Data were reconstructed from CSRs for the six WHO/CIBA studies and, therefore, do not represent the original data. The reviewer identified at least 43 patients who were included in the efficacy analyses from three studies (Iran, Cuba and Peru) for which data on age and sex were missing in the datasets but were reported in the CSRs. For these patients, the reviewer reconstructed the missing fields using the patient line listings.

Across all studies in chronic fascioliasis, the primary endpoint was parasitological cure defined as the absence of *F. hepatica* eggs at a pre-specified time point (e.g. day 60). The stool assessment was commonly performed using the Kato-Katz (KK) technique, which is an established qualitative and semi-quantitative approach to diagnosis intestinal helminthic infestations. Refer to the Clinical Microbiology review in Section 8 for further details on this technique.

While there is no established primary endpoint in the assessment of acute fasciolosis treatment responses, absence or reduction of clinical signs and symptoms, including abdominal pain, are often used to assess treatment response.

#### **7.1.2. Compliance with Good Clinical Practices**

None of the three main publications (Hien, Keiser, or Maco) state that the studies were performed per GCPs; however, after the NDA submission the Applicant obtained verbal concurrence from the investigators that the studies were per GCP.

The six WHO/CIBA studies were all conducted in the 1980s prior to GCP requirements.

#### **7.1.3. Financial Disclosure**

The Applicant did not sponsor the studies supporting this application. CIBA provided the study drug used in the WHO/CIBA studies.

#### **7.1.4. Protocol Violations/Deviations**

Hien (2008)

Cannot be assessed given the lack of a study protocol or analysis plan.

Keiser (2011)

No protocol amendments were submitted. Differences between the study protocol and the published study design are outlined in 7.2.1.

Maco (2015)

No protocol amendments were submitted. The differences between the study protocol and the published study design are outlined in 7.2.2.

### **7.2. Studies with Patient-Level Data Supporting Efficacy**

#### **7.2.1. Hien et al. (2008)**

#### **Study Design and Endpoints**

##### **Study Design**

As described in the publication, this was a randomized, active-control, open-label pilot study of artesunate versus TCBZ for the treatment of fascioliasis conducted at a single center, in the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. The trial was registered online with the International Standardized Randomized Controlled Trial Number (ISRCTN) registry and assigned number 75869075.

Patients were randomly allocated in a 1:1 ratio to receive either two doses of Egaten® 10 mg/kg 12 hours apart or artesunate (b) (4) 4 mg/kg once a day for 10 days. All patients were hospitalized for 10 days and had directly-observed therapy for study drug. Food intake at the time of study treatment was unspecified.

All patients had a full history and physical examination. Complete blood count including absolute eosinophil count and percentage, alanine amino transferase (ALT), aspartate amino transferase (AST), serology using a *Fasciola*-specific ELISA, and liver ultrasound scan were performed at study entry, hospital discharge, and 3 months post-treatment.

*Statistical Comments:*

- 1) *The main issue in using this study to assess the efficacy of TCBZ in acute fascioliasis is that the dose of TCBZ evaluated was (b) (4) the proposed dose. Efficacy from this trial (b) (4)*
- 2) *This study was conducted with the primary objective to evaluate the efficacy of artesunate. TCBZ served as the standard-of-care against which artesunate was evaluated. However, given the poor long-term results of artesunate, efficacy of TCBZ may be supported based on its superiority to artesunate at 3 months.*
- 3) *Per the publication, a random sequence was generated using Microsoft Excel. No other information is given regarding this random sequence approach and, therefore, it cannot be determined how valid this approach was in generating the sequence for randomization.*

**Key Inclusion and Exclusion Criteria**

Key inclusion criteria were age > 8 years and meeting the case definition consisting of all the following:

- abdominal pain, fever, itch, uticular rash, jaundice;
- ultrasound scan of the liver consistent with fascioliasis
- Positive *Fasciola* serology
- Eosinophilia > 400,000 cells/mL
- Living in an endemic area for *fasciolosis*

**Endpoints**

**Primary Endpoint:** Resolution of abdominal pain at hospital discharge (day 10)

*Statistical Comment: The primary endpoint stated in the publication is different than that stated on the ISCRTN listing, which is ‘clinical improvement in presenting complaint’.*

**Secondary Endpoint:** Complete response rate at three months post-treatment defined as all three of the following a) resolution of clinical symptoms; b) normalization of eosinophil count (value ≤ 400 counts/μL); and c) improvement in ultrasound appearance. These parameters were also evaluated individually at three months post-treatment.

Although the authors evaluated response at 10 days post-treatment, this review will focus on the results at three-months post-treatment, which is a more informative measure of treatment response.

### **Statistical Methodology**

*Statistical Comment: There is no Statistical Analyses Plan for this study.*

The authors calculated a required sample size of 100 patients assuming a 70% cure rate in the TCBZ arm and at least 80% power to detect a difference of 27% between the treatment arms with a type-I error of 5%. The statistical reviewer verified this sample size calculation using both an exact and a normal distribution methodology. Using either approach, the power exceeds 90% given the stated assumptions.

Baseline characteristics were described using frequency and proportion for categorical variables and median, interquartile range and range for continuous variables.

The Fisher's exact test was used to analyze the primary endpoint of resolution of abdominal pain at discharge (day 10) and the secondary endpoint of complete response. The primary endpoint was analyzed in all randomized patients, defined as the ITT population. The publication includes several findings in the per protocol population; however, the population was not defined.

Other findings at hospital discharge were compared using analysis of covariance (ANCOVA) for continuous endpoints and the Fisher's exact test for discrete endpoints. The relative risk and associated 95% confidence interval was calculated for complete response, eosinophil  $\leq 400$  counts/ $\mu\text{L}$ , improvement in ultrasound scan appearance and no clinical symptoms all measured at 3 months and being abdominal pain free at discharge.

*Statistical Comment: Additional study data collected by the investigators, but not presented in the publication, include ultrasound findings, ELISA results, and eosinophil count at months 6, 9, 12, and 18. There are limitations with these data due to a large amount of missing data after month 3.*

### **Results**

#### **Patient Disposition, Demographics and Baseline Characteristics**

Patients were evaluated up through hospital discharge and at month 3 post-discharge. No details are provided on patients lost to follow-up at the 3-month assessment. There were 4/50 (8%) and 8/50 (16%) TCBZ and artesunate patients missing data at 3 months follow-up, respectively; however, no details were provided as to reasons for missing data. Of these subjects with missing data, 1 TCBZ and 2 artesunate patients had some information at a 6

months follow-up.

Baseline characteristics appear balanced except for days of illness. There is a broader spread of days of illness in the TCBZ arm than the artesunate arm. This spread was identified in the paper as well. There were seven subjects with duration of illness longer than 100 days on the TCBZ arm and none on the artesunate arm. Given the observed numerical imbalance in days of illness at baseline, the statistical reviewer calculated the standardized difference-or Cohen's d, which is a qualitative measure of the average difference between means or proportions, expressed in units of the standard deviation and therefore is not influenced by sample size. The standardized difference in days of illness is -0.48, which suggests a medium lack of complete overlap between groups on this baseline factor and therefore this factor can be further explored in the primary endpoint analysis to determine any influence on the overall results.

**Table 7.2: Patient Demographics and Characteristics (Hien, 2008)**

| Variable                                         | TCBZ<br>10 mg/kg BID x 1 day | Artesunate<br>4 mg/kg QD x 10 days | Standardized<br>Difference <sup>^</sup> |
|--------------------------------------------------|------------------------------|------------------------------------|-----------------------------------------|
| <b>N Randomized</b>                              | 50                           | 50                                 |                                         |
| <b>Sex (%)</b>                                   |                              |                                    |                                         |
| Female                                           | 28 (56)                      | 34 (68)                            | 0.21                                    |
| Male                                             | 22 (44)                      | 16 (32)                            |                                         |
| <b>Age</b>                                       |                              |                                    |                                         |
| Mean (SD)                                        | 32.0 (14.2)                  | 31.7 (11.5)                        | 0.02                                    |
| Median (range)                                   | 29.5 (13, 74)                | 29.5 (9, 65)                       |                                         |
| <b>Days of Illness</b>                           |                              |                                    |                                         |
| Mean (SD)                                        | 55.9 (60.5)                  | 33.2 (21.0)                        | -0.48                                   |
| Median (range)                                   | 30 (7, <b>365</b> )          | 30 (7, 90)                         |                                         |
| <b>Abdominal Pain</b>                            | 49 (98)                      | 50 (100)                           | 0.20                                    |
| <b>Fever (%)</b>                                 | 20 (40)                      | 14 (28)                            | 0.21                                    |
| <b>Itching (%)</b>                               | 6 (12)                       | 4 (8)                              | 0.11                                    |
| <b>Eosinophil (%)</b>                            |                              |                                    |                                         |
| Mean (SD)                                        | 35.5 (14.2)                  | 33.7 (14.9)                        | 0.12                                    |
| Median (range)                                   | 34 (11, 69)                  | 30 (8, 67)                         |                                         |
| <b>Eosinophil count (cell/<math>\mu</math>L)</b> |                              |                                    |                                         |
| Mean (SD)                                        | 4323.1 (2880)                | 4011.5 (2715.5)                    | 0.11                                    |
| Median (range)                                   | 3354 (942, 12900)            | 3250 (756, 10400)                  |                                         |
| <b>ALT (UI/L)</b>                                |                              |                                    |                                         |
| Mean (SD)                                        | 29.9 (11.0)                  | 28.2 (12.0)                        | 0.14                                    |
| Median (range)                                   | 27 (15, 65)                  | 25 (14, 75)                        |                                         |
| <b>AST (UI/L)</b>                                |                              |                                    |                                         |
| Mean (SD)                                        | 37.3 (18.0)                  | 36.4 (18.4)                        | 0.05                                    |
| Median (range)                                   | 32.5 (16, 91)                | 32 (12, 105)                       |                                         |

<sup>^</sup>Cohen's d defined as the difference in means (or proportions)/pooled standard deviation

Source: Reviewer created table using patient-level data

## Efficacy Results – Primary Endpoint

The majority of the 100 randomized patients were abdominal pain free at the time of discharge with the results favoring the artesunate arm (100% vs. 88%) (Table 7.3). Note that there was one patient in the TCBZ arm without abdominal pain at randomization but omitting this patient in a sensitivity analysis does not alter the overall findings. Less than half of the patients in each arm reported fever at baseline. Results are reported based on the ITT population and on the subset of those with fever at baseline. Note that seven subjects on the artesunate arm had fever at Day 10 but did not have fever at baseline. Finally, few patients achieved an eosinophil count less than or equal to 400 count/ $\mu\text{L}$  by time of discharge (day 10)-a finding consistent with the clinical expectations of the amount of time needed to return to normal in eosinophil count after the treatment for fascioliasis.

Again, it is important to highlight that the evaluated dose of TCBZ dose was 10 mg/kg BID, (b) (4)

**Table 7.3: Clinical Outcomes at Hospital Discharge (Day 10) (Hien, 2008)**

|                                                            | TCBZ (T)<br>10 mg/kg BID x 1d | Artesunate (A)<br>4 mg/kg QD x 10d | Diff (T-A) 95% CI, p <sup>^</sup> |
|------------------------------------------------------------|-------------------------------|------------------------------------|-----------------------------------|
| <b>No Abdominal Pain</b> (primary endpoint in publication) | <b>44/50 (88)</b>             | <b>50/50 (100)</b>                 | <b>-12 (-21.5, -1.5), 0.027</b>   |
| No Abdominal Pain *                                        | 43/49 (87.8)                  | 50/50 (100)                        | -12.2 (-22.0, -1.6), 0.023        |
| No Fever                                                   | 50/50 (100)                   | 42/50 (84)                         | 16 (4.4, 26.3), 0.006             |
| No Fever *                                                 | 20/20 (100)                   | 13/14 (92.9)                       | 7.1 (-10.4, 26.3), 0.41           |
| Eosinophil $\leq$ 400 counts/ $\mu\text{L}$ #              | 0/50 (0)                      | 3/50 (6)                           | -6 (-13.9, 2.4), 0.12             |

TCBZ=triclabendazole; <sup>^</sup>Fisher's Exact test

\*Subset with symptoms at baseline; #missing eosinophil (n=2 TCBZ, n=4 artesunate) imputed as >400 counts/ $\mu\text{L}$

Source: Reviewer created using patient-level data

Results at three months post-treatment are summarized in Table 7.4. The proportion of patients with no clinical symptoms (abdominal pain, fever, itchiness, urticarial rash or jaundice) per patient self-report or report by the patient's relatives (treating missing as a failure) numerically favored the TCBZ arm yielding a 16% difference, 95% CI (1.7%, 30.8%). Specifically, four and eight patients in the TCBZ and artesunate groups, respectively, were missing at the 3-month assessment are therefore imputed as failures. Among patients with reported clinical outcome at three months, zero and four patients in the TCBZ and artesunate groups, respectively, reported one or more clinical symptoms (specific symptoms unspecified).

A sensitivity analysis treating missing as success yielded proportions of patients with no clinical symptoms at three months of 100% and 92% in the TCBZ and artesunate groups, respectively (p=0.09, Boschloo's exact test). Boschloo's test is an unconditional exact test that is uniformly

more powerful than the Fisher's exact test and therefore often preferred. This is a conservative analysis given that there were more missing on the artesunate arm than the TCBZ arm thus treating missing as success can artificially deflate the TCBZ effect size. There is still a trend for higher success for TCBZ, though significance is not maintained. Finally, a post-hoc, per-protocol analysis omitting patients with missing data, yielded a proportion of no clinical symptoms at month 4 of 100% and 90.5% in the TCBZ and artesunate arms, respectively yielding a p-value of 0.038, 95% CI (13.5, 22.2).

The proportions of patients with a normal ultrasound study or a decrease in eosinophil count below 400/uL favored the TCBZ arm. A value above 400/uL was imputed for the four and eight TCBZ and artesunate patients, respectively, missing data at month 3. These findings are consistent with those reported in the publication.

An additional endpoint, which was derived by the reviewer, comprising absence of abdominal pain and eosinophil count below 400/ $\mu$ L-both required to be considered having reached the additional endpoint-also trended in favor of the TCBZ arm over artesunate at three months post-treatment (Table 7.4). These findings suggest that while artesunate performed better than TCBZ on initial symptom resolution at day 10, that TCBZ fared better long term as measured by a return to normal eosinophil count. Note that all patients with normal eosinophil counts were also abdominal pain free at three months. That said, three months post-treatment is potentially too short a measure for a return to normal eosinophil count. This can be deduced by the finding that less than 20-45% of the study population achieved a normal count. In the publication discussion, the authors address this finding by stating that "*The background presence of other enteric parasites in our population is high (for example, hookworm ova positivity approaches 65%), and the difference in eosinophilia resolution might represent differences in other antihelminthic activity of artesunate and TCBZ, although TCBZ is notable for its narrow spectrum.*" Ultimately, this illustrates the challenge in defining the appropriate clinical measure in treating acute fascioliasis.

A measure of stool parasite count would have added to the overall interpretation of treatment effect; however, no stool samples were collected in this study.

**Table 7.4: Clinical Outcomes at Month 3 in ITT (Hien, 2008)**

|                                                 | TCBZ (T)<br>10 mg/kg BID x 1d | Artesunate (A)<br>4 mg/kg QD x 10d | Diff (T-A) 95% CI                              |
|-------------------------------------------------|-------------------------------|------------------------------------|------------------------------------------------|
|                                                 | n/N (%)                       | n/N (%)                            |                                                |
| No Clinical Symptoms*                           | 46/50 (92)                    | 38/50 (76)                         | 16 (1.7, 30.8)<br><i>p</i> =0.035 <sup>^</sup> |
| Presence of Clinical Symptoms                   | 0                             | 4                                  |                                                |
| Missing Assessment                              | 4                             | 8                                  |                                                |
| Normal Ultrasound**                             | 19/50 (38)                    | 10/50 (20)                         | 18 (0.012, 35.0)                               |
| Eosinophil ≤ 400 (ITT)#                         | 21/50 (42)                    | 8/50 (16)                          | 26 (8.3, 42.4)                                 |
| Eosinophil ≤ 400 <b>and</b> No Abdominal Pain*# | 21/50 (42)                    | 8/50 (16)                          | 26 (8.3, 42.4)                                 |

TCBZ=triclabendazole

\*The no clinical symptoms endpoint is based on no reported abdominal pain, fever, itchiness, urticarial rash or jaundice among persons with a follow-up report at month 3. This included information by self-report or by patient's relatives.

<sup>^</sup>Boschloo's test

\*\*Ultrasound missing in 4 TCBZ and 8 artesunate patients; imputed as non-normal

#Missing eosinophil (n=4 TCBZ, n=8 artesunate) imputed as >400/uL

Source: Reviewer created table using patient-level data

In addition to the sensitivity analyses discussed above, we fully explored the impact of missing data on the endpoints of no clinical symptoms, normal ultrasound and eosinophil count ≤ 400/uL at the month 3. For the endpoints of normal ultrasound and eosinophil count ≤ 400/uL, we utilized data from the month 6 assessment for those patients who were missing data at month 3 but had an available month 6 assessment (one TCBZ and two artesunate subjects). The one TCBZ subject had a normal ultrasound and eosinophil count of 389/uL. The two artesunate subjects did not have normal ultrasounds and had eosinophil counts of 571 and 574/uL. Results of these analyses further strengthened the results supporting the overall efficacy of TCBZ when considering improvements in eosinophil counts and ultrasound along with clinical response. We also conducted a thorough assessment considering all possible ways the subjects with missing data could have impacted the results. The results for no clinical symptoms are sensitive to the handling of missing data, while the results of normal ultrasound are slightly less sensitive. However, the results of eosinophil count ≤ 400/uL are very strong and not overly impacted by missing data.

### Findings in Special/Subgroup Populations

Subgroup findings were not reported in the publication by Hien and colleagues; however, the reviewer assessed a few endpoints by sex (Table 7.5) and age (results not displayed). Results at discharge and at month 3 for the absence of clinical symptoms endpoint were consistent between sexes; however, there were inconsistent results for return to normal eosinophil level. More female patients in the TCBZ group were pain free with a return to normal eosinophil level compared to females in the artesunate arm; however, no differences between groups were observed among male subjects. A similar trend was observed among females with a normal

ultrasound study at three months post-treatment with a larger effect seen in females than males. It is difficult to draw any conclusions regarding possible interactions by sex given the small numbers in each subgroup. Note that there were no TCBZ patients and only 1 artesunate patient less than 13 years of age.

**Table 7.5: Efficacy by Sex (Hien, 2008)**

|                                           | TCBZ (T)<br>10 mg/kg BID x 1d | Artesunate (A)<br>4 mg/kg QD x 10d | Diff (T-A) 95% CI  |
|-------------------------------------------|-------------------------------|------------------------------------|--------------------|
| <b>Abdominal Pain at Discharge</b>        |                               |                                    |                    |
| Male                                      | 2/22 (9)                      | 0/16 (0)                           | 9 (-10, 23.9)      |
| Female                                    | 4/28 (14.3)                   | 0/34 (0)                           | 14.3 (-0.5, 28.3)  |
| <b>Month 3</b>                            |                               |                                    |                    |
| <b>No Clinical Symptoms*</b>              |                               |                                    |                    |
| Male                                      | 20/22 (90.9)                  | 12/16 (75)                         | 15.9 (-9.3, 39.8)  |
| Female                                    | 26/28 (92.9)                  | 26/34 (76.5)                       | 16.4 (-2.7, 32.7)  |
| <b>Eosinophil <math>\leq</math> 400 #</b> |                               |                                    |                    |
| Male                                      | 4/22 (18.2)                   | 3/16 (18.7)                        | -0.6 (-26.5, 23.7) |
| Female                                    | 17/28 (60.7)                  | 5/34 (14.7)                        | 46.0 (22, 64.7)    |
| <b>Normal Ultrasound<sup>^</sup></b>      |                               |                                    |                    |
| Male                                      | 7/22 (31.8)                   | 4/16 (25)                          | 6.8 (-22.4, 33.6)  |
| Female                                    | 12/28 (42.9)                  | 6/34 (17.7)                        | 25.2 (1.9, 45.8)   |

TCBZ=triclabendazole

#missing eosinophil (n=4 TCBZ, n=8 artesunate) imputed as  $>400/\mu\text{L}$  (2 and 4 per sex)

\*The no clinical symptoms endpoint is based on no reported abdominal pain, fever, itchiness, urticarial rash or jaundice among persons with a follow-up report at month 3. This included information by self-report or by patient's relatives. Patients with missing critical measurements are considered failures.

<sup>^</sup>Ultrasound missing in 4 TCBZ and 8 artesunate patients; imputed as non-normal (2 and 4 per sex)

Source: Reviewer created table using patient-level data

The reviewer constructed logistic regression models including age only, sex only, sex and days ill, and days ill only covariates and treatment as a predictor variable. Age, sex, and days ill, were not shown predictive of resolution of clinical symptoms outcome when included in simple logistic regression models. A significant ( $p=0.022$ ) treatment by sex interaction was identified when fitting a logistic regression model on the eosinophil count of  $\leq 400/\mu\text{L}$  at month 3. This is a finding consistent with the subgroup analyses above by sex.

Analyses by race and region/country are not relevant as this study was conducted in a sample of Vietnamese patients at a single site.

### 7.2.1. Keiser et al. (2011)

#### Study Design and Endpoints

##### Study Design

The publication describes findings from two small, single-arm, non-concurrent studies conducted in separate locations in lower Egypt. The stated purpose was to evaluate the safety and efficacy of two artemether regimens in the treatment of asymptomatic *Fasciola*-infected patients (Current Controlled Trials reference no. ISRCTN10372301). Study 1 evaluated artemether 6 x 80 mg over three consecutive days and Study 2 evaluated artemether 3 x 200 mg within 24 hours. In Study 2 only, patients who remained *Fasciola*-positive after artemether treatment were treated with a single 10 mg/kg dose of TCBZ and re-treated again if remaining positive with a 20 mg/kg regimen of TCBZ, in two divided doses. No details were provided in the publication regarding possible re-treatment for artemether failures in Study 1 or food intake at the time of study treatment administration.

After written informed consent, participants provided a stool sample to screen for *F. hepatica* and/or *F. gigantica* eggs. Two additional stool samples were collected on consecutive days from participants who had *Fasciola* eggs in the first stool sample, with preparation of 9 KK thick smears (3 smears from each of 3 stool specimens). A blood sample was collected from these patients prior to drug administration – for hematologic, liver, and kidney function. A full clinical examination was performed at enrollment.

**Monitoring:** AEs were monitored using a standardized questionnaire on each treatment day and for 24-48 hours following dosing. Full clinical examinations were performed on all participants. AEs were graded – mild, moderate, severe, serious; appropriate therapy, judged by the study physician, was offered to patients presenting with adverse events. Follow-up after treatment was on days 4-6, and 4-5 weeks later, at which times clinical examination was done along with a CBC, ESR, WBC and differential, BUN, serum creatinine, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT) and bilirubin.

Blood samples for chemistry were collected on days 5 and 28. In Study 2, stool samples were collected starting on study day 28 for 3 consecutive days with determination of cure rates and egg reduction ratios (ERRs). In Study 2, patients on the TCBZ 10 mg/kg single treatment who were still positive for *Fasciola* eggs were retreated with TCBZ 10 mg/kg x 2 24 hours apart. Blood samples were taken from TCBZ-treated patients for liver, renal, and hematological parameters 5 and 28 days after drug administration.

Laboratory procedures were reviewed and found to be standard. Intensity of AEs was judged as mild – present, but did not require intervention; moderate – present, required medication for symptomatic relief and/or interfered with normal daily activities; severe – present and required medical intervention beyond symptomatic relief. Relatedness of AEs to study medication was determined by the study physician. Adverse events were recorded.

### **Key Inclusion and Exclusion Criteria**

Inclusion criteria: stool positive for eggs of *F. hepatica* or *gigantica*.

Exclusion criteria: age < 5 years; pregnancy; major systemic illnesses (e.g., cancer, diabetes, hypertension, chronic heart, liver or renal disease, severe liver disease of other etiology); recent

history of anthelmintic treatment (e.g., albendazole, bithionol, dehydroemetine, mebendazole, praziquantel, TCBZ taken within the past 4 weeks).

### **Statistical Methodology**

Cure rate was calculated as the proportion of individuals excreting *Fasciola* eggs before treatment and absence of eggs at study end over five consecutive days. Infection intensity was determined by the number of *Fasciola* eggs per KK thick smear (41.7 mg of stool) multiplied by a factor of 24 to obtain eggs per gram of stool (EPG). Fecal egg counts (FECs) of multiple slides per individual were averaged. To calculate reduction in infection intensity, individual egg counts were transformed logarithmically, and the geometric mean (GM) expressed as the antilog of the mean. The egg reduction rate (ERR) was  $1 - \text{GM FEC after treatment} / \text{GM FEC at admission}$  multiplied by a factor of 100. Infections were classified into two intensities: light (1-99 EPG) and moderate/heavy ( $\geq 100$  EPG).

This study was designed to compare two different regimens of artemether. The statistical analysis was not focused on clinical outcome among patients receiving TCBZ. In addition, since all TCBZ-treated patients were artemether failures, it is likely that the level of infection among these patients differs from that in a de novo population. Therefore, comparisons using data from the TCBZ-treated patients from this study against either a historical control or other data from de novo TCBZ-treated patients are difficult to interpret.

Despite this study not providing primary data on the efficacy of TCBZ, it does provide useful patient-level data on the historical control estimate using the artemether results. Artemether-treated patients likely fared better than, or least no worse than placebo/untreated patients and therefore represent a conservative comparator group. These data will serve as a control arm for comparison to the results from TCBZ-treated patients in the Maco study (7.2.2) and the WHO/CIBA studies 7.2.3. This approach, albeit suffering from limitations due to indirect comparisons, was taken given the access to patient-level data collected in these studies.

### **Protocol Deviation**

The protocol states an age range of 11-70 years; however, the publication reports an age  $\geq 5$  years.

### **Results**

#### **Patient Disposition, Demographics and Baseline Characteristics**

Few patients (n=37) were treated in this study with ages ranging from 5 to 70 years, roughly half were males, and a median pre-treatment EPG of 23-28.

**Table 7.6: Baseline Characteristics in Artemether-Treated Patients (Keiser, 2011)**

| Variable               | Artemether<br>6 x 80 mg<br>N=20 | Artemether<br>3 x 200 mg<br>N=17 | Artemether<br>Combined<br>N=37 |
|------------------------|---------------------------------|----------------------------------|--------------------------------|
| Median Age (range)     | 11 (5, 70)                      | 14 (5, 26)                       | 12 (5, 70)                     |
| Sex (m/f)              | 10/10                           | 7/10                             | 17/20                          |
| Screening EPG Sample 1 | n=20                            | n=11                             | N=31                           |
| Mean (SD)              | 61.2 (85.3)                     | 38.2 (42.7)                      | 53.0 (73.1)                    |
| Median (range)         | 32 (0, 344)                     | 16 (8, 152)                      | 32 (0, 344)                    |
| Screening EPG Sample 2 | n=20                            | n=17                             | N=37                           |
| Mean (SD)              | 83.6 (122.8)                    | 51.8 (83.0)                      | 69.0 (106.2)                   |
| Median (range)         | 16 (0, 392)                     | 32 (0, 312)                      | 24 (0, 392)                    |
| Screening EPG Sample 3 | n=20                            | n=13                             | N=33                           |
| Mean (SD)              | 39.6 (87.3)                     | 54.5 (76.8)                      | 45.5 (82.4)                    |
| Median (range)         | 8 (0, 392)                      | 16 (0, 244)                      | 8 (0, 392)                     |
| Screening EPG*         |                                 |                                  |                                |
| Mean (SD)              | 61.5 (74.1)                     | 50.0 (50.1)                      | 55.7 (63.6)                    |
| Median (range)         | 22.7 (0, 219) ^                 | 28 (3, 156)                      | 24 (0, 219)                    |

\*Arithmetic average among screening samples (missing values omitted)

^one patient with zero values for all three screening samples but had positive stool in post-enrollment assessment.

Source: Reviewer created

### Efficacy Findings

Among 20 patients treated with 6 x 80 mg artemether, 7 (35%) were cured on day 28 after final dosing (Study 1). In the second study of patients who received artemether 3 x 200 mg over 24 hours, only one out of 17 (6%) was cured on day 28. All 37 patients had at least one stool assessment on day 28. All seven patients in the artemether 6 x 80 mg group had five consecutive negative stool samples. The patient in the artemether 3 x 200 mg group had three negative stool samples (missing final two).

**Table 7.7: Day 28 Parasitological Cure in Artemether-Treated Patients (Keiser study)**

|                               | Artemether<br>6 x 80 mg<br>N=20 | Artemether<br>3 x 200 mg<br>N=17 | Artemether<br>Combined<br>N=37 |
|-------------------------------|---------------------------------|----------------------------------|--------------------------------|
| Parasitological Cure (Day 28) | 7 (35%)                         | 1 (6%)                           | 8 (21.6%)                      |
| 95% CI (Clopper-Pearson)      | 15.4, 59.2                      | 0.1, 29.7                        | 9.8, 38.2                      |

Source: Reviewer created

### Efficacy of TCBZ Rescue Treatment

Of the 16 artemether failures in study 2 who were treated with TCBZ, 10 (62.5%) were female,

mean (SD)/median age of 14.3 (5.8)/14 years. Eleven (68.7%) of these 16 patients were cured by day 28 after TCBZ treatment (Table 7.8). The EPGs stool counts of the five patients remaining positive were 0, 5, 6, 20 and 10. The patient <sup>(b) (6)</sup> with the zero count on the third assessment failed to achieve three consecutive negative counts (first measure was 15). Of the TCBZ failures, three out of four re-treated with 20 mg/kg (split dose) TCBZ were cured.

**Table 7.8: Day 28 TCBZ Cure Rate (Keiser, 2011)**

|                            | Pre-Trt <i>Fasciola</i> Egg Stool<br>GM (range)* | Cured        | Failure        |
|----------------------------|--------------------------------------------------|--------------|----------------|
| TCBZ 10 mg/kg single dose^ | 37.7 (5-285)                                     | 11/16 (68.7) | 5/16 (31.3) ** |

TCBZ=triclabendazole, ^ patients treated with TCBZ after failing prior regimen of artemether 3 x 200 mg over 24 hours

\*GM=geometric mean, 5 patients omitted due to missing values

\*\*3 out of 4 re-treated with 20 mg/kg TCBZ (split-dose)

Source: Reviewer created

Too few patients were treated with TCBZ in this study (n=16) to allow for an interpretative analysis by sex, age or any other subgroup.

### 7.2.2. Maco et al. (2015)

#### Study Design and Endpoints

##### Study Design

This was an open-label, randomized, Phase 2, dose-response, multicenter trial conducted between 2001 and 2006 in five rural areas in Peru with known fascioliasis endemicity. When the study began, Egaten<sup>®</sup> was unavailable in Peru; therefore, the veterinary preparation - Fasinex<sup>®</sup> - was used at one (Asillo) site. Later after Egaten became available, four additional sites were added, and all patients treated at these sites received Egaten.

##### *Statistical Comments:*

- 1) *The protocol appears to be more like a study concept sheet with some details on the Fasinex product but is otherwise lacking in detail concerning study visit data collection and data analyses.*
- 2) *The protocol is specific only to the evaluation of Fasinex at a single site in the Asillo-Azangaro district in approximately 60 children with fascioliasis infection. However, the Maco publication describes the results conducted across five areas in Peru in 84 children. Several other differences were noted between the protocol and the study design described in the publication; however, no protocol amendments were noted in the Applicant's submission. The differences are listed in Table 7.9.*
- 3) *As stated in Section 7.1, an audit of this study was unable to verify all patient-level data submitted in this NDA. Therefore, findings from this study are viewed as supportive only.*

**Table 7.9 Differences Between Original Study Protocol and Maco Published Study Design**

| Variable           | Study Protocol                                                                  | Study Design in Publication                                          |
|--------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Age Range          | 4-15 years                                                                      | 2-16 years                                                           |
| Study Site         | Single site – Progreso, Azangaro, Puno (Asillo)                                 | Multiple sites – 5 endemic areas                                     |
| Inclusion Criteria | Eggs in >2 stool samples + pos Fas2-ELISA                                       | Eggs in at least 1 stool sample + Fas2-ELISA offered                 |
| Drug               | Fasinex only                                                                    | Fasinex at one site; Egaten at the other 4 sites                     |
| Patient Monitoring | Stool samples on Days 1, 3, 5, 10, 20, 30, 60, 90 post-treatment in Asillo site | Stool samples on Days 5, 10, 30 and 60 post-treatment in other sites |

As per the protocol, the study objective was to evaluate the therapeutic efficacy of Fasinex in children infected with *Fasciola hepatica*. The protocol-stated hypotheses were:

- Null: The efficacy of the 7.5 mg/kg body weight two-dose regimen is greater than or equal to single dose of 10 mg/kg body weight regimen.
- Alternative: The 7.5 mg/kg body weight two-dose regimen has a lower efficacy than or equal to single dose of 10 mg/kg body weight regimen.

### Key Inclusion and Exclusion Criteria

Inclusion criteria: Eligible patients had to meet the case definition that included (as outlined in the publication) age 2-16 years residing in a study site at the time of recruitment with confirmed fascioliasis (presence of characteristic eggs of *F. hepatica* [130-150 µm x 80-85 µm operculate eggs] in at least 1 stool sample using the rapid sedimentation technique (RST) and/or the KK method.

Exclusion criteria: acute or severe illness during the study period; known chronic liver disease; known pregnancy, lactation or a positive urine test for β-human chorionic gonadotrophin hormone; drug therapy for *F. hepatica* or other parasitic infection administered 30 days before enrollment; history of allergy to benzimidazoles; and/or concurrent use of drugs with known TCBZ interactions.

### Endpoints

**Primary Endpoint:** Presence (parasitological failure) or absence (parasitological cure) of eggs compatible with *F. hepatica* in stool diagnosed either by the rapid sedimentation technique (RST) or KK preparation.

**Secondary Endpoint:** TCBZ tolerability assessed by evaluation for symptoms and signs at each site (Peripheral Primary Health Care Centers) daily during the first 7 days post-treatment for close surveillance and directed intervention with any adverse events. A physician at each site recorded demographic data and daily signs, symptoms, AEs. Pain was stratified as: severe (symptoms required observation and treatment by the physician at the health care center); moderate (symptoms were managed at home and did not require physician intervention); or

mild (symptoms did not require intervention and were reported to the physician during follow-up). Routine physical examinations were performed on a periodic schedule until day 90.

### **Treatment and Assessments**

Eligible patients were sequentially assigned to 1 of 2 therapies using block (size not specified) randomization:

- Group 1: TCBZ 15 mg/kg orally in two 7.5 mg/kg doses after breakfast and dinner separated by a 12-hour interval
- Group 2: TCBZ 10 mg/kg single dose of 30 minutes after breakfast or dinner.

One pre-treatment KK thick smear was performed on all stool samples, and 6 post-treatment stool samples were examined on post-treatment days 1, 3, 5, 10, 30 and 60 in Asillo and days 30, 60, 90, 120, 150 and 180 in Lachaqui, Anta, Sicuani, and Jauja. All stool samples were transported to, and examined by, a central laboratory in Lima, Peru and examined by an experienced technician using RST for qualitative diagnosis.

Quantitative assessment of infection intensity was only performed on participants from the district of Asillo. Post-treatment stool samples were collected for KK thick smears every other day during the first week (days 1,3,5) and then on days 10, 30 and 60. Serology and eosinophilia were assessed to evaluate the subgroup homogeneity prior to treatment allocation. An ELISA assessment for IgG against the 25 KDa excretory/secretory antigen Fas2 was offered; a value of >0.2 units of optical density (OD) measured at 450 nm was considered positive. A CBC to measure baseline eosinophilia (>500/cc) was also performed.

### **Statistical Methodology**

*Statistical Comment: No SAP was provided. Additionally, the section in the protocol on analysis and interpretation of data is incomplete. The section on inferential analyses states the 'results will be analyzed in SPSS 9.0 and Epi Info' only. No additional details are provided. Therefore, the reviewer is unable to verify that the methods used to analyze the data are the methods originally intended.*

Per the authors, a sample size calculation was not performed as the study was designed to estimate the dose-response and safety of TCBZ. As per the authors, univariate analyses for frequencies, percentages and 95% confidence intervals for discrete variables and mean and standard deviation for continuous variables were performed using SPSS and STATA software. Bivariate analyses using Chi-square and Student's t-tests were performed for discrete and continuous variables respectively, and a p-value of <0.05 was considered statistically significant for all tests. AEs were reported and tabulated for each regimen.

### **Results**

#### **Patient Disposition, Demographics and Baseline Characteristics**

The study enrolled 84 pediatric patients with an average age of 9.2 and 9.3 years and mean EPG stool counts of 190 and 202 in the 7.5 mg/kg BID and 10 mg/kg single dose arms, respectively. The authors note that ‘none of the children had a high-intensity infection [ $>400\text{EPG}$ ]’; however, the data suggest otherwise. There were two patients-both at the Asillo site-with baseline EPGs of 480 and 528, respectively. In a subset of patients with a baseline eosinophil measurement, the median values were 328 and 497 cells/cc.

**Table 7.10: Baseline Demographics and Characteristics (Maco, 2015)**

| Variable               | TCBZ                         | TCBZ                         |
|------------------------|------------------------------|------------------------------|
|                        | 7.5 mg/kg BID, 1 day<br>N=44 | 10 mg/kg single dose<br>N=40 |
| Mean Age (range)       | 9.2 (4, 15)                  | 9.3 (2, 13)                  |
| Sex (m/f)              | 18/26                        | 20/20                        |
| EPG Stool              |                              |                              |
| Mean (SD)              | 190 (104)                    | 202 (102)                    |
| Median (range)         | 168 (24, 528)                | 180 (48,480)                 |
| Fas 2 ELISA            | N=25                         | N=23                         |
| Median (range)         | 0.38 (0.01, 0.5)             | 0.41 (0.02, 0.5)             |
| Eosinophils (cells/cc) | N=21                         | N=16                         |
| Mean (SD)              | 745 (1121)                   | 1049 (1730)                  |
| Median (range)         | 328 (0, 5124)                | 497 (0, 7150)                |

Source: Reviewer created

### Efficacy Results

This study yielded a day 60 parasitological cure rate (negative stool) of 100% and 95% in the TCBZ 7.5 mg/kg BID x 2 days and 10 mg/kg single dose groups, respectively (Table 7.11). Rates were similar at the earlier day 30 assessment. In the subset of patients who received the Egaten formulation, all were cured by day 60 and among patients receiving Fasinex (patients enrolled at the Asillo site), all but two in the 10 mg/kg single dose group were cured by day 60. These two patients received an additional dose of 10 mg/kg TCBZ between day 30 and day 60 and are therefore counted as failures by the reviewer. In the supplied datasets, there were no missing values for the day 30 and day 60 stool assessments.

**Table 7.11: Parasitological Cure Rates (Maco, 2015)**

|                     | TCBZ                 | TCBZ                 | Diff (95% CI), p <sup>^</sup> |
|---------------------|----------------------|----------------------|-------------------------------|
|                     | 7.5 mg/kg BID, 1 day | 10 mg/kg single dose |                               |
| <b>All Enrolled</b> |                      |                      |                               |
| Day 30              | 43/44 (97.7)         | 38/40 (95)           |                               |
| Day 60              | 44/44 (100)          | 38/40 (95) *         | 5% (-4.1, 14.1), 0.43         |
| Received Egaten     |                      |                      |                               |

|                    | TCBZ<br>7.5 mg/kg BID, 1 day | TCBZ<br>10 mg/kg single dose | Diff (95% CI), p <sup>^</sup> |
|--------------------|------------------------------|------------------------------|-------------------------------|
| Day 30             | 12/13 (92.3)                 | 12/12 (100)                  |                               |
| Day 60             | 13/13 (100)                  | 12/12 (100)                  |                               |
| Received Fasinex** |                              |                              |                               |
| Day 30             | 31/31 (100)                  | 26/28 (92.9)                 |                               |
| Day 60             | 31/31 (100)                  | 26/28 (92.9)                 |                               |

\* One patient was cleared on Day 60 but had received a second dose of 10 mg/kg on or around day 30 and therefore counted as a failure at Days 30 and 60.

\*\*Patients enrolled at the Asillo site only

<sup>^</sup>chi-square test for proportions

Source: Reviewer created

Given the high parasitological cure rate close to 100% at days 30 and 60 subgroup analysis by sex or age subgroup would not yield results that differ from the overall. The day 60 cure rates by age groupings of 2-5 years, 6-11 years, and 12-15 years was 100% (5/5), 97% (60/62) and 100% (17/17), respectively. Finally, no post-enrollment data on blood count or serology were provided.

### Comparison with Historical Controls

Since no dose response was observed in the Maco study, assessment of the study on its own does not help in the assessment of the efficacy of TCBZ. However, to further evaluate the efficacy of TCBZ, findings from the Maco study were compared against the artemether treatment findings from the Keiser study. This was reasonable given that both studies performed stool assessments using the KK method from samples collected at or near day 30 and both studies were performed in the early 2000s. Both studies enrolled children (Keiser also enrolled adult patients) with chronic fascioliasis with similar proportions of female and male patients. The key difference between studies is that the median baseline EPGs was numerically larger in the Maco study (168 EPGs) compared to the Keiser study (24 EPGs). Although both studies report using the KK method to estimate the egg count, the Maco study reports data from one specimen compared to up to three used in the Keiser study. Differences could also be associated with the fact that the Maco study was conducted in Peru and Keiser in Egypt where epidemiological differences might exist. Consequently, the higher baseline EPG in the TCBZ arm may likely lead to conservative results. These indirect comparisons of each TCBZ group to the Keiser historical control yield large differences in cure rates with confidence intervals excluding zero. Clearly, these results have limitations including the indirect comparisons of estimates derived from disparate studies conducted at different times in different regions. Despite these limitations, there is an apparent large treatment effect favoring TCBZ.

**Table 7.12:** Indirect Comparison of Parasitological Cure (Maco v. Keiser Historical Control)

| TCBZ | Historical Control<br>(Keiser) | TCBZ-Keiser Historical<br>Control, 95% CI |
|------|--------------------------------|-------------------------------------------|
|------|--------------------------------|-------------------------------------------|

|                                      | TCBZ         | Historical Control<br>(Keiser) | TCBZ-Keiser Historical<br>Control, 95% CI |
|--------------------------------------|--------------|--------------------------------|-------------------------------------------|
| <b><i>Maco (Day 30) 10 mg/kg</i></b> | 38/40 (95)   | 8/37 (21.6)                    | 73.4, (55.3, 85.1)                        |
| <b><i>Maco (Day 30) 15 mg/kg</i></b> | 43/44 (97.7) | 8/37 (21.6)                    | 76.1, (59.3, 87.0)                        |

Source: Reviewer created

Findings in an additional analysis utilizing data only from patients  $\leq 16$  years of age in the Keiser study (all Maco patients met this age cut-off) resulted in similar findings (day 28 cure of 13% in historical control).

To account for the difference between the Maco and Keiser historical control on baseline stool EPG count, a logistic regression model on cure was constructed including baseline stool EPG count (log transformed to account for skewed distribution). Treatment remains a significant predictor of cure even though baseline stool was significantly greater in the Maco TCBZ treatment arms compared to the Keiser historical control.

Age and sex were not predictive in separate models including treatment.

### 7.2.3. WHO/CIBA Studies

In collaboration with the WHO, CIBA (now Novartis) conducted six, uncontrolled, non-randomized, clinical studies using the veterinary formulation of TCBZ for treatment of chronic fascioliasis. The objectives of these studies were to explore various TCBZ doses and food effects. All but one study was conducted at a single-center and all, but one studied an adult population.

### **Study Design and Endpoints**

#### **Study Design**

All six studies were uncontrolled, single arm studies conducted in patients who were *F. hepatica* positive based on stool assessment, non-pregnant females or male adults. The exception is the pediatric study conducted in Bolivia that enrolled patients  $\leq 13$  years of age. All studies utilized the TCBZ veterinary formulation, Fasinex. For studies that evaluated more than one regimen, dosing was sequential without randomization. The following table outlines the TCBZ regimens by study and timing of parasitological cure where cure was defined as the absence of *Fasciola* eggs in fecal samples or duodenal drainage. The most commonly used approach for fecal egg counting was the KK method.

The Applicant's analysis of the day 60 parasitological cure differs slightly from the reviewer's method. Specifically, using the KK assessments (between 1 and 3 depending on the study), the Applicant chose the last non-missing assessment egg measurement and if the value was zero,

then the patient record was coded as a cure. In contrast, the reviewer’s approach considered the non-missing KK assessments for the day of interest and treated missing for that day as a failure. In addition, this approach could not be programmed directly for Study B2202 and instead cures were determined via direct evaluation of the line listing data. The reviewer also considered parasitological cure at Day 30. Only one study, B2212, collected data at day 90 preventing a pooled assessment at day 90.

**Table 7.13: WHO/CIBA Treatment Regimens**

| <b>Study</b>                      | <b>TCBZ* Regimen (Efficacy Population)</b>                                                                                                                                                        | <b>Parasitological Assessment</b> |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| <b>B2207</b><br>Bolivia           | 10 mg/kg single dose, fed (n=22)                                                                                                                                                                  | Day 30, 60                        |
| <b>B2203</b><br>Cuba              | 10 mg/kg single dose, fasting (n=14)                                                                                                                                                              | Day 30, 60                        |
| <b>B2202</b><br>Chile             | 10 mg/kg single dose, fasting (n=24)                                                                                                                                                              | Day 30, 60                        |
| <b>B2201</b><br>Iran              | <u>Sequential dosing</u><br>A. 5 mg/kg daily for 3 days, fasting (n=17)<br>B. 2 x 5 mg/kg 1 day, fasting (n=14)<br>C. 10 mg/kg single dose, fasting (n=17)<br>D. 10 mg/kg single dose, fed (n=20) | Day 30, 60                        |
| <b>B2212</b><br>Peru              | <u>Sequential dosing</u><br>A. 10 mg/kg fasting on day 1, 10 mg/kg fed on day 3 (n=10)<br>B. 10 mg/kg fed on day 1, 10 mg/kg fasting on day 3 (n=12)                                              | Day 30, 90                        |
| <b>B2208</b><br>Bolivia<br>(peds) | <u>Sequential dosing</u><br>A. 5 mg/kg single dose, fed (n=20)<br>B. 10 mg/kg single dose, fed (n=20)<br>C. 2 x 5 mg/kg fed, 1 day (n=20)                                                         | Day 30, 60                        |

*\*All received the Fasinex formulation; efficacy population includes those with positive stool for F. hepatica pre-treatment*

*Source: Reviewer created*

## **Results**

### **Patient Disposition, Demographics and Baseline Characteristics**

The following table presents patient sex and age by TCBZ total dose and fed state among all six WHO/CIBA studies. Data on demographics are limited to age and sex. The table also includes median and ranges of baseline stool counts based on the KK method. These data exclude Study B2202, which relied on rapid sedimentation for baseline eligibility determination. Baseline stool

values were similar among all studies except Study 2203 (Cuba) for which the calculated median (range) stool was 124 (32, 296) based on n=14 (10 mg/kg single dose, fasted). It is unclear why the values reported in the Cuba study vary so greatly from those in the other five studies. When excluding these data, the median values in the 10 mg/kg fasted group are similar to the median values in the other dose groups. The median values for the 20 mg/kg dose group, which comes from Study B2212, were numerically lower than the other dose group median values. It is unclear why the values differ but might be due to different sampling techniques used across study locations, varying levels of circulating fascioliasis, or other characteristics. The potential impact of this imbalance is considered below in the efficacy assessment.

**Table 7.14: WHO/CIBA Study Characteristics by Dose**

| Dose             | N (efficacy population) * | M/F   | Median Age (range) | Median (range) EPG Stool Count                       |
|------------------|---------------------------|-------|--------------------|------------------------------------------------------|
| 5 mg-fed         | 20                        | 13/7  | 9.5 (8, 12)        | 5 (2, 25)                                            |
| 10 mg-fed        | 82                        | 43/39 | 13 (7, 65)         | 6 (1, 86)                                            |
| 10 mg-fasted     | 69                        | 24/45 | 30 (11, 70)        | 13.7 (0.3, 296) ** (n=45)<br>5 (0.3, 165) *** (n=31) |
| 15 mg-fasted     | 17                        | 1/16  | 34 (10, 60)        | 4.7 (0.7, 45.7)                                      |
| 20 mg fasted/fed | 10                        | 5/5   | 44.5 (13, 62)      | 1 (1,4)                                              |
| 20 mg fed/fasted | 12                        | 6/6   | 12 (6, 50)         | 1.5 (1, 6)                                           |

\*All received the Fasinex formulation; efficacy population includes those with positive stool for *F. hepatica* pre-treatment

\*\*Based on pre-treatment Kato-Katz Slides 1-3 in all studies except study B2202 which enrolled patients based on *F. hepatica* eggs in stool using the rapid sedimentation technique.

\*\*\*Median (range) when excluding data from B2203.

Source: Reviewer created

## Efficacy Findings

The main efficacy outcome across the six WHO/CIBA studies was parasitological cure at day 60 except for Study B2212, which assessed outcome at day 90 (for purposes of the pooled analysis the day 60 was imputed using findings reported on day 30). Cure was defined as absence of *Fasciola* eggs in the stool based on the KK method in patients who were egg positive at baseline. Missing data for the day 60 measure of cure were imputed as failures. Few patients received a 5 mg/kg dose and the overall 50% cure is suboptimal. The overall combined day 60 cure rate given a 10 mg/kg total dose of TCBZ was approximately 80% (121/151). At higher doses of 15 mg/kg or 20 mg/kg total dose, the overall cure rate was between 88% and 96%. These findings suggest a dose response with the largest cure rate achieved for a total dose of

20 mg/kg (Table 7.15).

The reviewer performed a logistic regression model on day 60 cure including dose as a continuous predictor and study. The model estimate for dose was 0.42 ( $p=0.0002$ ) suggesting a significant treatment effect and that for each increase in dose, an increase in the odds of cure by 1.5-fold. When including baseline stool in the model, a significant dose response remains, and baseline stool was not shown to be significant predictor of cure. These findings were similar in logistic models on day 30 cure.

In Study B2201 (Iran), it is important to highlight that among the 54 patients enrolled to the 10 mg/kg fed regimen, only 20 were included in the efficacy analysis based on having at least one KK/Telemann slides positive for *F. hepatica* eggs at study entry. It is unclear as to why all 54 patients were originally enrolled if only 20 were positive for eggs and no explanation is given in the CSR. The overall quality of this study-specific information supplied from group D of the study appears to be lower than that of the other WHO/CIBA studies. Also, there were 1, 4, 3, and 2 patients missing the day 60 assessment in the 5 mg/kg x 3, 5 mg/kg x 2, 10 mg/kg (fasted) and 10 mg/kg (fed) dose groups, respectively. The reviewer counted missing as failure in the Day 30 and 60 assessments. Note that the Applicant's analysis included missing as success, if the prior stool assessment, e.g. Day 30, was negative.

In Study B2212, data were missing at day 60 for one patient (positive stool on day 30) and for three patients in Study B2202 at days 30 and 60.

All the remaining failures were parasitological failures, as none of the other studies reported missing EPG values at day 60.

**Table 7.15: WHO/CIBA Studies: Day 30 and 60 Cure Rates by Study and Overall**

| Study                   | Regimen (food state)                 | D30 Cure*    | D60 Cure*    |
|-------------------------|--------------------------------------|--------------|--------------|
|                         |                                      | n/N (%)      | n/N (%)      |
| B2212 Peru              | 10 mg/kg day 1 (fasted), day 3 (fed) | 9/10 (90)    | 9/10 (90)    |
|                         | 10 mg/kg day 1 (fed), day 3 (fasted) | 12/12 (100)  | 12/12 (100)  |
| B2207 Bolivia           | 10 mg/kg single dose (fed)           | 22/22 (100)  | 22/22 (100)  |
| B2208 Bolivia<br>(peds) | 5 mg/kg single dose (fed)            | 8/20 (40)    | 10/20 (50)   |
|                         | 10 mg/kg single dose (fed)           | 14/20 (70)   | 17/20 (85)   |
|                         | 2 x 5 mg/kg, 1 day (fed)             | 12/20 (60)   | 20/20 (100)  |
| B2203 Cuba              | 10 mg/kg single dose (fasted)        | 10/14 (71.4) | 12/14 (85.7) |
| B2201 Iran**            | 5 mg/kg, days 1, 2, and 3 (fasted)   | 14/17 (82.4) | 15/17 (88.2) |
|                         | 5 mg/kg x 2, 1 day (fasted)          | 9/14 (64.3)  | 7/14 (57.10) |
|                         | 10 mg/kg single dose (fasted)        | 12/17 (70.6) | 12/17 (70.6) |
|                         | 10 mg/kg single dose (fed)           | 11/20 (55)   | 12/20 (60)   |
| B2202 Chile             | 10 mg/kg single dose (fasted)        | 19/24 (79)   | 19/24 (79)   |
| Pooled                  | 5 mg/kg single dose                  | 8/20 (40)    | 10/20 (50)   |

| Study        | Regimen (food state)                        | D30 Cure*      | D60 Cure*      |
|--------------|---------------------------------------------|----------------|----------------|
|              |                                             | n/N (%)        | n/N (%)        |
| (unweighted) | 10 mg/kg (single dose or 2 x 5 mg/kg day 1) | 109/151 (72.2) | 121/151 (80.1) |
|              | 15 mg/kg (5 mg/kg daily x 3 days)           | 14/17 (82.4)   | 15/17 (88.2)   |
|              | 20 mg/kg (10 mg/kg on days 1 & 3)           | 21/22 (95.5)   | 21/22 (95.5)   |

\*Cure defined as absence of eggs in stool. Missing data on the day of focus was imputed as failure. Day 30 outcome imputed for Day 60 outcome for study B2212 Peru.

\*\*As per the CSR, “those patients who were positive for at least one Kato-Katz or Telemann slide on entry into the study” used to estimated cure rate

Reviewer created table based on STOOL.xpt dataset

A further exploration of efficacy was performed by food state. At day 30 there appears to be no clear difference; however, at day 60, the overall cure rate in the 10 mg/kg fed group is higher than that in the fasted. As discussed in Section 6, there appears to be a difference in exposure based on food state. The available data do not support analyses by food state in the 5, 15 and 20 mg/kg dose groups.

**Table 7.16 Pooled Cure of WHO/CIBA Studies by Food State**

| Regimen           | D30 Cure     | D60 Cure     |
|-------------------|--------------|--------------|
|                   | n/N (%)      | n/N (%)      |
| 10 mg/kg (fasted) | 50/69 (72.5) | 50/69 (72.5) |
| 10 mg/kg (fed)    | 59/82 (72)   | 71/82 (86.6) |

Table based on pooled results from the 10 mg/kg dose arm from studies B2201, B2202, B2203, B2207 and B2208

Source: reviewer created

Within study, subgroup analyses by age or sex were not feasible given the small sample sizes by study; however, analyses by age and sex were performed using the pooled data. This was reasonable, again, given the similar design, population and endpoint across studies. As shown below, the cure rate was numerically lower in females compared to males at the 10 mg/kg TCBZ regimen. At 20 mg/kg, cure rates do not appear to differ between sexes though the numbers are smaller. The same trends were seen when assessing treatment effect based on day 30 cure (results not shown).

**Table 7.17 Pooled Cure Rate (Day 60) from WHO/CIBA Studies by Sex**

| TCBZ Regimen                                   | All            | Males        | Females      |
|------------------------------------------------|----------------|--------------|--------------|
| 5 mg/kg single dose                            | 10/20 (50)     | 8/13 (61.5)  | 2/7 (28.6)   |
| 10 mg/kg (single dose or 2 x 5 mg/kg on day 1) | 121/151 (80.1) | 59/67 (88.1) | 62/84 (73.8) |
| 15 mg/kg (5 mg/kg daily x 3 days)              | 15/17 (88.2)   | 1/1 (100)    | 14/16 (87.5) |
| 20 mg/kg (10 mg/kg on days 1 and 3)            | 21/22 (95.5)   | 10/11 (90.9) | 11/11 (100)  |

Regimens pooled across studies regardless of food state

Source: reviewer created

Age treated as a continuous variable was not shown to be predictive of day 60 cure in the model including dose and there was no finding of an interaction between age and dose in a logistic regression model (results not shown). Day 60 cure by assessed by age groupings of 6-11 years, 12-16 years and 17 or older (Table 7.18). Results are consistent with those shown in the overall results, again suggestive of a dose response favoring the 20 mg/kg total dose group.

**Table 7.18 Pooled Cure Rate (Day 60) from WHO/CIBA Studies by Age Group**

| TCBZ Regimen                                   | Age at Enrollment |             |            |
|------------------------------------------------|-------------------|-------------|------------|
|                                                | 6-11 years        | 12-16 years | +17 years  |
| 5 mg/kg single dose                            | 10/19 (53)        | 0/1 (0)     | nd         |
| 10 mg/kg (single dose or 2 x 5 mg/kg on day 1) | 31/34 (91)        | 23/28 (82)  | 67/89 (75) |
| 15 mg/kg (5 mg/kg daily x 3 days)              | 1/1 (100)         | nd          | 14/16 (88) |
| 20 mg/kg (10 mg/kg on days 1 and 3)            | 4/4 (100)         | 5/5 (100)   | 12/13 (92) |

nd=no data

Regimens pooled across studies regardless of fed state

Source: reviewer created

### Indirect Comparison of Efficacy Against Historical Estimate of Cure

The reviewer's comparison of parasitological cure between TCBZ-treated patients and non-TCBZ treated patients is summarized below. The approach utilized the artemether day 28 cure rate derived and verified from the Keiser patient-level data to compare against the TCBZ cure rates from the combined day 30 estimates from the WHO/CIBA studies. Almost all studies used the same method (KK) to assess for parasites in the stool. As shown below, the difference in cure rates for the 10, 15 and 20 mg/kg dose groups exceeds 50% with evidence of a dose response supporting the 20 mg/kg dose group.

**Table 7.19: Indirect Comparisons of WHO/CIBA Pooled Cure Rates vs. Historical Estimate**

| Pooled CIBA/WHO (Day 30) | TCBZ           | Historical        | Difference (TCBZ-Historical) |
|--------------------------|----------------|-------------------|------------------------------|
|                          |                | Estimate (Keiser) | 95% CI                       |
| 5 mg/kg                  | 8/20 (40)      | 8/37 (21.6)       | 18.4 (-5.9, 43.2)            |
| 10 mg/kg                 | 109/151 (72.2) | 8/37 (21.6)       | 50.6 (33.4, 63.3)            |
| 15 mg/kg                 | 14/17 (82.4)   | 8/37 (21.6)       | 60.7 (33.2, 77.9)            |
| 20 mg/kg                 | 21/22 (95.5)   | 8/37 (21.6)       | 73.9 (52.4, 85.9)            |

Regimens pooled across studies regardless of fed state

95% CIs calculated using the Wilson method

Source: reviewer created

A logistic model including all WHO/CIBA dose groups, the historical estimate, and baseline EPGs revealed that treatment was predictive on cure; however, baseline EPG was not shown to be a significant predictor. The estimated odds ratio for treatment was 1.3 suggesting a 30% increase in the odds of cure by day 30 as a function of increasing TCBZ dose versus no treatment (imputed using data from the artemether-treated patients). A further exploration of day 30 cure of the combined WHO/CIBA studies for the 10 mg/kg and 20 mg/kg groups only and data

on the Keiser historical control assessed effects of age, sex and country. Country effect was solely driven by the low cure rates in the Keiser study. Sex and age ( $\leq 16$  v. 16 years old) alone were not predictive in subset analyses nor in a multivariable logistic regression.

### 7.3. Supportive Information from other Studies

Seven additional studies (4 published and 3 unpublished but for which clinical study reports were provided) were referenced and summarized in the application as supportive information. No patient-level data were provided for any of the seven studies summarized below.

#### **Talaie et al. (2004) [28]**

This study was conducted in Iran and evaluated 10 mg/kg TCBZ (Egaten) given once, twice or three times. The treatment regimen was randomly assigned using a table of random numbers. The study utilized a single-blind approach; patients were aware of treatment assignment while investigators remained blinded throughout the study.

Patients between 10-65 years of age were placed into two groups defined as ‘cases’ and ‘suggestive cases’ where a ‘case’ was a subject positive for *Fasciola* eggs in the stool, independent of any clinical or laboratory findings. Suggestive cases included patients with a combination of three of the following: fever, shoulder pain, abdominal pain, severe pruritus or urticaria, tender hepatomegaly, serum IgG titer  $\geq 128$  and  $>5\%$  eosinophilia. Pregnant women and persons with a history of severe liver disease were excluded.

Variables collected at baseline, days 7, 14, 30 and 60 included clinical symptoms obtained via a questionnaire, temperature and physical examination. Blood (including eosinophil count and IgG level) and stool assessments were performed at baseline and on days 30 and 60.

**Primary Endpoint:** Cure among the ‘cases’ was defined as complete absence of *Fasciola* eggs after treatment. Cure among the ‘suspected cases’ was defined as absence of *Fasciola* eggs, a decrease or complete cessation of clinical signs and symptoms and IgG level  $\leq 128$  after treatment (all three conditions had to be met to be considered cured).

**Results:** The study enrolled 165 patients (35 cases and 130 suggestive cases) of which 51, 56, and 55 were assigned to receive a single, double and triple dose of 10 mg/kg of TCBZ, respectively. The average age was 40, 35 and 34 years in the single, double and triple dose groups respectively. Overall, most patients were female (75%), 90% complained of abdominal pain, 55% presented with a fever ( $\geq 38^\circ$ ), 20% were positive for *fasciola* eggs in the stool, and all had some level of eosinophilia at baseline.

The following table summarizes the day 30 and day 60 cure by cases and suggestive cases in the overall enrolled (ITT) and in the per-protocol (PP), i.e. patients with a coprological exam to assess for parasites in the stool. **As shown, a large proportion of patients did not have the day 30 and 60 exam leading to a large amount of missing data.** The missing data, along with the

fact that the trial enrolled too few patients positive for *Fasciola* infection at baseline ('cases'), prevents a meaningful dose response analysis among cases; the group that are chronically-infected patients. The bulk of data summarized in the publication is captured in patients for which fascioliasis infection cannot be confirmed.

**Table 7.20: Findings from Supportive Study**

| Population Randomized*  | 10 mg/kg single dose | 10 mg/kg day 1 & 2 | 10 mg/kg days 1, 2, & 3 |
|-------------------------|----------------------|--------------------|-------------------------|
| <b>Cases</b>            | <b>N=11</b>          | <b>N=11</b>        | <b>N=13</b>             |
| Day 30 cure (ITT)       | 8/11 (72.7)          | 10/11 (90.9)       | 10/13 (76.9)            |
| Day 60 cure (ITT)       | 7/11 (63.6)          | 9/11 (81.8)        | 9/13 (69.2)             |
| Day 30 cure (PP)        | 8/8 (100)            | 10/11 (90.9)       | 10/12 (83.3)            |
| Day 60 cure (PP)        | 7/7 (100)            | 9/9 (100)          | 9/9 (100)               |
| <b>Suggestive Cases</b> | <b>N=44</b>          | <b>N=45</b>        | <b>N=41</b>             |
| Day 30 cure (ITT)       | 9/44 (20.5)          | 15/45 (33.3)       | 17/41 (41.5)            |
| Day 60 cure (ITT)       | 23/44 (52.3)         | 24/45 (53.3)       | 30/41 (73.2)            |
| Day 30 cure (PP)        | 9/37 (24.3)          | 15/39 (38.5)       | 17/35 (48.6)            |
| Day 60 cure (PP)        | 23/36 (63.9)         | 24/35 (68.6)       | 30/36 (83.3)            |

\*Cases include only patients with stool positive for *Fasciola* at baseline; suggestive cases include patients with a combination of three of the following: fever, shoulder pain, abdominal pain, severe pruritus or urticaria, tender hepatomegaly, serum IgG titer  $\geq 128$  and  $>5\%$  eosinophilia.

Source: Reviewer constructed using information provide in Talaie et al. (2004) [28]

### El-Morshedy et al. (1999) [23]

This was a randomized, open-label, dose-response study conducted to evaluate 10 mg/kg TCBZ as a single or double dose (10 mg/kg on two consecutive days) in 134 asymptomatic patients with chronic fascioliasis based on repeated positive stool assessments. The publication states that '*cases were randomly divided into two groups...*' and therefore it suggests that treatment was not randomly assigned in a sequential manner but rather that patients were placed into groups and then given treatment according to grouping, which is not random treatment assignment.

The study was performed in Egypt and included 68 patients (40 females, 28 males) in the 10 mg/kg single dose (mean age 16 years +/-11.9) and 66 (47 females, 19 males) in the 10 mg/kg double-dose (mean age 14.2 years +/- 10.9). The parasitological assessment for cure using the KK method was performed in a single stool sample at week 5.

The reported cure rate at week 5 was 54/68 (79.4%) and 62/66 (93.9%) in the 10 mg/kg single and double dose regimens, respectively, yielding a difference between groups of -14.5% favoring the 10 mg/kg double dose, and a 95% CI of -12.7, -16.4,  $p=0.03$  (reviewer calculated). There do not appear to be any missing data at week 5 though this is not directly addressed in the publication.

Those who remained stool positive at week 5 were re-treated with a two-dose (10 mg/kg for 2 consecutive days) TCBZ regimen and all were cured. The authors report that there were no

differences in outcome by age, sex and by co-infection with *Schistosoma mansoni*.

**Milan et al (2000) [24]**

This was a non-randomized, non-comparative study conducted by Ciba-Geigy (now Novartis) in Cuba following a flood-related fascioliasis epidemic. Adults and children excreting *Fasciola hepatica* ova in their stool and who previously failed at least one antihelminthic therapy completed more than 30 days before enrollment were eligible. Patients were initially followed and treated as in-patients for one week and then followed as outpatients on days 15, 30, 60 and 90. All enrolled patients received two 10 mg/kg doses given 12 hours apart following a fatty meal.

A total of 82 (51 females) patients between 15-81 years of age (mean age 42 years) were enrolled of which three were lost to follow-up by the Day 60 assessment. In addition, while not stated, it appears that measurement of eggs in the stool was not performed or incomplete for an additional two patients. Therefore, the authors report cure in 77 patients. On day 60, the publication reports that 71/77 patients (92%) were negative for parasite eggs in the stool via the KK method. The reviewer-estimated, more-conservative estimate imputing missing as failure in all treated patients yields a day 60 cure of 87% (71/82). The publication does not provide results at the earlier study visits.

**Villegas et al. (2012) [1]**

In 2008, the Bolivian ministry of health opted for a large-scale distribution of TCBZ in fascioliasis-endemic areas. Prior to implementation of this plan, a small pilot study was performed to evaluate the safety and efficacy of TCBZ. This study is described in Villegas *et al* (2012) as a non-randomized, non-comparative study in children ages 5-14 years infected with chronic fascioliasis in Bolivia in 2008. The region where the study was performed, Huacullani, has reported prevalence of fascioliasis among school-aged children ranging from 31% to 38% (data from the 1990s).

This study initially began as a survey study in which 459 school-aged children were provided a plastic container for stool sample collection. Of the 459, 447 children returned the sample of which 95 (21%) were positive for *F. hepatica* eggs. Five of the 95 children did not participate. TCBZ was administered as a single-dose of 10 mg/kg to 90 children (10 patients with baseline EPG count >300 were treated as inpatients) of which 70 (77.8%) were cured (absence of eggs in stool viva KK method) at month 3. The 20 patients who failed initial treatment were re-treated with a second TCBZ 10 mg/kg dose of which 18/20 were cured two months later.

**Egyptian Government-Sponsored Studies (B2209, B2210, B2211)**

In the mid-1990s the Egyptian government sponsored three non-randomized, non-comparative studies; B2209, B2210 and B2211, to evaluate TCBZ (Fasinex, veterinary formulation) for the treatment of chronic fascioliasis in children and adults. The same endpoint, clearance of parasites in stool at Day 60, was utilized to evaluate either a 10 mg/kg single dose or 2 x 5

mg/kg single-day dose of TCBZ. Results obtained from the clinical study reports are outlined below showing cure rates ranging between 80% and 96%. Dose comparisons are not feasible given that all patients received a total TCBZ dose of 10 mg/kg; however, the study reports (B2209 and B2211) state that the comparisons of cure rates between the TCBZ 10 mg/kg single and split-dose regimens were not statistically significant ( $p$ -value  $>0.05$ ). From a quality perspective, the summary reports for these studies are limited in detail and scope. Therefore, the overall quality of these studies cannot be determined.

### Summary of Additional Information

A summary of the reported cure rates among the supportive studies (excluding data on the suspected cases reported in the Talaie study) described above is provided in Table 7.21. Only the dose response data from the El-Morshedy study provide information regarding the efficacy of TCBZ. The remaining studies are useful in providing additional information regarding the efficacy of TCBZ; however, they should be viewed in context with the information previously summarized based on assessment of the patient-level data. The reported cure rates among patients who received TCBZ at a total dose of 10 mg/kg (either single 10 mg/kg or 2 x 5 mg over one day) ranged between 78% and 100%. Fewer data exists for the 20 mg/kg total dose (i.e. 10 mg/kg x 2); however, rates are slightly higher ranging between 92% to 100%.

**Table 7.21: Summary of Cure Rates from Supportive Studies in Chronic Fascioliasis**

| Study                   | Regimen                           | Parasitological Cure <sup>^</sup> (%)                 |
|-------------------------|-----------------------------------|-------------------------------------------------------|
| Talaie (2004) * (cases) | 10 mg/kg single dose              | 7/7 (100)                                             |
|                         | 10 mg/kg double dose              | 9/9 (100)                                             |
|                         | 10 mg/kg triple dose              | 9/9 (100)                                             |
| El-Morshedy (1999) *    | 10 mg/kg single dose              | 54/68 (79.4)                                          |
|                         | 10 mg/kg double dose              | 62/66 (93.9)                                          |
| Milan (2000)            | 10 mg/kg double dose (fed)        | 71/77 (92)                                            |
| Villegas (2012) *       | 10 mg/kg single dose              | 70/90 (77.8)                                          |
|                         | Re-treatment 10 mg/kg single dose | 18/20 (98%) (Day 60 after 1 <sup>st</sup> assessment) |
| B2209 Egypt*            | 10 mg/kg single dose              | 24/30 (80)                                            |
|                         | 2 x 5 mg/kg, 1 day                | 26/30 (87)                                            |
| B2210 Egypt             | 10 mg/kg single dose (fed)        | 22/25 (88)                                            |
| B2211 Egypt             | 10 mg/kg single dose (fed)        | 23/25 (92)                                            |
|                         | 2 x 5 mg/kg, 1 day (fed)          | 24/25 (96)                                            |

<sup>^</sup>Cure based on measurements obtained on Day 60 for studies B2209, B2210, B2211, Milan and Talaie on Day 90 for Villegas and at Week 5 for El-Morshedy (rates exclude missing)

\*Relationship to food unspecified

Source: Reviewer created

## 7.4. Integrated Review of Effectiveness

### 7.4.1. Estimating the Historical Treatment Effect for Chronic Fascioliasis

There is a paucity of comparative data evaluating TCBZ for the treatment of fascioliasis. Consequently, it is difficult to interpret estimated cure rates across the various available non-comparative studies without putting the results into context with respect to an estimated historical treatment effect. The historical treatment effect might be estimated using data from prior experiences in patients with fascioliasis and who were either untreated or treated with a sub-optimal (as presently viewed) treatment. The reviewer's attempt to elucidate the historical treatment effect utilized data from the following three, independent published studies (no patient-level data provided) and the patient-level data provided from the Keiser study (7.2.1).

#### **Favennec et al (2003) [21]**

This was a randomized, double-blind, placebo-controlled clinical trial performed in Peru among 50 children and 50 adults with chronic fascioliasis infection. The study evaluated efficacy of a 7-day nitazoxanide regimen compared to placebo on day 90 cure. Patients were considered cured when three post-treatment stool examinations done at 30-60 days (at least 24 hours apart) and again at 90 days following enrollment were negative. Twenty patients (10 adults/10 children) were randomized to receive placebo treatment of which 4 (2 adults/2 children) were lost to follow-up. Eighty patients (40 adults/40 children) were randomized to receive nitazoxanide of which 10 adults and 5 children were lost to follow-up.

The day 90 cure rate among patients who had three stool assessments between days 30 and 90 (i.e. omitting missing) was 6.3% (1/16), 95% CI exact (0.2%, 30.2%) and 49.2% (32/65), 95% CI exact (36.6%, 61.9%) in the placebo and nitazoxanide groups, respectively. Treating missing as success leads to a cure rate in the placebo group of 5/20 (25%, 95% CI: 8.7%, 49.1%, Clopper Pearson method) and 47/80 (58.8%, 95% CI: 47.2%, 69.6%) in the nitazoxanide group. Pooling the placebo and nitazoxanide groups, and counting missing as success, yields an estimated cure rate of 52% (52/100), 95% CI: (41.8%, 62.1%), suggesting that the most-optimistic estimate of cure in patients who received a suboptimal treatment of nitazoxanide or placebo treatment is 62% based on the upper bound of the 95% CI.

#### **Knobloch et al (1985) [29]**

This was a non-randomized, single arm study performed in Peru in 35 patients with chronic fascioliasis treated with praziquantel. Cure was defined as a day 90 negative stool assessment.

The 90-day cure rate was 20% (7/35), exact (Clopper-Pearson) 95% CI (8.4%, 36.9%).

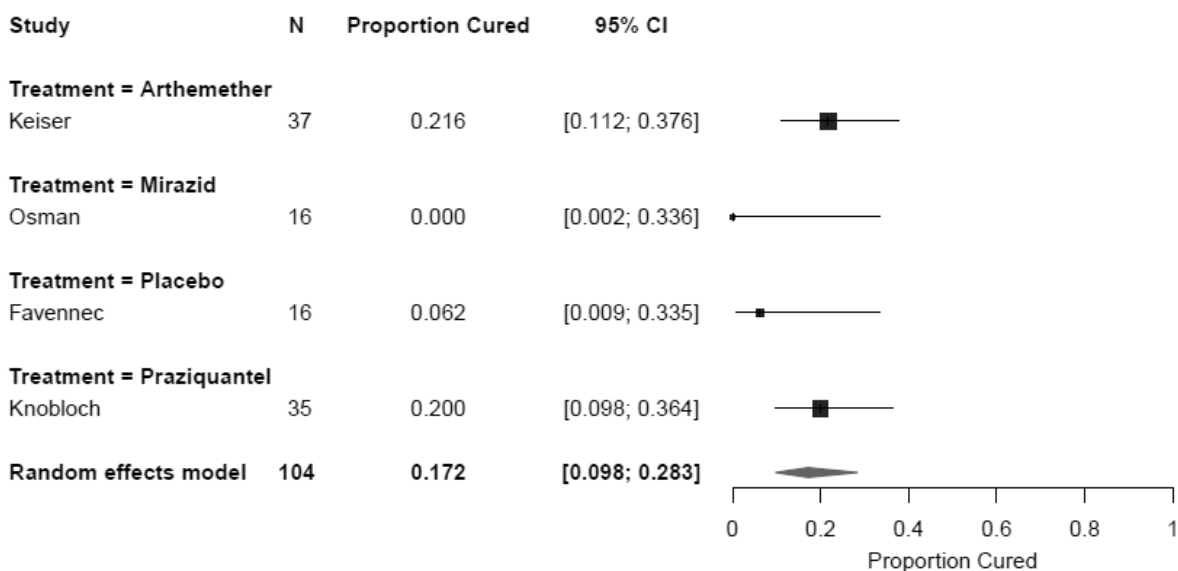
#### **Osman et al (2010) [30]**

This study was non-randomized, single arm performed in Egypt among 16 patients with chronic fascioliasis. Patients received a 6-day course of 600 mg Mirazid (myrrh, derived from a natural plant source) with follow-up for cure (negative based on absence of parasites using the KK method) performed on days 30 and 60. None of the treated patients were clear of parasites in their stool by days 30 or 60 (exact 95% CI: 0%, 17%).

### Summary of Historical Controls

Historical cure rates, and respective 95% confidence intervals, are illustrated in the following forest plot. Among 104 patients who received a sub-optimal, non-TCBZ regimen or placebo, 16 (15.4%) were negative for parasites based on stool assessment. Note that the timing of the assessment was 28, 60, 90 and 90 in the Keiser, Osman, Favennec, and Knobloch studies, respectively. Given that these data were obtained from disparate studies, the pooled, weighted estimate should not be viewed as a definitive value but rather as an estimate only. Given the variability across studies, the most liberal historical cure estimate is 40%, which is based on an assessment of the upper confidence bound for each study. The point estimates and upper bound of the 95% CIs summarized in Osman, Favennec, and Knobloch are consistently near or below the historical control estimate derived from the artemether-treated patients in the Keiser study. As such, the artemether historical estimate of 22% can be viewed as a conservative comparator for purposes of estimating the TCBZ treatment effect.

**Figure 7-1: Historical Estimate of the Cure Rate in Chronic Fascioliasis**



### 7.5. Assessment of Efficacy Across Studies in Chronic Fascioliasis

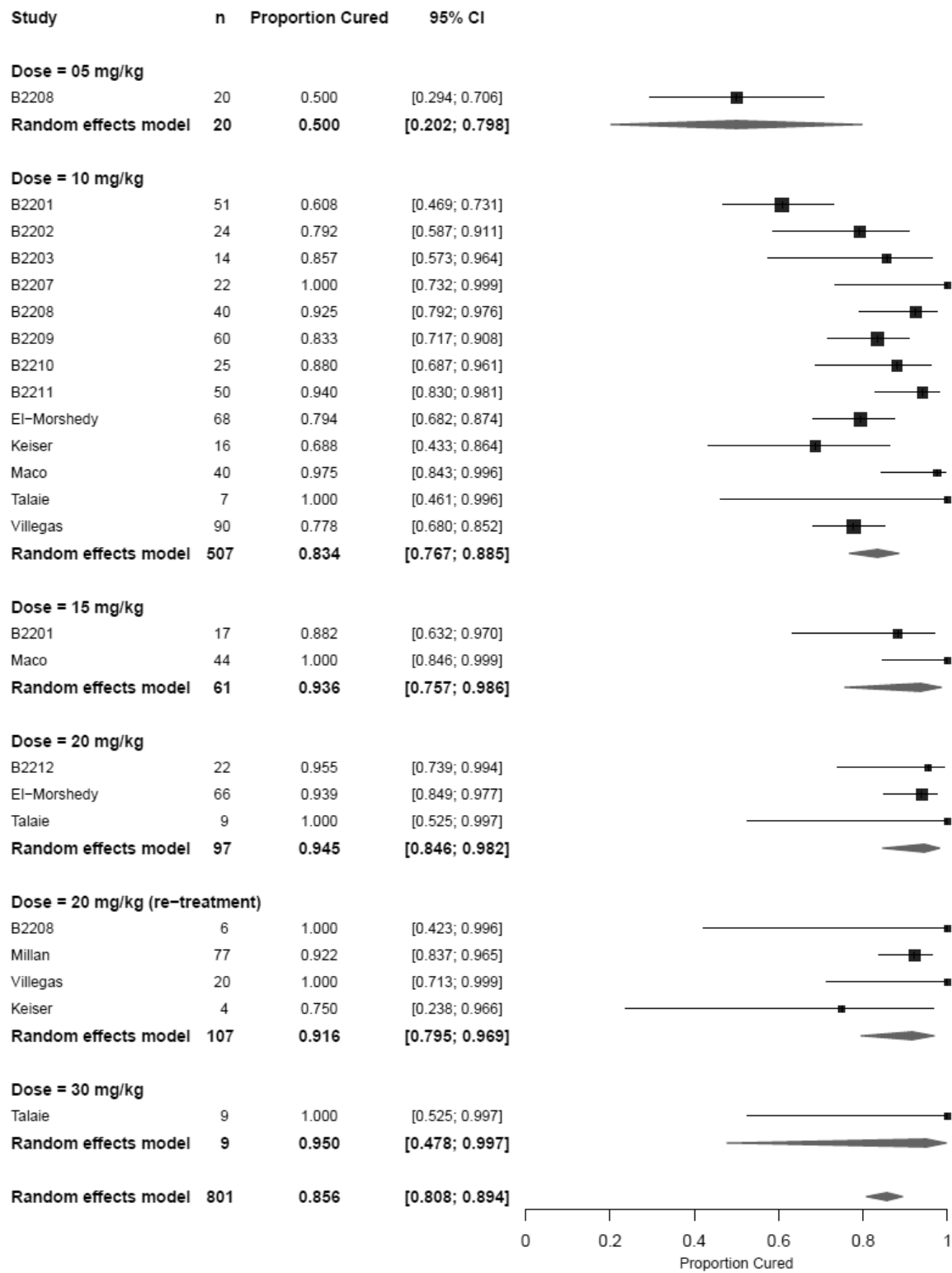
Among the available studies, several TCBZ regimens were evaluated with total doses ranging from 5 mg/kg to 30 mg/kg dose. The forest plot (Figure 7-2) includes individual cure rates and

95% confidence intervals along with pooled, random effects weighted summary estimates by total dose and overall among all the studies in chronic fascioliasis (all studies discussed except Hien and the suspected cases in Talaie). As shown, the estimated cure rate for a 5 mg/kg dose is only 50% though this estimate is based on limited data. More information exists for the 10 mg/kg total dose regimen and combined the estimate of cure is approximately 83.4%, 95% CI (76.7, 88.5). Overall, pooled cure is 94.5% (75.7, 98.6) from data on the 20 mg/kg total dose regimen in treatment naïve patients. Among patients failing a prior antihelminthic treatment, re-treatment with 20 mg/kg TCBZ yielded a combined cure rate of 91.6%, 95% CI (79.5, 96.9). Finally, too few data are available on the highest dose of 30 mg/kg total to draw conclusions.

An analyses by food state for the 10 mg/kg total TCBZ performed in the WHO/CIBA studies (discussed in Section 7.2.3) suggests that a fed state (pooled, unweighted cure rate 86.6%) might confer a numerically higher cure rate versus a fasted state (pooled, unweighted cure 72.5%). This finding is further strengthened when including data (summarized in Section 7.3) from some supportive studies (all fed state). Unfortunately, an analysis by food state cannot be performed for the 20 mg/kg total TCBZ dose due to lack of data in each food state separately.

There are limitations with these pooled estimates, specifically the amount of missing data previously summarized, that the data are drawn from different studies conducted in various locations and in patients of varying age and that cure was assessed at different times, i.e. day 60 (WHO/CIBA and Egyptian government studies), day 28 (Keiser), week 5 (El-Morshedy), day and 90 (Villegas). In available data, there is considerable agreement between findings at day 30 and day 60; therefore, we do not expect these cure rates to differ to a large extent. It is unclear if fascioliasis varies by region; however, there are some reports of sporadic drug resistance in regions of South America. Specifically, some epidemiological data suggest that infection can be more severe in children compared to adults. That said, there does not appear to be a difference in cure between pediatric and adult patients at the proposed dose. Despite these limitations, the data demonstrate a numerical dose-response of TCBZ.

Figure 7-2: Forest Plot of Cure Rates in Studies of Chronic Fascioliasis



## 7.6. Summary and Conclusions - Statistics and Clinical

The evidence provided to support the efficacy of TCBZ for treatment of fascioliasis is based on patient-level data and information summarized in published studies. A single site, randomized, open-label, comparative study in pediatric and adult patients with symptomatic fascioliasis by Hien and colleagues found that treatment with TCBZ 10 mg/kg twice, 12 hours apart (20 mg/kg total dose) was less effective than artesunate 4 mg/kg per day for 10 days in reducing abdominal pain at day 10, 88% versus 100%. However, at three months post-treatment, a timepoint considered more relevant in the assessment of cure, TCBZ was shown to be more effective compared to artesunate in resolution of clinical symptoms based on self-report. Specifically, at three months post-treatment 92% and 76% of patients in the TCBZ and artesunate groups, respectively, reported no clinical symptoms yielding a risk difference of 16%, 95% CI (1.7%, 30.8%), nominal  $p=0.035$ . While the trial results favored artesunate on the 10-day abdominal pain endpoint, the proportion of patients without abdominal pain in the TCBZ arm was reasonably large (88%). However, the 10-day assessment is likely too proximal to the start of infection to fully capture treatment response; hence, the rationale for assessing clinical response at three-months post-treatment. In summary, results from the Hien study confirmed through patient-level data review, provide evidence supporting the efficacy of a 10 mg/kg twice, 12 hours apart regimen of TCBZ for the treatment of symptomatic fascioliasis.

Extensive efforts were undertaken in this comprehensive review and analysis to elucidate the historical control estimate in patients with chronic fascioliasis. Given the paucity of data in placebo-treated patients, the analysis included reported cure rates in patients who received treatments that are now considered clinically sub-optimal. These efforts led to an estimated 21.6% cure rate when using patient-level data only (Keiser study) and a more liberal estimate of 40% based on the upper bound around the cure rate when using patient-level and published data.

Analysis of data from the Maco study of two TCBZ regimens for treatment of chronic fascioliasis reported a day 30 cure rate of 95% and 97.7% and a day 60 cure rate of 95% and 100% in the 10 mg/kg and 7.5 mg/kg BID TCBZ groups, respectively. Compared against the 21.6% historical control estimate, the difference in day 30 cure is at least 73.4% demonstrating a large treatment effect of TCBZ.

Data from six, single arm studies, with similar designs and the same endpoint of cure based on negative stool assessments, conducted by WHO/CIBA in the 1980s were evaluated in efforts to determine an effective TCBZ dose. TCBZ doses studied ranged from 5 mg/kg to 20 mg/kg with results suggest a trend favoring a 20 mg/kg (10 mg/kg given twice) dose. Combined, unweighted analyses yielded cure rates of 40%, 72.2%, 82.4%, and 95.5% at day 30 and cure rates of 50%, 80.1%, 88.2% and 95.5% at day 60 in the 5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg dose regimens, respectively. Compared against the 21.6% historical control, the treatment effect at day 30 from the WHO/CIBA studies shows a large treatment effect of 73.9% (95% CI: 52.4%, 85.9%) strongly favoring 20 mg/kg TCBZ. A logistic regression analyses

confirmed a dose response demonstrating an increase in the odds of cure by 1.5 for each increase in dose.

These comparisons against the derived 21.6% historical estimate of effect, albeit limited in the fact that it is based on data from separate studies, was performed using patient-level data and therefore can be viewed as more reliable than an assessment of published findings only.

Overall, efficacy was assessed using patient-level data from only one randomized study for treatment of the acute/symptomatic stage of infection. Findings from the single RCT support efficacy of TCBZ 20 mg/kg for acute infection. Other, and more copious, information exists to support use of TCBZ for treating chronic fascioliasis; however, no patient-level data are available from RCTs in chronic infection. Using various information extracted from published studies and supplied patient-level data from non-published, non-randomized studies, a thorough assessment demonstrated efficacy of TCBZ using a parasitological cure endpoint as early as day 30. The analyses (including findings from a publication [23] of dose response) provide sufficient evidence of a dose response favoring a total TCBZ dose of 20 mg/kg.

In conclusion, we recommend a TCBZ dose of 10 mg/kg x 2 for treatment of fascioliasis in children and adult patients.

## 8 Clinical Microbiology Review

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### 8.1. Nonclinical Microbiology

#### 8.1.1. Mechanism of Action

The mechanism by which TCBZ exhibits activity against *Fasciola* species is not fully understood. Some of the studies supporting the mechanism of action of TCBZ and its metabolites are summarized below:

##### **8.1.1.1. Effect on resting membrane potential and microtubules in the tegument**

Studies suggest that TCBZ and/or its metabolites are taken up by diffusion through the tegument, accumulate within both immature and adult worms of *F. hepatica* and alter the resting membrane potential. TCBZ, at concentrations between 10 and 25  $\mu\text{M}$  (i.e., 3.6 – 9.0  $\mu\text{g}/\text{mL}$ ) decreased the resting tegumental membrane potential of both immature and adult worms; similarly, TCBZ-SO was shown to decrease the resting tegumental membrane potential of both immature and adult worms of *F. hepatica*. In the presence of bovine serum albumin (BSA), the uptake of TCBZ as well as its effect on the resting membrane potential of the tegument was decreased [31, 32].

Alteration in resting potential was associated with stimulation of parasite's glucose derived metabolic products such as acetate and propionate formation at TCBZ concentrations of up to 10  $\mu\text{M}$  (i.e., 3.6  $\mu\text{g}/\text{mL}$ ); however, higher concentrations were associated with a decrease in metabolic products. The adenosine triphosphate (ATP) levels were not changed at TCBZ concentrations up to 25  $\mu\text{M}$  (i.e., 9.0  $\mu\text{g}/\text{mL}$ ).

Alteration in the resting tegumental membrane potential was associated with decreased motility. Within 8 hours of incubation, TCBZ was more effective than TCBZ-SO, in inhibiting motility of the immature worms; however, at 24 hours, both TCBZ and TCBZ-SO, at a concentration of 10  $\mu\text{M}$  (i.e., 3.6 and 3.8  $\mu\text{g}/\text{mL}$ , respectively), were equally active. This may be due to a more rapid penetration of TCBZ into the parasite compared to TCBZ-SO; however, the activity increased as the metabolite accumulated within the parasite. Several other studies have reported the ability of TCBZ and its metabolites to inhibit motility (for details see Appendix 15.4.1, Table 15.26).

Fetterer [33] reported that TCBZ at a concentration of 10  $\mu\text{M}$  i.e., 3.6  $\mu\text{g}/\text{mL}$  was not effective in inhibiting colchicine binding to *F. hepatica* homogenates whereas TCBZ-SO<sub>2</sub> or TCBZ-SO were effective in inhibiting colchicine binding to adult worm homogenate within 5 minutes; TCBZ-SO was more effective than TCBZ-SO<sub>2</sub>. However, Bennett and Kohler [31] reported the inhibition of the binding of TCBZ to the purified tubulin from the adult worms. Also, TCBZ at the same concentration was effective in inhibiting the binding of colchicine to tubulin purified from porcine brain in addition to that from the parasite. Fetterer [33] reported that TCBZ at a

concentration of 10  $\mu\text{M}$  i.e., 3.6  $\mu\text{g}/\text{mL}$  was not effective in inhibiting colchicine binding to *F. hepatica* homogenates whereas TCBZ-SO<sub>2</sub> or TCBZ-SO were effective in inhibiting colchicine binding to adult worm homogenate within 5 minutes; TCBZ-SO was more effective than TCBZ-SO<sub>2</sub>. However, Bennett and Kohler [31] reported the inhibition of the binding of TCBZ to the purified tubulin from the adult worms. Also, TCBZ at the same concentration was effective in inhibiting the binding of colchicine to tubulin purified from porcine brain in addition to that from the parasite.

Robinson *et al.* [34] reported disruption of the tubulin organization in the tegument of worms known to be TCBZ-sensitive but not in the worms of the TCBZ-resistant strain of *F. hepatica* after incubation with TCBZ-SO (50  $\mu\text{g}/\text{mL}$ ) for 24 hours. The studies were conducted by immunochemical staining and immunofluorescence using anti-tubulin antibody raised in rabbits against the 13-day-old chicken embryo tubulin. Robinson *et al.* [34] reported disruption of the tubulin organization in the tegument of worms known to be TCBZ-sensitive but not in the worms of the TCBZ-resistant strain of *F. hepatica* after incubation with TCBZ-SO (50  $\mu\text{g}/\text{mL}$ ) for 24 hours. The studies were conducted by immunochemical staining and immunofluorescence using anti-tubulin antibody raised in rabbits against the 13-day-old chicken embryo tubulin.

Overall, the studies suggest that TCBZ and its metabolites, like other benzimidazoles, can decrease resting potential, bind and disrupt tubulin as well as interfere with its function. However, there does not appear to be any effect on ATP levels.

#### **8.1.1.2. Effect on protein synthesis**

A high level of protein synthesis occurs particularly in the vitellaria (i.e., the egg shell protein produced by vitellaria cells and used in egg formation), spermatogenic cells, tegument, and other parts of the *Fasciola* parasites. Stitt *et al.* [35] reported that TCBZ-SO at a concentration of 15  $\mu\text{g}/\text{mL}$  inhibited protein synthesis in tissue slices of adult worms of *F.* [35] reported that TCBZ-SO at a concentration of 15  $\mu\text{g}/\text{mL}$  inhibited protein synthesis in tissue slices of adult worms of *F. hepatica*; tissue slices were incubated with the drug and <sup>14</sup>C-leucine for 3 hours; radiolabel uptake was measured by liquid scintillation counting. The TCBZ-SO induced inhibition of protein synthesis was comparable to that of cycloheximide and actinomycin D, known inhibitors of protein and RNA synthesis, respectively.

Stitt and Fairweather [36] reported the effect of TCBZ-SO on spermatogenesis using adult worms and tissue slices of *F.* Stitt and Fairweather [36] reported the effect of TCBZ-SO on spermatogenesis using adult worms and tissue slices of *F. hepatica* that were incubated for up to 24 hours in 15  $\mu\text{g}/\text{mL}$  and 12 hours in 50  $\mu\text{g}/\text{mL}$ , respectively. Ultrastructural changes were examined by transmission electron microscopy (TEM). The spermatogonial stages were mitotically inactive and detached from their normal position close to the wall of the tubule after 3 hours of incubation. By 12-24 hours the testis tubules were almost completely empty with few spermatogenic stages or mature spermatozoa present. The authors proposed that inhibition of protein synthesis appears to be associated with the interference in spermatogenesis and egg formation.

In another study, Stitt and Fairweather [37] reported ultrastructural changes on the vitelline cells by TEM, of intact worms incubated with TCBZ-SO (15 µg/mL) for 12 to 24 hours. In another study, Stitt and Fairweather [37] reported ultrastructural changes on the vitelline cells by TEM, of intact worms incubated with TCBZ-SO (15 µg/mL) for 12 to 24 hours. The changes reported include a swelling of the granular endoplasmic reticulum (GER) cisternae with decreased ribosomal covering in the intermediate-type cells and condensation of chromatin and disappearance of the nucleolus in the nucleus of the stem cell. Similar changes were observed earlier, within 6 hours of incubation of adult worms or 3 hours of adult worm tissue slices with the higher concentration (50 µg/ml) of TCBZ-SO.

It is unclear whether inhibition of protein and nucleic acid synthesis is a direct effect of TCBZ-SO or indirect due to changes induced by tegument binding and inhibition of tubulin or a combination of the two.

#### **8.1.1.3. Effect on enzyme synthesis**

Bennett and Kohler [31] reported that TCBZ inhibited the release of proteolytic enzymes from immature and adult worms of *F. hepatica*. After a 24-hour exposure to 3 µM (i.e., 1.08 µg/mL) of TCBZ, minimal to no protease enzyme activity was detected although the parasites were very active. Higher concentrations of TCBZ were effective in inhibiting motility. Bennett and Kohler [31] reported that TCBZ inhibited the release of proteolytic enzymes from immature and adult worms of *F. hepatica*. After a 24-hour exposure to 3 µM (i.e., 1.08 µg/mL) of TCBZ, minimal to no protease enzyme activity was detected although the parasites were very active. Higher concentrations of TCBZ were effective in inhibiting motility.

#### **8.1.1.4. Transport mechanism**

Mottier *et al.* [38] evaluated the transport mechanism using the adult worms of *F. hepatica*. Briefly, live and dead worms as well as worms with oral route closed off by ligation were incubated with 1–30 nM/mL (i.e., 0.4 – 11.3 ng/mL) TCBZ-SO, in the presence or absence of bovine serum albumin, for up to 90 minutes. At different time intervals, the parasite material was extracted and processed for the high-performance liquid chromatography (HPLC) to measure the metabolite concentration. With an increase in TCBZ-SO concentration in the medium, an increased concentration of TCBZ-SO was recovered within the parasites. In the presence of BSA, there was about 85% decrease in the TCBZ-SO concentrations inside the worms compared to that in the absence of the protein. The drug concentrations within ligated and non-ligated adult worms were similar. Also, the TCBZ-SO concentrations were about 2-fold higher within the live worms, compared to dead worms. Overall, the study suggests that TCBZ-SO penetrates mainly passively by trans-tegumental diffusion.

Barrera *et al.* [39] reported the inhibitory effect of TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> on ABCG2 activity using mammalian cells; ABCG2/BCRP is a member of the ABC transporter family, a group of proteins that transport certain chemicals out of cells. The role of different transporters in the uptake and/or efflux of TCBZ or its metabolites by *Fasciola* worms was not evaluated.

#### **8.1.1.5. Effect on mitochondria**

The effect of TCBZ or its metabolites on mitochondria of *Fasciola* parasites was not evaluated. However, studies with rat liver show that TCBZ and its metabolites TCBZ-SO and TCBZ-SO<sub>2</sub> were effective in uncoupling mitochondrial oxidative phosphorylation and lowered electrical resistance of the planar bimolecular lipid membranes; such an effect was concentration-dependent. In the presence of 0.35% BSA a decrease in the uncoupling activity was reported [40]. In the presence of 0.35% BSA a decrease in the uncoupling activity was reported [40].

**Reviewer's Comments:**

*Overall, the studies suggest that TCBZ and its metabolites penetrate the immature (migrating through the hepatic parenchyma) and adult (present in the biliary ducts) worms of F. hepatica by trans-tegumentary absorption, and not by the oral route. Exposure to TCBZ and its metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>) leads to an alteration of the resting tegumental membrane potential, interference with the microtubule structure and function, inhibition of synthesis of proteins and proteolytic enzymes. It is possible that TCBZ inhibits protein synthesis through binding to the  $\beta$ -tubulin in the parasite, leading to depolymerization and disruption of the microtubule-dependent secretory processes, severe surface damage, and disintegration of the tegument of the parasite. TCBZ-SO has also been shown to inhibit the mitotic division of the spermatogenic and vitelline cells in the parasite, preventing reproduction.*

*The tegument is known to be the first line of defense and important in maintaining the viability of the Fasciola parasites as it plays an important role in nutrient uptake, osmoregulation and immunoprotection. TCBZ effect on tegument is probably related to the destruction of the microtubular structure, resulting in the death of the parasite. The loss of integrity of the parasites in the presence of TCBZ and/or its metabolites leads to penetration in to the cells and tissues and disruption of parasite functions that include inhibition of the division of the primary spermatogonia and vitelline cells. The role of host factors such as immune response and bile in inducing parasite damage cannot be ruled out.*

**8.1.2. Activity in vitro**

Methods for measurement of in vitro sensitivity of *Fasciola* species are not standardized and limited to testing in research laboratories. Some of the studies supporting the activity of TCBZ against different stages of *F. hepatica* and *F. gigantica* are summarized below.

**8.1.2.1. Activity against the immature and adult worms of Fasciola species**

The activity of TCBZ and its metabolites, against the juvenile/immature (3-week old) and adult worms (> 12-week old) of *Fasciola* species, was measured by alteration in motility, morphology and/or ultrastructure.

**8.1.2.1.1. Effect on motility**

• ***Fasciola hepatica***

Several studies reported the effect of TCBZ and its metabolites on the motility of the juvenile and/or adult worms (for details see Appendix-15.4.1, Table 15.26). The worms were incubated

with different concentrations of TCBZ, TCBZ-SO, and/or TCBZ-SO<sub>2</sub> for 24 to 72 hours at 37°C. Complete details of the methods used were not available for review. Overall, the studies suggest that TCBZ, TCBZ-SO as well as TCBZ-SO<sub>2</sub> are effective in inhibiting motility of *F. hepatica*. Duthaler *et al.*, reported that TCBZ was more active against adult worms than immature worms whereas TCBZ-SO and TCBZ-SO<sub>2</sub> were more active against immature worms than adult worms [41]. [41].

The activity of TCBZ was reduced in the presence of BSA suggesting that protein binding reduces the activity of the drug. The reduction in activity in the presence of BSA appears to be due to reduced uptake of TCBZ [31]. The activity of TCBZ was reduced in the presence of BSA suggesting that protein binding reduces the activity of the drug. The reduction in activity in the presence of BSA appears to be due to reduced uptake of TCBZ [31].

- ***Fasciola gigantica***

No studies were available for review.

#### **8.1.2.1.2. Effect on morphology/ultrastructure**

- ***Fasciola hepatica***

Several studies [34, 42-46] reported the effect of TCBZ and/or its metabolites on the disruption of morphology and ultrastructure of the immature and adult worms of *F. hepatica* (for details see Appendix-15.4.1, Table 15.26). Briefly, the immature or adult worms were incubated with TCBZ or its metabolites at a concentration of  $\geq 10$   $\mu\text{g/mL}$  for up to 18 and 24 hours, respectively, and processed to examine ultrastructural changes by scanning electron microscopy (SEM) or TEM. The results show that disruption of the ultrastructure progressed over time; these changes include progressive convolution at the apex, severe vacuolation at the basal regions, accumulation of T1 or T2 secretory bodies in the tegumental cells, abnormal tegument with accumulation of secretory bodies towards the base of the syncytium; the tegument was completely sloughed away and the tegumental cells became synthetically inactive after longer incubation times.

Halferty *et al.* [43] reported a comparison of the effect of TCBZ and the two metabolites, at a concentration of 15  $\mu\text{g/mL}$  and 24 hours of incubation, on adult worms of the drug sensitive strain (Cullompton) of *F. hepatica*. Overall, the results suggest that the type and severity of changes induced by TCBZ and its metabolites varied depending on the parameter measured. For example, Halferty *et al.* [43] reported a comparison of the effect of TCBZ and the two metabolites, at a concentration of 15  $\mu\text{g/mL}$  and 24 hours of incubation, on adult worms of the drug sensitive strain (Cullompton) of *F. hepatica*. Overall, the results suggest that the type and severity of changes induced by TCBZ and its metabolites varied depending on the parameter measured. For example,

- Motility: The effect of TCBZ-SO > TCBZ-SO<sub>2</sub> > TCBZ.
- Morphology (swelling and blebbing): TCBZ-SO<sub>2</sub> was more disruptive anteriorly and TCBZ-SO posteriorly.
- Overall ultra-structural changes: TCBZ-SO<sub>2</sub> > TCBZ-SO > TCBZ.

Similar changes in morphology/ultrastructural were reported in another study [42] against the adult worms of Cullompton strain incubated with TCBZ or TCBZ-SO. However, in the drug resistant strain (Oberon), there was no change in morphology in the apical cone region; some swelling and/or disruption were observed in the interspinal tegument and/or tail region. Overall, there was greater disruption of the worms of TCBZ-sensitive strain than the TCBZ-resistant strain in the presence of TCBZ or TCBZ-SO. Similar changes in morphology/ultrastructural were reported in another study [42] against the adult worms of Cullompton strain incubated with TCBZ or TCBZ-SO. However, in the drug resistant strain (Oberon), there was no change in morphology in the apical cone region; some swelling and/or disruption were observed in the interspinal tegument and/or tail region. Overall, there was greater disruption of the worms of TCBZ-sensitive strain than the TCBZ-resistant strain in the presence of TCBZ or TCBZ-SO.

- ***Fasciola gigantica***

Meaney *et al.* [47] and Shalaby *et al.* [48] reported the effect of TCBZ-SO on the adult worms of *F. gigantica*. The adult worms were incubated with 10 or 20 µg/mL TCBZ-SO for 24 hours at 37°C and processed for SEM. The results show alteration in the surface architecture of the tegument that include eruption, blebbing, swelling or sloughing; the effect was more pronounced at a concentration of 20 µg/mL compared to 10 µg/mL of TCBZ-SO. Meaney *et al.* [47] and Shalaby *et al.* [48] reported the effect of TCBZ-SO on the adult worms of *F. gigantica*. The adult worms were incubated with 10 or 20 µg/mL TCBZ-SO for 24 hours at 37°C and processed for SEM. The results show alteration in the surface architecture of the tegument that include eruption, blebbing, swelling or sloughing; the effect was more pronounced at a concentration of 20 µg/mL compared to 10 µg/mL of TCBZ-SO.

#### **8.1.2.1.3. Effect on egg hatching**

The effect of TCBZ and/or TCBZ-SO on hatching of the eggs of TCBZ sensitive and/or resistant strains was reported in three studies [33, 49, 50]. Fetterer [33] reported that TCBZ at concentrations of ≤ 3.6 µg/mL was not effective in preventing embryonation of *Fasciola* eggs. [33] reported that TCBZ at concentrations of ≤ 3.6 µg/mL was not effective in preventing embryonation of *Fasciola* eggs. Similar observations were reported by Alvarez *et al.* [49]; TCBZ and TCBZ-SO concentrations of up to 7-8 µg/mL were not effective in inhibiting egg hatching of drug sensitive (Cullompton) and drug resistant (Sligo) strains of *F.* [49]; TCBZ and TCBZ-SO concentrations of up to 7-8 µg/mL were not effective in inhibiting egg hatching of drug sensitive (Cullompton) and drug resistant (Sligo) strains of *F. hepatica* when exposed for about 2 hours. No effect on egg hatching was observed after longer (15 days) incubation of eggs with TCBZ or TCBZ-SO at a lower concentration of ~2 µg/mL. Fairweather *et al.* [50], however, reported that incubation of eggs of several drug sensitive strains (Cullompton, Fairhurst, Leon, and Patagonia) with higher concentration of TCBZ-SO (60 µg/mL) for 14 days was effective in inhibiting egg hatching. Against the drug resistant strains (Dutch and Oberon), the hatch rate decreased by about 3- to 5-fold (for details see Appendix-15.4.1, Table 15.27). The effect of TCBZ-SO on hatching appears to be due to a reduction in the number of cells that reached cell division; the authors state that these findings are compatible with an anti-microtubule action, involving cell

division and differentiation. Inhibition of microtubules is likely to affect the motility of miracidia that move by means of cilia and inhibit the hatching process.

**Reviewer's comments:**

*TCBZ and its metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>), at a concentration of ≥10 µg/mL, are effective in inhibiting motility and disrupting the tegument as well as the ultrastructure of immature and adult worms of *F. hepatica* within 18 to 24 hours. The relative activity of the TCBZ and its two metabolites appears to vary depending on the stage of the parasite and previous exposure; the activity of TCBZ and its metabolites was reduced against the resistant strains. Overall, the studies suggest that TCBZ and its metabolites are active against *Fasciola* worms; the activity appears to vary against the immature and adult worms.*

*The effect of TCBZ-SO on egg hatching in vitro, against the drug sensitive strains, appears to be at a 5-6-fold higher concentration compared to that against the resistant worms. Based on a limited number of strains tested; the egg hatching assay appears to discriminate between TCBZ-sensitive and -resistant strains.*

### 8.1.3. Activity in vivo

The activity of TCBZ was measured in animals with experimentally induced or natural infection with *Fasciola* species.

#### 8.1.3.1. Experimentally induced infection with *F. hepatica* or *F. gigantica*

The activity of TCBZ was reported in animals experimentally infected with *F. hepatica* or *F. gigantica*:

- ***F. hepatica***
  - Rats [51].
  - Sheep [52-56].
  
- ***F. gigantica***
  - Guinea pigs [57].
  - Cattle/buffaloes [58-60].

The infection was induced with metacercaria stage of *F. hepatica* or *F. gigantica*; however, the experimental design varied for different studies (for details see Appendix-15.4.2, Table 15.28). Some of the variations include the number of metacercariae used for infection, route of infection, time of initiation of treatment post-infection, dose and route of TCBZ administration. The activity of TCBZ was based on either a reduction in immature and mature worm burden (examined at the time of euthanasia/slaughter) in gall bladder and liver/bile duct, egg count in fecal specimens, coproantigen levels, and/or liver function. In some of the studies, effects of TCBZ treatment on egg hatching ex vivo and morphology and ultrastructure were reported.

***Effect on parasite burden:***

Overall, the studies show that TCBZ is effective in reducing parasite burden (immature and mature worms, egg count as well as coproantigen) and restoring liver function. The worms recovered were shorter in length.

The effect of different parasite burden on TCBZ activity was reported in one study [53]. Briefly, cattle were infected with 3 different inoculum concentrations (100, 200, and 500) of metacercariae of *F. hepatica*. Animals were treated with TCBZ on Day 84 post-infection and followed for egg excretion and presence of coproantigens in fecal specimens as well as serum antibodies (IgG) at different time interval post-treatment. In animals with higher worm burden, coproantigen positives preceded fecal egg excretion. Majority of the animals (11 of 12) were antibody positive on Day 28, i.e., prior to becoming coproantigen positive. All animals were excreting eggs and coproantigens at the time of initiation of treatment (Day 84) and were serum antibody positive. No eggs or coproantigens (based on OD <0.014) were detected in fecal specimens within a week of treatment with TCBZ or at the time of slaughter; no worms were detected in gall bladder or liver/bile duct at the time of slaughter. All the untreated animals were egg, coproantigen, and worm positive at the time of slaughter. However, all animals, irrespective of the treatment group, remained serum antibody positive. There appears to be a correlation between egg excretion and coproantigen levels as well as coproantigen and worm burden.

***Effect on egg hatching ex vivo:***

One study [55] in sheep, reported the effect of treatment with TCBZ on egg development; treatment with a dose of 0.5 mg/kg of TCBZ for 5 days had an inhibitory effect on egg development ex vivo. One study [55] in sheep, reported the effect of treatment with TCBZ on egg development; treatment with a dose of 0.5 mg/kg of TCBZ for 5 days had an inhibitory effect on egg development ex vivo.

***Effect on morphology and ultrastructure of worms:***

Halferty *et al.* [56] reported morphological and ultrastructural changes of immature worms collected from TCBZ treated sheep that were infected with a drug sensitive strain (Cullompton) of *F. hepatica*. The changes induced, by treatment with TCBZ, progressed and became more severe overtime. For example, the worms collected at 48 hours post-treatment, with a single dose of TCBZ, were active and had full gut content; this is similar to the worms from untreated sheep. However, at 72 hours the worms were dead and had sparse gut content; at 96 hours, the worms were dead, and no gut content was observed. By SEM more severe disruptive changes were reported that include absence of tegument with deep lesions and internal tissues exposed. Overall, there was a progressive increase in the level of disruption over the 72-hour period. The ventral surface was more severely affected than the dorsal surface and the disruption was greater in the posterior region of the fluke and along the lateral margins.

**8.1.3.2. Natural infection with *F. hepatica* or *F. gigantica***

The activity of TCBZ was reported in naturally infected livestock animals that include sheep, goat, cattle, and horses; the studies were conducted in animals living on farms or regions

known to be endemic for either *F. hepatica* [55, 61, 62] or *F. gigantica* [63, 64]. The activity of TCBZ was based on a reduction in egg excretion. In one study [55], animals were slaughtered at Week 10 after the last dose and the number of immature and mature worms recovered counted. In one study [55], animals were slaughtered at Week 10 after the last dose and the number of immature and mature worms recovered counted. Overall, the studies show that TCBZ is effective in reducing egg secretion and pasture contamination. Recurrence of eggs in fecal specimens was reported in some of the studies; this could be due to re-infection. Overall, the studies suggest that TCBZ is effective against immature and mature worms and reduces egg secretion (for details see Appendix 15.4.2, Table 15.28).

One study [61] suggests that treatment with TCBZ may be effective in reducing pasture contamination in addition to egg excretion. One study [61] suggests that treatment with TCBZ may be effective in reducing pasture contamination in addition to egg excretion. Briefly, animals living on a farm that include Coopworth sheep (lambs, ewes, and rams), cows and horses that were naturally infected with *F. hepatica* in New Zealand were treated with TCBZ. The results show that TCBZ at a dose of 10 mg/kg was effective in clearing the fecal eggs at Month 14 after treatment. This was associated with a reduction in pasture contamination to a negligible level after the final treatment, as measured by survey of snails present on the farm for the presence of larvae to determine infectivity and comparing with snails on neighboring property where no treatment was administered.

**Reviewer's comments:**

*Overall, the studies support the activity of TCBZ against *F. hepatica* and *F. gigantica* in rodents and livestock animals that were either experimentally infected with metacercariae or living on farms known to be endemic for Fasciola infection. Activity was measured by the egg count and/or coproantigens in fecal samples by ELISA or enumeration of the number of worms in liver/bile duct and gall bladder. Overall, the studies suggest that TCBZ is effective in reducing egg counts as well as effective against immature (acute phase), late immature, and mature flukes (chronic phase).*

*One study reported the ex vivo inhibitory effect of TCBZ treatment of egg development. Also, TCBZ treatment was associated with a reduction in pasture contamination.*

#### **8.1.4. Drug Resistance**

Studies in vitro and in vivo in livestock animals and humans suggest a potential for development of resistance to TCBZ and its metabolites. However, there are no standardized tests for the determination of drug resistance in subjects with *F. hepatica* or *F. gigantica* infection. Some of the studies supporting development of resistance as well as the mechanism of resistance are summarized below.

##### **8.1.4.1. Potential for development of resistance**

- **Studies in vitro**

Studies in vitro show reduced surface disruption of the worms of the TCBZ-resistant strains, compared to sensitive strains, after incubation with TCBZ or its metabolites (for details see Section 8.1.1 above and Appendix-15.4.1, Table 15.27). Fairweather *et al.* [50] reported that incubation of eggs of several TCBZ-resistant strains with TCBZ-SO (60 µg/mL) for 14 days was less effective in inhibiting egg hatching compared to that of eggs from drug-sensitive strains.

- **Studies in vivo**

Boray [65] reported selection of a resistant strain of *F. hepatica* in sheep that were treated with TCBZ every 8 weeks for 2 years. Boray [65] reported selection of a resistant strain of *F. hepatica* in sheep that were treated with TCBZ every 8 weeks for 2 years.

Resistance to TCBZ, based on persistence of eggs in fecal specimens on Days 14 or 21 post-treatment, has been reported in *F. hepatica*-infected livestock animals in several countries including Australia, UK, Netherlands, Scotland, Spain, Republic of Ireland, New Zealand, Peru, Chile, Turkey, and Argentina [18, 26, 66, 67] reported resistance based on a lower (<90%) reduction in coproantigen levels in fecal specimens from livestock animals (beef/dairy cattle) on an Australian dairy farm.

In humans, persistence of *F. hepatica* infection or failure to respond to TCBZ treatment has been reported in several countries, including Chile (n=4), Turkey (n=1), Peru (n=7) as well as a sheep farmer in Netherlands [25, 68-70]. Also, there were several patients that failed to respond to TCBZ after an outbreak in Northern Islamic Republic of Iran.

#### **8.1.4.2. Mechanisms of resistance**

The mechanism of resistance development by *Fasciola* species to TCBZ appears to be multifactorial that include changes in target molecules, drug uptake/efflux mechanisms, and drug metabolism. Some of the studies supporting mechanism of resistance are summarized below:

##### **8.1.4.2.1. Effect on $\beta$ -tubulin**

Robinson *et al.* [34] reported disruption of the tubulin organization in the tegument of TCBZ-sensitive worms but not in the TCBZ-resistant strain of *F. hepatica* after 24 hours of incubation with 50 µg/mL of TCBZ-SO; disruption was measured by immunostaining with anti-tubulin antibody and indirect fluorescent antibody test. However, there was no difference in the amino acid sequence of  $\beta$ -tubulin cDNAs from TCBZ-sensitive and TCBZ-resistant worms suggesting that disruption of tubulin in drug-resistant strain is not associated with changes in amino acid sequence of  $\beta$ -tubulin. Inhibition of disruption of the tubulin may lead to resistance.

Ryan *et al.* [71] reported some differences in amino acid sequence of the  $\beta$ -tubulin among the isotypes of the 7 worms of a TCBZ-sensitive strain (Cullompton). However, based on a comparison of the RT-PCR sequence of the 7 worms of the TCBZ-sensitive worms with 7 worms from the 2 resistant strains (Sligo and Oberon), no differences were reported. It is unclear

whether these observations are due to a small number of worms and strains tested. Also,  $\alpha$ -tubulin was not evaluated.

**8.1.4.2.2. Effect on drug uptake/efflux mechanisms - transtegmental diffusion**

Alvarez *et al.* [72] reported differences in the ability of TCBZ sensitive (Cullompton) and resistant (Sligo) strains of *F. hepatica* adult worms, to uptake TCBZ or its metabolites. The worms were recovered from the common bile ducts and the gall bladder of lamb. The worms were incubated with 5 nM/mL of either TCBZ (1.8  $\mu\text{g}/\text{mL}$ ), TCBZ-SO (1.9  $\mu\text{g}/\text{mL}$ ) or TCBZ-SO<sub>2</sub> (2.0  $\mu\text{g}/\text{mL}$ ) for up to 180 minutes and washed at different time points (15, 45, 90, 120 and 180 min) and processed to measure concentrations of TCBZ and the metabolites by HPLC. The drug concentration reflects drug diffusion in to the parasites. The results show lower concentration of TCBZ in the resistant parasites, compared to the sensitive parasite for up to 120 minutes; this was followed by an increase at 180 minutes. TCBZ-SO concentrations were reduced in the resistant strain, compared to the sensitive strain at all the time points tested. TCBZ-SO<sub>2</sub> concentrations were higher for up to 45 minutes in the sensitive strain compared to the resistant strain; thereafter, the concentrations were the same in sensitive and resistant strains. Protein content was similar between the resistant and sensitive strain.

Several studies [44, 73, 74] suggest a role of ABC transporters such as P-glycoprotein (PgP) in increased TCBZ efflux. For example, Mottier *et al.* [73] reported that ivermectin, a substrate of PgP, increased the concentrations of TCBZ and TCBZ-SO by decreasing efflux from the resistant strain (Sligo) compared to sensitive strain (Cullompton). Meaney *et al.* [44], reported an increased disruptive effect on the morphology of resistant worm (Oberon strain) in the presence of TCBZ-SO and verapamil, a PgP inhibitor, compared to the worms of the TCBZ-sensitive (Cullompton) strain of *F. hepatica*; the sensitivity of worms of the TCBZ-sensitive strain to TCBZ-SO was not altered in the presence or absence of the PgP inhibitor.

Savage *et al.* reported altered drug efflux in TCBZ-resistant (Sligo strain) worms of *F. hepatica*. Briefly, the adult worms of the Sligo strain were incubated with either TCBZ-SO (50  $\mu\text{g}/\text{mL}$  – 133.1  $\mu\text{M}$ ), R(+)-verapamil (a PgP inhibitor), or a combination of TCBZ-SO and R(+)-verapamil. Changes in the testis tubules and vitelline follicles following drug exposure and following PgP inhibition were assessed by means of light microscope histology and TEM. Incubation of the Sligo strain with either R(+)-VPL or TCBZ-SO had a limited impact on the worm morphology. However, greater disruption was observed when exposed to R(+)-VPL or TCBZ-SO; these changes include a block in the development of the spermatogenic and vitelline cells as well as the apoptotic breakdown of the remaining cells leading to an impairment of sperm formation. Also, large spaces appeared in the vitelline follicles and synthesis of shell protein was disrupted. The potentiation of TCBZ-SO activity in vitro by co-incubation with R(+) VPL is similar to that observed with ketoconazole [42]. Although ketoconazole is a recognized CYP inhibitor, it has dual activity in that it is also regarded as an inhibitor of Pgp linked drug efflux pumps.

Wilkinson *et al.* [75] reported a difference in the DNA alleles for the PgP in worms from cattle raised on farms that were either TCBZ-sensitive or -resistant (the authors state that the sensitive and resistant designations are functional designations for the populations present on

the two farms: the "resistant" populations contained up to 36% sensitive worms and the "sensitive" population may contain a minority (<10%) of resistant worms). A greater diversity in *Pgp* haplotypes in the worms from the farm exhibiting TCBZ resistance was reported compared to those from the farm with sensitive worms.

Elliott and Spithill [76] analyzed the *Pgp* gene from TCBZ-sensitive and TCBZ-resistant worms from Australia to determine if the T687G SNP in the *Pgp* gene is associated with TCBZ resistance. Based on the 21 worms tested, the results showed that T687G SNP in *Pgp* gene was not associated with TCBZ resistance in the Australian *F. hepatica* worms evaluated.

Overall, the studies suggest that drug transporters, such as Pgp, may play a role in the development of TCBZ resistance against *F. hepatica*.

#### **8.1.4.2.3. Effect on drug metabolism by the parasite**

Robinson *et al.* [77] reported differences in the metabolism of TCBZ-SO by adult worms of the TCBZ-sensitive (Cullompton) and resistant (Sligo) strains of *F. hepatica* in vitro. Briefly, adult worms of the Cullompton and Sligo strains were incubated with TCBZ-SO (50 µg/mL) at 37°C for up to 24 hours and metabolism to 6 metabolites was monitored by HPLC. No measurable spontaneous oxidation of TCBZ-SO was reported in controls. The levels of both TCBZ-SO and TCBZ-SO<sub>2</sub> were higher in the TCBZ-resistant worms, compared to the sensitive worms at the different time points (3, 6, 12, and 24 hours) tested; such an effect was observed within 3 hours of incubation. TCBZ-SO levels were higher than TCBZ-SO<sub>2</sub> levels up to 12 hours in both TCBZ-sensitive and resistant-strains; at 24 hours, however, the levels were similar. The concentration of the TCBZ-SO<sub>2</sub> remained constant within the TCBZ-sensitive worms following 3 and 6 hours of incubation; this was followed by a trend towards an increase in TCBZ-SO<sub>2</sub> levels at 12 hours and a decrease at 24 hours. Although the concentration of both TCBZ-SO and TCBZ-SO<sub>2</sub> within the TCBZ-resistant worms fluctuated over the time course, these concentrations remained higher than that within the TCBZ-sensitive worms at all time periods. Overall, the study suggests differences in uptake of TCBZ-SO as well as metabolism to TCBZ-SO<sub>2</sub> between the worms of the TCBZ-resistant and-sensitive strains. The study also suggests ability of the parasite to metabolize/convert TCBZ-SO to TCBZ-SO<sub>2</sub>.

Alvarez *et al.* [72] reported the effect of microsomal fraction of *F. hepatica* on biotransformation of TCBZ to TCBZ-SO by incubating a homogenate of TCBZ sensitive and resistant strains with TCBZ (15 nM in 10 µL i.e., 5.4 µg/mL), in the presence of NADPH, for 60 minutes. The results show that the microsomal fraction from both TCBZ-sensitive and -resistant strains was effective in oxidizing TCBZ to TCBZ-SO; however, the sulphoxidative metabolic rate was significantly lower in the TCBZ-sensitive compared to the TCBZ-resistant worms. Only trace amounts of TCBZSO<sub>2</sub> were recovered. Formation of TCBZ-SO was reduced after inhibition of cytochrome P450 system or flavin monooxygenase enzymes in both sensitive and resistant worms; TCBZ-SO<sub>2</sub> was not observed after the inhibition of both enzymatic systems.

Devine *et al.* [42] reported that ketoconazole (KTZ), an inhibitor of the cytochrome P450 (CYP 450) system within *F. hepatica*, was effective in increasing the sensitivity of the resistant strain

(Oberon) to TCBZ or TCBZ-SO as measured by SEM. However, the effect on a TCBZ-sensitive strain (Cullompton) was less, that too with TCBZ-SO.

#### **8.1.4.2.4. Effect on enzymes / isoenzyme**

An increase in the activity of xenobiotic metabolizing enzymes (XMEs) is thought to be associated with increased detoxification of the anthelmintics and resistance. In TCBZ-resistant worms, compared to TCBZ-sensitive worms, an increase in the activity of some of the XMEs of phase I (carboxylesterase) and phase II [glutathione S-transferases (GST) and carbonyl reductases] was reported. For example, Scarcella *et al.* [78-80] reported an increased activity of carboxylesterase enzyme, that catalyze Phase I biotransformation and produce hydrolytic reactions, in the parasites recovered from lambs infected and treated with TCBZ. Briefly, lambs were infected experimentally with 200 metacercariae of *F. hepatica* and treated orally with 10 mg/kg of TCBZ at Week 16 post-infection and slaughtered at different time points post-treatment (0, 3, 24, 48 and 60 hours); worms were collected and processed for measuring TCBZ-SO levels as well as carboxylesterase enzymatic activity. The results show an increase in enzyme activity within 3 hours post-treatment; the enzyme activity increase followed behind the peak of TCBZ-SO concentration and decreased to baseline at 60 hours post-treatment. In another study in sheep treated with TCBZ, an increase in the activity of XMEs of phase I (carboxyl esterases) and phase II (GST and carbonyl reductases) of worms recovered was reported. The XMEs analyzed were increased in the TCBZ-resistant strain (Sligo) compared to the -sensitive strain (Cullompton); the XMEs appear to play a role in the development of resistance to TCBZ in *F. hepatica*.

Fernandez *et al.* [81] characterized the *GST mu* gene isolated from the TCBZ-sensitive (Cullompton) and TCBZ-resistant (Sligo) *F. hepatica* strains. Total RNA was transcribed into cDNA by reverse transcription and a 657 bp amplicon corresponding to the *GST mu* gene was obtained. The comparative genetic analysis showed three nucleotide changes and one amino acid change at position 143 in the *GST mu* isozyme of the TCBZ-resistant strain compared to the TCBZ-sensitive strain.

#### **8.1.4.2.5. Proteomics**

Brennan *et al.* [82] reported increased production of several soluble proteins by the Sligo (TCBZ-resistant) compared to the Cullompton (TCBZ-sensitive) strain after exposure to the drug. HSP-70 was only over-produced in resistant flukes following TCBZ-SO exposure in culture. These proteins are thought to protect cells from cellular stress by binding to partially denatured proteins and preventing aggregation.

#### **Reviewer's comments**

*Overall, the studies in vitro and in vivo in livestock animals and humans suggest a potential for development of resistance to TCBZ and its metabolites. The mechanism of resistance appears to be multi-factorial that include disruption of  $\beta$ -tubulin, altered drug influx/efflux and enhanced metabolic capacity of TCBZ-resistant worms of Fasciola.*

## 8.2. Clinical Microbiology

The Applicant has submitted study reports and/or publications for several clinical studies to support the efficacy of Egaten. The parasitological evaluations in the clinical trials included detection of eggs of *Fasciola* species in fecal specimens and/or serology.

### 8.2.1. Parasitological assessments by fecal smears

Parasitological assessments of the patients enrolled were based on evaluation of fecal specimens, for the presence of *Fasciola* eggs; these assessments were conducted prior to initiation of therapy for confirming diagnosis/patient enrollment and post-treatment follow-up. In one study, efforts were made to identify the *Fasciola* species.

- **Patient enrollment and post-treatment follow-up:**

The parasitological evaluations, in all the clinical studies in subjects with chronic fascioliasis, were based on detection of eggs of *Fasciola* species in fecal specimens prior to treatment for patient enrollment and at follow-up visits to evaluate efficacy; the primary endpoint was based on absence of eggs (Maco *et al.* and Keiser *et al.* [4, 5]; 6 CIBA/WHO studies; 3 Egyptian government studies). The Kato-Katz method was used for detection of eggs in a majority of the studies to determine cure rates. In some of the studies other methods were used that include concentration tests such as sedimentation test (Appendix-15.4.3, Table 15.30). In addition to detection of eggs in fecal specimens, duodenal aspirate was collected and processed for detection of eggs by Enterotest on Day 60 for subjects with chronic fascioliasis enrolled in the 6 CIBA/WHO studies. Most of the testing was conducted at the site laboratories. The information on the details of the quality control measures implemented was not available for review.

Overall, the results show TCBZ is effective in decreasing egg excretion in subjects with chronic fascioliasis. Quantitative assessment of egg density, by the Kato-Katz method was performed in some of the studies. The results show a decrease in egg count/g stool overtime.

- **Identification of *Fasciola* species**

The *Fasciola* species, known to be endemic in the geographic areas where all the clinical trials (except one - EGA230B2209) were conducted, was based on epidemiological findings. The identification of *Fasciola* species was performed in Study EGA230B2209 that was sponsored by the Egyptian government; the species identification was based on the egg size. For details on the *Fasciola* species in different countries where clinical trials were performed see (Appendix-15.4.3, Table 15.30).

Overall, the studies support activity of TCBZ against *F. hepatica* and *F. gigantica*.

**Reviewer's comments:**

*The Kato-Katz method, used in most of the studies, is an appropriate method for patient enrollment and measuring efficacy in patients with chronic fascioliasis. The production of eggs*

*by the adult worms can be intermittent as adult worms of Fasciola are producing eggs that are carried into the intestinal tract. The Kato-Katz technique is not useful for diagnosis during the incubation phase and the acute phase, i.e., infections that occur 3–4 months after exposure can be missed.*

*Cure rates based on absence of Fasciola eggs is an appropriate measure of efficacy in patients with chronic disease.*

*Quantitative assessment of egg density, by the Kato-Katz method was performed in some of the studies. The results show a decrease in egg count/g stool overtime in subjects treated with TCBZ (for details see Section 7).*

### 8.2.2. Parasitological assessments by serology

Detection of serum antibodies by an enzyme linked absorbent assays (ELISA) was conducted in three studies:

- Subjects with acute fascioliasis (Hien *et al.* [3]) conducted in Vietnam.
- Subjects with chronic fascioliasis (Maco *et al.* [5]) conducted in Peru.
- Subjects with chronic fascioliasis (Apt *et al.* [17]; EGA230B2203 AH/F2) conducted in Cuba.

The ELISA used in the three studies varied. The variability includes type of antigen used for detecting serum antibodies; complete details of the methods used as well as the performance of the assays were not available for review (for details see Appendix-15.4.3, Table 15.30).

#### **Reviewer's comments:**

*ELISAs used in some of the studies to detect the circulating IgG antibodies may reflect past infection. The details of the methods used, and performance characteristics of the assay were not available for review. The results of the serum antibody assays should be interpreted with caution.*

### 8.2.3. Interpretive Criteria

The Applicant has not requested any interpretive criteria in the labeling. This is appropriate as the tests to measure in vitro sensitivity of parasites of the *Fasciola* species are not standardized and their use is limited to research laboratories.

## 9 Review of Safety

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The review of safety for Egaten was complex given its unusual clinical development program; this is outlined here to provide necessary background and context. TCBZ was developed by CIBA-Geigy (Novartis' predecessor) in 1978 and introduced for veterinary use as Fasinex in 1983. Early studies in sheep showed efficacy of 90-100% at doses between 2.5 mg/kg and 10 mg/kg [52]. Its first human use was in 1986 in 2 individuals with fascioliasis who had failed multiple other treatments; the drug was tolerated well at doses of 12 mg/kg (patient #1) and 5 and 10 mg/kg on 2 consecutive days (patient #2), and both patients were cured [83].

In 1989, Fasinex was successfully used to treat human fascioliasis in an extensive Iranian outbreak [84]; a year later, the World Health Organization's (WHO) Division of Control of Tropical Diseases (CTD) and CIBA-Geigy established a Memorandum of Understanding to conduct 6 clinical trials of TCBZ in the treatment of fascioliasis (in Iran, Bolivia, Peru, Cuba, and Chile) and 3 trials in paragonimiasis (in Cameroon and Ecuador). CIBA-Geigy agreed to perform all the non-clinical studies required, while WHO assumed responsibility for developing a clinical trial protocol, supporting clinical development, and analyzing the data from clinical trials (referred to in this section as the CIBA/WHO Trials). These trials, conducted between 1989 and 1992, were designed as Phase 2 dose-ranging studies; Phase 1 studies in healthy humans were not conducted.

Multiple toxicology and dose-ranging studies of Fasinex conducted in animals are reviewed by Dr. Tessie Alapatt in Section 5.5. Early published studies in animals using TCBZ doses of 2.5-10 mg/kg indicated efficacy of 90-100% in eliminating both immature and adult flukes [52]. Presumably based on these reports, the initial doses for treatment of infected humans were 5-12 mg/kg [83]. Following analysis of results from the CIBA/WHO trials, a dose of 10 mg/kg was chosen [Fact Sheet No. 191 – WHO] and is the standard dose used worldwide, although a 10 mg/kg dose given 12-24 hours apart is generally recommended for treatment failures.

*Reviewer Comment: The Applicant was requested to provide a formal justification of dose selection and stated that 10 mg/kg is the dose that seemed most effective following the CIBA/WHO studies and that has been used worldwide for fascioliasis treatment. The human dose appears to have initially been chosen to be equivalent to effective doses in animals – the only dose-ranging studies submitted to this NDA are the CIBA/WHO studies which were not conducted under GCP and would not meet current standards of study conduct.*

The human formulation, Egaten, was developed in the early 1990's by the Applicant and approximately 2.6 million doses have been donated and distributed through WHO for treatment of human fascioliasis in 34 countries since 2006. Because both Fasinex and Egaten have been used extensively in clinical trials, mass drug treatment programs, and for treatment of fascioliasis since the late 1980's, the Applicant contended that the safety record of this drug at their proposed dosing regimen ( (b) (4) ) has been well-established.

Efficacy of TCBZ in the 3 IITs, the 6 CIBA/WHO studies, and relevant literature was discussed in Section 7. For demonstration of safety of Egaten<sup>®</sup>, the Applicant used the following:

- The published IITs, by Maco et al. and Keiser et al. (full details provided in Section 7.1.1), for which right of reference for patient-level data was obtained from the Principal Investigators (PIs).
- 6 CIBA/WHO trials for which Novartis owns legacy data.

*Reviewer Comment: Safety data were apparently not collected in the Hien study, and are not mentioned in the publication; thus, this study is not discussed further in this section. Given the lack of a protocol, it is uncertain whether safety data collection was not specified in the protocol, or whether there were issues with data collection. Nonetheless, it is a significant issue because the Hien study was the only one of the IITs to enroll patients with acute fascioliasis, and the dose used was 20 mg/kg (10 mg/kg q24h x 2).*

*All of the studies listed above enrolled patients with the chronic stage of fascioliasis as assessed by egg excretion in stool. In addition to having different protocols, the formulation of TCBZ used in these studies was not uniform – Fasinex was used in 59/84 (70.2%) patients in the Maco study, and in all but 6 patients in the CIBA/WHO studies, while Egaten was used in the remaining 29.8% of patients in the Maco study, the 16 patients in the Keiser study, and in 6 patients in the CIBA/WHO studies.*

*An audit of the Maco study completed late in the NDA review revealed several deficiencies in source data – those that impacted efficacy are detailed in Section 7.1.1. In addition, absence of subject exclusion criteria was not documented for any subject and some treatment records were available for only 42/84 subjects. In addition, documentation of AE monitoring was limited to early post-treatment – Days 1-5; no monitoring records were available for review for Days 10-60. The Maco study is viewed as supportive for purposes of this review.*

*For the purposes of this review, Egaten and Fasinex will be considered equivalent as the Biopharmaceutical reviewer, Dr. Gerlie Geiser, has agreed that bioequivalence between the two formulations has been established.*

Supportive evidence of safety was provided by:

- 3 historical studies of Fasinex for treatment of paragonimiasis, caused by the lung fluke *Paragonimus westermanii*.
- 3 historical studies sponsored by the Egyptian government using TCBZ (CGP 23030, the interim human formulation) for fascioliasis
- Selected literature studies

- Report from the Named Patient Program, comprising individuals with fascioliasis for whom TCBZ was obtained directly from the legacy originator company CIBA.
- The Applicant's Periodic Safety Update Report (PSUR) for TCBZ, 2012-2017

Over the course of the review, the review team concluded that a change to the Applicant's proposed dosing regimen was required. Based on the fact that the only randomized clinical trial submitted to this NDA – the Hien study – used a total of 20 mg/kg in divided doses for treatment of acute fascioliasis and was pivotal in demonstrating the efficacy of TCBZ, and that a dose-response for efficacy was demonstrated in the WHO/CIBA studies for chronic fascioliasis with 20 mg/kg being the most effective, the labeled dose for treatment of fascioliasis is 10 mg/kg q12h x 2. Thus, evidence for safety of 20 mg/kg TCBZ is specifically addressed in this section.

### 9.1. Safety Review Approach

Analysis of the legacy evidence for TCBZ safety as outlined above was challenging as each of the safety data streams above were problematic in different ways and none were designed as registrational trials. Safety data from the Maco and Keiser IITs, though apparently conducted under GCP, were very limited and recorded the presence/absence and severity of selected AEs identified in approved TCBZ package inserts from France and Egypt (which were based on safety data from the CIBA/WHO studies), rather than a standard open-ended collection of these events.

*Reviewer comment: In their response to an IR, the Applicant noted that an open-ended query for adverse events was conducted during the Keiser study in addition to recording the presence/absence of selected AEs; according to the Applicant's response, no other AEs were reported in the publication because none others were recorded.*

Patient-level data from line listings and study reports for the 6 CIBA/WHO trials were constructed into datasets and formed the foundation of the safety analysis. Table 7.1 in Section 7 provides details of the Maco, Keiser, and CIBA/WHO trials.

The studies providing supportive evidence (detailed above), primarily as clinical and study reports, were also problematic – virtually all, except the PSUR, were old studies, not conducted under GCP and non-uniform in their methods of obtaining and recording safety data. However, a descriptive analysis of the Egyptian government-sponsored studies and the paragonimiasis studies was attempted by this reviewer; in particular, the latter afforded a useful opportunity to analyze the safety of TCBZ in patients with a condition of pathophysiology different from fascioliasis.

Finally, in addition to the literature references provided by the Applicant, an independent literature search was conducted for studies assessing TCBZ safety – these studies are detailed in

Section 9.1.8. In the supportive studies, various formulations of TCBZ (Fasinex, CGP23030, and Egaten) were used; where possible, the specific formulation used in each study is noted.

## 9.2. Review of the Safety Database

**Overall Exposure** A total of 345 subjects were exposed to varying doses of TCBZ in the primary safety population (Table 9.1):

**Table 9.1 Primary Safety Population for TCBZ**

| Study/Design                                   | Number exposed to TCBZ | Dose of TCBZ                                                                        | Age (years) | Safety Data Available |
|------------------------------------------------|------------------------|-------------------------------------------------------------------------------------|-------------|-----------------------|
| Keiser <sup>1</sup> /open-label rescue therapy | 16                     | 10 mg/kg x 1 (n=16)<br>10 mg/kg x 2 after failure of the 1 <sup>st</sup> dose (n=4) | 11-70       | Targeted              |
| Maco <sup>2</sup> /dose-ranging, open-label    | 84                     | 7.5 mg/kg q12h x 2 (n=44)<br>10 mg/kg x 1 (n=40)                                    | 2-16        | Targeted              |
| CIBA/WHO studies                               | 245                    | Various regimens of 5-20 mg/kg                                                      | 6-75        | Yes                   |

<sup>1</sup>TCBZ was given as rescue therapy to 16 patients who failed artemether, AEs collected for 72 hours post-treatment in these patients

<sup>2</sup>59/84 patients received Fasinex®, the veterinary preparation, both are considered together for safety purposes. AEs were monitored on Days 1-5.

*Reviewer comment: The Keiser study focused on efficacy of artemether with the stated recognition that TCBZ was the only effective drug for treatment of fascioliasis, that others (bithionol, emetine, dihydroemetine, etc.) were associated with unacceptable adverse events and that novel anti-fasciolicidal agents were needed. Targeted safety information based on adverse events identified in TCBZ package insert in countries where this drug is registered (France, Egypt) were collected in the Keiser and Maco studies.*

Details of the supportive safety database are provided in Table 9.2:

**Table 9.2 Supportive Safety Data**

| Source                                                 | Number exposed to TCBZ | Dose of TCBZ                                         |
|--------------------------------------------------------|------------------------|------------------------------------------------------|
| Egyptian Government Sponsored Studies for Fascioliasis | 135                    | 5 mg/kg q6h x 2<br>10 mg/kg x 1                      |
| Named Patient Program                                  | 115                    | Various                                              |
| Paragonimiasis Studies                                 | 236                    | 5 mg/kg x 3 q24h<br>10 mg/kg q6h x 2<br>10 mg/kg x 1 |
| Publications referenced by the Applicant               | 558*                   | Various                                              |

\*These represent selected uncontrolled trials, though some were randomized. Many other patients are represented in other smaller trials, case reports and case series. While contributing to the overall evidence, these smaller reports were not specifically cited.

In addition, through Novartis' donation of TCBZ for treatment of fascioliasis, an estimated 1,888,719 treatment courses have been dispensed worldwide (through WHO) through 2017.

*Reviewer comment: A later IR response from the Applicant updated those numbers by noting that from 2006 through 2018, the total number of treatment courses distributed worldwide was 2.6 million.*

#### **Relevant characteristics of the safety population with patient-level data:**

The 6 CIBA/WHO studies, and the Keiser and Maco studies enrolled patients with established chronic fascioliasis, i.e. those excreting *Fasciola* eggs in stool. Pediatric and adult patients of both genders, were included in the Keiser study and in 5 of 6 CIBA/WHO studies (ages 16-75 years); the 6<sup>th</sup> was an exclusively pediatric study in Bolivian children. The Maco study enrolled only pediatric patients aged 2-16 years.

#### **Adequacy of the safety database:**

The size of the safety population (N=345) in the 8 studies mentioned above is considered reasonable; however, the reliability of the safety information is questionable and sometimes suboptimal, as detailed below. Summarized data were also available on around 1000 patients in the form of clinical/study reports and literature articles, which served to buttress the somewhat incomplete patient-level data. However, safety information from published studies in the literature was inconsistent: randomized studies collected safety information in non-standard ways, many case reports and case series mention no or only mild adverse events, and some make no mention of safety ascertainment in association with TCBZ use at all.

### **9.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

**IITs:** In both the Keiser and Maco trials, the presence/absence/severity of specific AEs were recorded, rather than open-ended queries of the patients. According to the investigators, these AEs were chosen based on existing labels for TCBZ in other countries. In addition, AE monitoring in the Keiser study was done for only 72 hours in the 16 patients who received TCBZ, while in the Maco trial, AE monitoring occurred on Days 1-5.

*Reviewer comment: In response to an IR dated 6/8/18, the Applicant noted that the specific AEs evaluated in the Maco and Keiser studies were based on AEs identified in the TCBZ package inserts approved in Egypt and France, which in turn, referenced AEs reported in the CIBA/WHO trials. However, the Applicant affirmed that an open-ended enquiry for post-treatment symptoms and signs in TCBZ patients was done in the Keiser study, and that no AEs other than those mentioned, were found.*

*As mentioned, none of the 3 IITs for which the Applicant obtained right of reference were designed as registrational trials, neither were they done under an IND; thus, neither FDA nor the*

*Applicant were involved in the protocol development or conduct. In response to an FDA query after the NDA submission, the Pls did confirm that these studies had been done in accordance with GCP.*

CRFs for the Keiser study were submitted to FDA under a separate pre-IND; CRFs were not available for subjects in the Maco trial.

**CIBA/WHO Trials:** CIBA and WHO developed the standard protocol for, and conducted 6 uncontrolled trials between 1989 and 1992, before the European Communities Directive 91/507/EEC on Good Clinical Practice was implemented. One trial each was conducted in Iran (EGA230B-2201), Chile (-2202), Cuba (-2203), and Peru (-2212); and two were done in Bolivia (adult [-2207] and pediatric [-2208] trials). CIBA supplied TCBZ (CGP 23030) for these trials and funded the analysis and reporting of results, which are summarized in respective CSRs and line listings. Patient-level data from these sources were transferred into datasets; however, safety data were not coded using MedDRA. Additionally, although they shared a common protocol, there appeared to be some differences in conduct of the studies and the dose of TCBZ (CGP 23030) used.

*Reviewer Comment: The Applicant explains that the CIBA/WHO studies were all uncontrolled because there was already evidence for efficacy of TCBZ in humans; thus, conduct of placebo-controlled trials was considered unethical. Additionally, production of bithionol, a commonly-used treatment for fascioliasis, had recently been discontinued.*

Because the trials were not done under GCP, the Applicant notes that the following were sometimes inadequately performed or documented: trial monitoring, drug accountability, patient information, source data verification; existence of the trial master file, definition of inclusion and exclusion criteria in the CRF, and definition of serious adverse events in the protocol.

As mentioned, all studies used CGP 23030 as the study formulation, except for 6 retreated patients in the Bolivian pediatric study who received Egaten. Also, according to the shared protocol, each trial was to have 4 treatment regimens: 5 mg/kg q24h x 3 (fasting), 10 mg/kg bid q12h x 2 (fasting), 10 mg/kg x 1 (fasting), and 10 mg/kg x 1 (post-prandial). However, none of the 6 trials had 10 mg/kg bid x 2 as a treatment arm, and 5 of 6 studies had less than 4 arms. A single trial (EGA230B2201, Iran) with 4 arms had slight different dosing for one of them, i.e. 5 mg/kg x 2. Each arm was to have 25 patients, for a total of 100 patients per study, but many study arms did not enroll these numbers.

For these studies, adverse events (AEs) were presented in Verbatim terms (VT) rather than in MedDRA Preferred terms (PT), resulting in splitting of similar AEs into related terms such as hypochondrial pain, epigastric pain and abdominal pain upper. In addition, frequency of AEs was reported as number of events rather than number of patients, which also resulted in multiple similar AEs in the same patient. The Applicant addressed these deficiencies – individual patient data listings in the CSRs were considered as source documents as the original paper

CRFs were no longer available, Verbatim Terms for AEs were coded to PTs per MedDRA version 20.0, and the occurrence of a specific AE in a patient was counted once despite multiple occurrences of that AE.

The AE table and listings are missing in the CSR for EGA230B2202 (Chile); the description of AEs in Section 6.1 of the body of the CSR and List 5 (pre-defined and free text symptomatology at Days 0, 1, 2, 3, 4, 6, 30 and 60) were used to prepare patient level AE data.

***Reviewer comment:** Shortcomings in the data and inconsistencies in the CSRs for these studies make the safety analyses challenging; where applicable, the shortcomings are noted in the review. Some of these inconsistencies are listed in the footnotes for Table 9.8. For example, in the adult Bolivian trial, EGA230B2207, 100% of patients were listed as having ultrasound results showing hepatic abscesses pre-treatment, but 100% of patients were also listed as having the same findings post-treatment. The Applicant questions the data themselves and speculates that “Accurate data recording in this study is questioned.” Numerically different estimates for efficacy and safety were sometimes presented in the same document (see footnote #6 of Table 9.8). In addition, there were significant variations in symptomatology at baseline, and the collection of information was incomplete and inconsistent from study to study.*

*In the Iranian, Chilean, and Cuban studies, abdominal pain was prominent at baseline (75%, 41.7%, and 79%, respectively) as were nausea, vomiting, constipation, diarrhea, and sweating. As the stage of egg excretion, i.e. chronic fascioliasis, is sometimes thought of as primarily asymptomatic, the symptoms reported at baseline in these studies underscore the fact that there is considerable clinical overlap between the so-called acute and chronic stages. Hepatomegaly appeared fairly common in some studies but not in others. Inconsistent collection and quality control of the safety data were notable. The CSR for the Bolivian adult study specifically noted the absence of signs and symptoms at baseline, while it is unclear what percentage of subjects in the Peruvian study had signs and symptoms at baseline.*

Datasets were not available for the 3 Egyptian fascioliasis and 3 CIBA/WHO-sponsored paragonimiasis studies which were also conducted prior to GCP requirements; thus, verification of the safety results presented in the study reports was not possible.

***Reviewer comment:** At the Late-Cycle Meeting, it was noted that the majority of safety information for the 20 mg/kg divided dose of TCBZ comes from the WHO paragonimiasis studies. The Applicant was asked to provide patient-level data from these studies in .xpt format to allow FDA analysis – these datasets were provided on 2/6/19 and are addressed in Section 9.7.1.*

### **Categorization of Adverse Events**

AEs were categorized differently in each of the 2 IITs considered for safety evaluation:

**Keiser:** At baseline (BL), a full clinical examination was done. Patients with acute fascioliasis were immediately treated with 10 mg/kg TCBZ and spasmolytic drugs and excluded from the

study. Patients with chronic fascioliasis who met the inclusion criteria were enrolled; a physician visited the patient on each treatment day (during the two 1- and 3-day artemether dosing regimens) and for 24-48h after final dosing; patients who reported AEs were examined and treated as needed. Details such as incidence, onset, cessation, duration, intensity, frequency, seriousness, and causality (as determined by the physician) of AEs were recorded. Follow-up after treatment was on Days 4-6 and at 4-5 weeks post-treatment for clinical examination and blood collection. AEs were monitored for 72 hours post-treatment in the patients who were retreated with TCBZ after failing artemether. The standardized questionnaire used to record AEs is shown in Table 9.3.

**Table 9.3 Adverse Event Collection Form and Grading of Adverse Events Used in the Keiser Study**

| ID       | Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |          |                   |         |       |        |          |          |              |                  |             |  |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------|---------|-------|--------|----------|----------|--------------|------------------|-------------|--|
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Headache | Allergic reaction | Fatigue | Fever | Nausea | Vomiting | Diarrhea | Constipation | Abdominal cramps | Yellow eyes |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                   |         |       |        |          |          |              |                  |             |  |
| Systemic | <b>Abdominal cramps:</b> 1= few episodes; 2= frequent episodes; 3= severe; 4= hospitalization<br><b>Headache</b> (1 = mild, no treatment required; 2 = moderate, treatment required; 3 = severe, treatment required; 4 = very severe)<br><b>Allergic reaction</b> (1 = mild pruritus without rash; 2 = localized urticaria; 3 = generalized urticaria; 4 = anaphylaxis)<br><b>Fatigue</b> (1 = normal activity reduced , 2 = normal activity reduced for more than 48 hours, 3 unable to work or care for self )<br><b>Yellow eyes 1= mild; 4= severe</b><br><b>Fever</b> (1 =37.7-38.5 C ; 2 = 38.6-39.5 C ; 3 = 39.6-40.5 C ; 4 = >40 C) |          |                   |         |       |        |          |          |              |                  |             |  |
|          | <b>Nausea</b> (1 = mild, 2 = moderate discomfort ; 3 = requires IV fluids ; 4 = hospitalisation)<br><b>Vomiting</b> (1 = 1 episode in 24 hours ; 2 = 2-5 episodes in 24 hours ; 3 = more than 6 episodes in 24 heures or IV fluids required ; 4 = hospitalisation)<br><b>Diarrhea</b> (1 = mild or transient (3-4 stools/day) ; 2 = moderate, (5-7 stools/day) ; 3 = more than 7 stools/day or bloody diarrhea and more than 2L IV fluids required ; 4 = hypotensive shock or hospita<br><b>Constipation</b> (1 = 1 stool every 2 days ; 2 = 1 stool every 3 days ; 3 = 1 stool every 3-4 days ; 4 = 1 stool per week)                     |          |                   |         |       |        |          |          |              |                  |             |  |

Source: Keiser Study Protocol, submitted to the NDA

According to the protocol provided, AEs were graded as mild, moderate, and severe, as follows:

- Mild – present, but no intervention required
- Moderate – present, and required medication for symptomatic relief, OR present, and interfered with normal daily activities
- Severe – present and required medical intervention beyond symptomatic relief.

*Reviewer comment: As noted on the AE recording form, only the presence or absence of specific AEs along with characterization of severity, was recorded. This severity characterization appears*

*specific to each individual AE and is more detailed than the general grading of AEs as provided in the protocol.*

**Maco:** Examination for signs and symptoms was done daily during the first 7 days post-treatment for surveillance and mitigation of any adverse events. A trained MD at each site recorded demographic data, daily signs, symptoms, and AEs (biliary colic, abdominal and epigastric pain, nausea or vomiting, diarrhea, anorexia, jaundice, pruritus, skin rash, headaches, dizziness, dyspnea, cough, cervical, thoracic, lumbar or muscular pain, use of antispasmodics). Any child with colicky abdominal pain was given an oral antispasmodic, and those with severe AEs such as jaundice, severe abdominal pain etc. were taken to the regional hospital for clinical evaluation. Routine physical exams were performed periodically until day 90.

*Reviewer comment: As noted previously, the OSI audit of the Maco study found that AE monitoring was only done on Days 1-5, and that no monitoring records for after that time period were available.*

**CIBA/WHO Studies:** The Protocol/Clinical Study Plan, identical for each of the 6 CSRs, was approved in 1990 by the Scientific Committee for Research in Human Subjects (SCRIHS) of the WHO. In general, the study period was 60 days; the treatment duration was 1-3 days; and patients were hospitalized for the first 7 days for treatment and observation, and then followed as outpatients until Day 60 after treatment.

The primary endpoint was fecal egg clearance at Day 60; egg counts were determined on Days 0, 6, 30, and 60. In the pediatric Bolivian trial, presence or absence of eggs in duodenal drainage fluid (Enterotest) was a primary endpoint. Secondary endpoints included presence or absence of live adult *F. hepatica* in the hepatobiliary system, changes in signs and symptoms of disease, and change in liver function tests and hematologic parameters. The protocol also outlined 4 dosing regimens for TCBZ (CGP 23 030) in each trial – 5 mg/kg q24h x 3 – fasting (Group A); 10 mg/kg q12h – fasting (Group B); 10 mg/kg x 1 – fasting (Group C); 10 mg/kg x 1 - post-prandial (Group D). However, each trial appears to have followed various components of these treatment regimens as outlined later in this section.

In the Bolivian pediatric study (EGA230B2208), the protocol was amended to allow for a pediatric population weighing between 27 and 33 kg to be recruited as follows:

- a low dose regimen of 5 mg/kg x 1 (this dose was 50% of the lowest dose approved for adult use and was not included in the approval from SCRIHS), then 5 mg/kg x 2 6-8hrs apart was introduced,
- no X-rays were taken
- patients or their families were permitted to refuse blood draws on Days 30 and 60 – the majority refused during the follow-up period
- for the detection of eggs, the Kato-Katz method was replaced by the rapid sedimentation technique.

All pediatric patients in EGA230B2208 (in common with the other 5 CIBA/WHO studies)

received the CGP 23030 formulation for initial treatment; 6 patients required retreatment and received Egaten for that. The CSR for EGA230B2208 notes however, that “there is no evidence of source data verification having been carried out at any of these visits. In addition, it is possible that patient case report forms were completed retrospectively” (page 17).

Clinical assessments were done after 4 pm on each day, and symptoms were graded on a 4-point scale for severity by the investigator. Vital signs (pulse, blood pressure, respiration rate), and assessment for hepatomegaly and jaundice were measured daily for the first 6 days, then on Days 30 and 60. The nature, duration, severity, and relationship to treatment of any sign and symptom not related to the trial indication or concomitant disease, and either observed by the investigator or reported by the patient, were recorded. Worsening of a medical condition present at the initial visit was considered a new AE.

Serious AEs were to be reported to WHO immediately. The score used for symptomatology assessment (anorexia, nausea, vomiting, pain in the right hypochondrium, abdominal pain, intercostal pain) was: 0 – none; 1 – mild; 2 – moderate; 3 – severe. Relationship to trial treatment was rated as: 0 – none; 1 – remote; 2 – possible, 3 – probable. The definition of “serious adverse experience” was not included in the clinical trial protocol.

*Reviewer comment: The definitions of mild, moderate, severe for symptomatology assessment were not provided.*

Tolerability was rated by the investigator as: “good” – if there were no AEs; “acceptable” – if signs/symptoms due to “biliary crisis” were mild, moderate, or severe and controlled by spasmolytics; and “unacceptable” if life-threatening complications occurred.

The schedule of assessments is provided below:

**Table 9.4 Schedule of Assessments Used in CIBA/WHO trials**

| Day                            | Pre-Treatment | In-Patient |   |   |   |   | Outpatient Follow-up |        |
|--------------------------------|---------------|------------|---|---|---|---|----------------------|--------|
|                                | Entry         | T          | T | T |   |   | 30                   | Final* |
|                                | 0             | 1          | 2 | 3 | 4 | 5 | 30                   | 60     |
|                                | 0             | 1          | 2 | 3 | 4 | 5 | 6                    | 7      |
| History                        | X             |            |   |   |   |   |                      |        |
| Physical Examination           | X             | X          | X | X | X | X | X                    | X      |
| Symptomatology                 | X             | X          | X | X | X | X | X                    | X      |
| Adverse Effects                |               | X          | X | X | X | X | X                    | X      |
| Laboratory Tests               | X             |            |   | X | X |   | X                    | X      |
| Stool Examination              | X             |            |   | X | X |   | X                    | X      |
| X-Rays                         | X             |            |   |   |   |   | X                    | X      |
| Sonography <sup>o</sup>        | X             |            |   |   |   |   |                      | X      |
| Concomitant Treatment          | X             |            |   |   |   | X | X                    | X      |
| Concomitant Medical Conditions | X             |            |   |   |   | X | X                    | X      |
| Duodenal Fluid Examination     |               |            |   |   |   |   |                      | X      |
| Global Assessment              |               |            |   |   |   |   |                      | X      |

T – Treatment according to groups A, B, C, and D.

<sup>o</sup> – Optional

\* – Or when trial is discontinued prematurely.

### Routine Clinical Tests

**Keiser:** Stool samples were evaluated for the presence of for *F. hepatica* and/or *F. gigantica* eggs as outlined in Section 7.2.1. Blood was collected at baseline and at Day 28 after treatment with Egaten® for complete blood count, including RBC, WBC and differential, ESR, liver parameters (alkaline phosphatase, ALT, GGT, bilirubin) and kidney function (BUN, serum creatinine).

Patients with stool positivity post-treatment with artemether were treated with TCBZ 10 mg/kg x 1 and stool was collected over 3 consecutive days post-treatment starting on Day 28. Patients with stool positivity following a single dose of TCBZ were retreated with TCBZ 10 mg/kg q12h x 2 and stool was again collected over 3 consecutive days post-treatment starting on Day 28. In both single- and double-dose TCBZ groups, liver and renal function and hematological parameters were determined at BL and Days 5 and 28 post-treatment. Laboratory investigations of blood included total leukocyte count, hemoglobin, eosinophil count, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total serum bilirubin, blood urea, and serum creatinine.

**Maco:** Stool samples were collected at BL (for randomization), then on post-treatment Days 1, 3, 5, 10, 30, and 60 at the Asillo site and on Days 30, 60, 90, 120, 150, and 180 at the Lachaqui, Anta, Sicuani and Jauja sites. All stool samples were transported to (b) (4)

and examined by an experienced technician using the Rapid Sedimentation Technique (RST) for qualitative diagnosis. Blood was obtained at baseline for ELISA for detection of IgG against the 25KDa excretory/secretory antigen Fas 2 and for evaluation of eosinophilia (defined as >500/ $\mu$ L).

**CIBA/WHO Studies:** Laboratory testing for hemoglobin, hematocrit, erythrocyte count, WBC count and differential, AST, ALT, BUN, creatinine, alkaline phosphatase, bilirubin, and urinalysis for the presence of glucose, albumin, and sediment were done during the in-patient period as noted in the schedule of assessments.

Because the 6 trials occurred in 5 countries, the common protocol specified that a “list of methods adopted and the “normal” values of the laboratory should be forwarded to WHO before the start of the trial. In case of doubtful results (i.e. suspicion of technical errors), the test should be repeated and the correct value reported” (source: Trial protocol provided in Module II [Administrative] of each CSR). All patients with significantly abnormal lab test were to be followed regularly until the values returned to normal or until a valid reason, other than drug-related adverse experience, was identified. In selected patients with “biliary crisis”, hepatobiliary ultrasonography was used to visualize worm expulsion and hematologic and biochemical tests were carried out to evaluate potential complications.

## 9.4. Safety Results

### 9.4.1. Deaths, SAEs, Disposition

No deaths were reported in the Keiser, Maco, or CIBA/WHO studies.

*Reviewer comment:* An IR was sent to Novartis on 3/5/18 to verify this information for the Maco and Keiser studies; the Applicant verified that no deaths, discontinuations, or SAEs were recorded in any of these studies.

### Serious Adverse Events

Keiser study – none.

Maco study – none.

CIBA/WHO Trials: The definition of SAE was not provided in the protocol, but CRFs of 2 patients in the EGA230B2201 study in Iran who were hospitalized were provided in the CSR. The narratives below were constructed by the reviewer from review of the CRFs (Study entry, Days 2, 3, 4, 6, 30, and 60), as very scanty narratives were provided in the CSR.

- Patient (b) (6) was a 27-year old male with a history of fascioliasis unsuccessfully treated with mebendazole and praziquantel, who had mild diarrhea and moderate abdominal pain on enrollment and 4-11 *F. hepatica* eggs on each of 3 Kato-Katz stool preparations. On Day 4 after receiving 5 mg/kg x 2 TCBZ, he developed severe epigastric pain, nausea, mild fever, sweating, chest discomfort; these events were thought related to study treatment. No imaging information was available. On Day 6, he experienced similar symptoms and RUQ pain, dark urine, and icterus. A handwritten note on the CRF form states that he was hospitalized for a week, treated with gentamicin, hyocin, and Belladonna tablets. However, “he got worse and was transferred to (b) (4) (b) (6)”. Blood work on Day 6 was as follows: WBC 10.7, Hb 14.8, ALT 21? [handwriting unclear] IU/L; AST 26; ALP 297 IU/L, and total bilirubin 7.6 mg/dL. Hepatitis B surface antigen was negative, creatinine was 1.4 mg/dL, BUN 17 mg/dL, *F. hepatica* serology was 1:320, and stool exam was negative. He was prematurely discontinued from the study due to hospitalization for presumed cholangitis. No information regarding length of hospital stay, further investigations or hospitalization outcome were available.

A handwritten addendum on the Day 60 CRF form for this patient noted that at follow-up 1 year later, he had: “sometimes diarrhea and RUQ pain”, stool negative for eggs, *Fasciola* serology 1:80, and eosinophilia of 6%.

- Patient (b) (6) was a 36-year old woman with epigastric pain radiating to the back on enrollment. Stool examination at baseline by the Kato-Katz method noted 4-14 eggs of *F. hepatica* on 3 slides; egg count was 0 by Day 4 after treatment and remained negative through Day 30. No medical history or concomitant medications were noted. On Day 4 post-treatment with 10 mg/kg x 1 TCBZ, she experienced severe abdominal pain, nausea, and sweating. Blood work that day showed Hb 12.1 g/dL, WBC  $8.3 \times 10^9/L$ , BUN 7 mmol/L, ALT 3 IU/L, AST 6 IU/L, bilirubin 7 mmol/L, ALP 9 IU/L. She continued to have abdominal pain on Day 6 accompanied by vertigo and vomiting and was prescribed Belladonna tablets. On Day 30, she experienced lumbar pain which was thought by the investigator to be unrelated to study medication. Blood work that day showed Hb 13.4 g/dL, WBC of  $6.4 \times 10^9/L$ , BUN 9 mmol/L, ALT 10 IU/L, AST 5 IU/L, ALP 23 IU/L. She remained in the study but did not return for the Day 60 visit.

A handwritten note on the otherwise-empty Day 60 CRF form notes that she was hospitalized for 30 days in another city (Isfahan); a follow-up 1 year later notes eosinophil percentage of 2%, resolution of symptoms and negative stool exam.

*Reviewer comment: The information in these narratives is incomplete as they were constructed by this reviewer from CRFs; all entries were hand-written and sometimes unclear with some words or lab results obscured. Both patients appear to have had abdominal pain at baseline, but patient # (b) (6) had very few eggs detected in his stool; it is possible that he may have been early in his infection. The time frame of occurrence of abdominal pain, right upper quadrant (RUQ) pain, nausea, vomiting, vertigo, and sweats in both patients following treatment suggests that these*

*symptoms were likely related to expulsion of the parasite, rather than to the drug per se. While the event that resulted in hospitalization for Patient (b) (6) was probably related to treatment with TCBZ, the event in Patient (b) (6) (lumbar pain) does not seem related to treatment.*

### **Dropouts and/or Discontinuations Due to Adverse Effects**

Keiser study: none

Maco study: none

CIBA/WHO trials: None were reported in 5 of the 6 trials. In the Iranian study (EGA230B2201), 4 patients in the 5 mg/kg x 2 arm, 2 in the 10 mg/kg x 1 fasting arm, and 4 in the 10 mg/kg x 1 post-prandial arm discontinued from the study (List 14, Module III Data Listings, EGA230B2201 CSR, page 488). No reason was provided other than: “Patient did not return”; thus, the exact cause of patient discontinuation from the study is unknown.

Because TCBZ treatment in all studies was short - mostly Days 1 and 2, and less commonly extended to Day 3, there were no recorded discontinuations of study treatment.

*Reviewer comment: It is unclear how complete this information is, especially from the legacy CIBA/WHO trials. In at least one trial (EGA230B2208 – Bolivian pediatric trial), the CSR notes that many lab values were missing, especially at the later time points, although the CSR was quite detailed. The same level of detail was not noted in the other CSRs.*

### **Significant Adverse Events**

No significant adverse events were reported in these studies.

#### **9.4.2. Treatment Emergent Adverse Events and Adverse Reactions**

##### **9.4.2.1. Keiser study**

There were 16 individuals exposed to TCBZ in this study; AEs were recorded at 24, 48 and 72 hours post-treatment. Four individuals exposed to TCBZ had dull abdominal pain or constipation. Abdominal pain was observed more often after treatment with TCBZ than after the artemether regimens, and the authors speculate that that could be related to the increased efficacy of TCBZ to cause death of the flukes compared with artemether. Headache and dizziness were also commonly reported.

Table 9.5 shows treatment-related AEs in the 16 patients who received TCBZ after failing artemether. The only AEs assessed were abdominal pain, fatigue, headache, diarrhea, nausea, dizziness, vomiting, and fever, and were of mild or moderate severity. As noted above, there were no severe AEs.

**Table 9.5 Treatment-Related AEs in 16 Patients Receiving TCBZ\***

| Treatment                           | Adverse event  | Grading  | No. of adverse events (%)               |          |          |
|-------------------------------------|----------------|----------|-----------------------------------------|----------|----------|
|                                     |                |          | Examination point (hours posttreatment) |          |          |
|                                     |                |          | 24                                      | 48       | 72       |
| Triclabendazole (10 mg/kg) (n = 16) | Abdominal pain | Mild     | 0                                       | 8 (50)   | 8 (50)   |
|                                     |                | Moderate | 0                                       | 1 (6.3)  | 3 (18.8) |
|                                     | Fatigue        | Mild     | 0                                       | 0        | 1 (6.3)  |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Headache       | Mild     | 0                                       | 5 (31.3) | 5 (31.3) |
|                                     |                | Moderate | 0                                       | 0        | 1 (6.3)  |
|                                     | Diarrhea       | Mild     | 0                                       | 0        | 4 (25)   |
|                                     |                | Moderate | 0                                       | 0        | 1 (6.3)  |
|                                     | Nausea         | Mild     | 0                                       | 0        | 0        |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Vomiting       | Mild     | 0                                       | 2 (12.5) | 2 (12.5) |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Fever          | Mild     | 0                                       | 0        | 1 (6.3)  |
|                                     |                | Moderate | 0                                       | 2 (12.5) | 0        |
| Dizziness                           | Mild           | 0        | 10 (62.5)                               | 4 (25)   |          |
|                                     | Moderate       | 0        | 0                                       | 0        |          |
| Triclabendazole (20 mg/kg) (n = 4)  | Abdominal pain | Mild     | 0                                       | 4        | 2        |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Fatigue        | Mild     | 0                                       | 2 (50)   | 0        |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Headache       | Mild     | 3 (75)                                  | 2 (50)   | 1 (25)   |
|                                     |                | Moderate | 0                                       | 0        | 1 (25)   |
|                                     | Diarrhea       | Mild     | 0                                       | 1 (25)   | 1 (25)   |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Nausea         | Mild     | 1 (25)                                  | 3 (75)   | 0        |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Vomiting       | Mild     | 0                                       | 1 (25)   | 1 (25)   |
|                                     |                | Moderate | 0                                       | 0        | 0        |
|                                     | Fever          | Mild     | 1 (25)                                  | 1 (25)   | 0        |
|                                     |                | Moderate | 0                                       | 0        | 1 (25)   |
| Dizziness                           | Mild           | 2 (50)   | 2 (50)                                  | 0        |          |
|                                     | Moderate       | 0        | 0                                       | 0        |          |

doi:10.1371/journal.pntd.0001285.t006

\*Reproduced from Keiser et al. Efficacy and Safety of Artemether in the Treatment of Chronic Fascioliasis in Egypt: Exploratory Phase-2 Trials PLoS Negl Trop Dis 2011; 5(9): e1285

Abdominal pain was the most common AE, mild in 8/16 (50%) of patients at 48 and 72 hours after treatment with 10 mg/kg x 1 TCBZ and moderate in 1 (6.3%) and 3/16 (18.8%) at 48 and 72 hours post-treatment, respectively. In the 4 patients who received a total of 20 mg/kg in two divided doses, all had mild abdominal pain 48 hours after end of treatment.

*Reviewer comment: Of note, none of 16 patients experienced any AEs in the 24 hours post-treatment. Abdominal pain was experienced starting on Day 2 post-treatment and the frequency of AEs increased at 72 hours. Unfortunately, data beyond that time point were not reported, so it is unknown what AEs were reported after 72 hours, or how long the reported AEs*

*lasted. The presence of abdominal pain in 50% of treated subjects in the first few days following treatment accords with the timeframe for this AE in many case series and studies in the literature following use of TCBZ. The authors conclude, and this reviewer concurs, that the abdominal pain is thought to be related to the dying of the fluke and its expulsion from the biliary tree.*

*Studies in sheep [85] have elucidated the time-scale for action of TCBZ on the fluke. After treatment of a Fasciola infection in sheep using a dose of 10 mg/kg, flukes were still active at 48h post-treatment with limited surface disruption. By 72h post-treatment, almost all flukes were dead, and many showed severe swelling over the surface with tegumental sloughing in the tail region. At 96h, all flukes were dead and grossly disrupted. Around 72h, the posterior end of the fluke's body becomes elongated, coinciding with the fluke's movement into the gall bladder and subsequent expulsion via the biliary tract. Most abdominal pain post-treatment appeared to occur between Days 2 and 4 post-treatment; association of this AE with expulsion of the worm appears therefore, to be biologically plausible.*

Mild headache occurred in 5/16 (31.3%) single dose patients at 48 and 72 hours post-treatment, and in the majority of patients (3/4) who received 20 mg/kg of TCBZ at 24 hours post-treatment. At 48 hours post-treatment, dizziness occurred frequently in both the single-dose [10/16 (62.5%)] and double-dose [2/4 (50%)] groups.

*Reviewer comment: The frequent occurrence of dizziness post-treatment did not appear, in this very small series, to be dose-related.*

#### Laboratory Findings

**Table 9.6 Liver and renal function and hematological parameters pre- and post-treatment with TCBZ**

| Parameter                                  | Reference range | 10 mg/kg triclabendazole (n = 16) |                                  |                                   | 20 mg/kg triclabendazole (n = 4) |                                  |                                   |
|--------------------------------------------|-----------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|----------------------------------|-----------------------------------|
|                                            |                 | Day of analysis                   |                                  |                                   | Day of analysis                  |                                  |                                   |
|                                            |                 | Pretreatment day 0 (mean ± SD)    | Post-treatment day 5 (mean ± SD) | Post-treatment day 28 (mean ± SD) | Pretreatment day 0 (mean ± SD)   | Post-treatment day 5 (mean ± SD) | Post-treatment day 28 (mean ± SD) |
| Alkaline phosphatase (ALP) (IU/l)          | 30–120          | 133.7 (38.8)                      | 137.3 (39.9)                     | 135.8 (37.7)                      | 111.0 (65.1)                     | 106.4 (59.2)                     | 99.5 (32.2)                       |
| Alanine transaminase (ALT) (IU/l)          | 9–60            | 10.9 (2.3)                        | 16.0 (11.4)                      | 11.9 (2.5)                        | 18.3 (3.2)                       | 19.3 (8.1)                       | 20.5 (9.3)                        |
| Aspartate transaminase (AST) (IU/l)        | 10–40           | 10.6 (3.9)                        | 19.6 (23.2)                      | 13.1 (3.0)                        | 23.5 (10.4)                      | 29.3 (13.7)                      | 29.3 (8.7)                        |
| Gamma glutamyl transpeptidase (GGT) (IU/l) | 0–51            | 7.0 (1.4)                         | 8.3 (2.6)                        | 7.7 (1.8)                         | 7.2 (1.1)                        | 9.4 (3.3)                        | 9.4 (3.3)                         |
| Bilirubin (mg/dl)                          | 0.2–1.2         | 0.6 (0.2)                         | 0.4 (0.3)*                       | 0.6 (0.2)**                       | 0.4 (0.1)                        | 0.6 (0.3)                        | 0.6 (0.1)                         |
| Urea (mg/dl)                               | 12–48           | 37.9 (11–0)                       | 35.2 (12.6)                      | 34.7 (6.6)                        | 23.8 (2.0)                       | 18.1 (6.3)                       | 22.2 (2.7)                        |
| Creatinine (mg/dl)                         | 0.6–1.3         | 0.8 (0.2)                         | 0.7 (0.2)                        | 0.8 (0.1)                         | 0.9 (0.3)                        | 1.1 (0.4)                        | 0.9 (0.2)                         |
| Eosinophils (%)                            | 0–6             | 4.5 (2.5)                         | 3.3 (1.5)                        | 3.5 (1.2)                         | 3.8 (1.0)                        | 3.5 (1.0)                        | 4.0 (0.8)                         |
| Hemoglobin (g/dl)                          | 11.5–17.5       | 12.8 (1.8)                        | 11.3 (1.1)*                      | 12.5 (1.3)**                      | 13.5 (0.6)                       | 13.3 (0.8)                       | 12.9 (0.6)                        |
| Total leucocytes (mm <sup>3</sup> )        | 3900–10,000     | 6356 (951)                        | 5950 (1074)                      | 6707 (918)                        | 5300 (902)                       | 5900 (1320)                      | 6350 (661)                        |

\*Statistically significant difference from baseline (p<0.05).

\*\*Statistically significant difference between first and second follow-up survey.

Source: Keiser et al. Efficacy and Safety of Artemether in the Treatment of Chronic Fascioliasis in Egypt: Exploratory Phase-2 Trials. PLoS 2011; 5(9): e1285

All tested blood parameters except hemoglobin were unchanged from BL to post-treatment in single- and double-dose TCBZ treatment groups. Significant decreases in hemoglobin level from baseline to post-treatment Day 5 in the single-dose patients had resolved by Day 28.

*Reviewer comment: Although there is trend to lower hemoglobin levels at Day 5 post-treatment (these values represent the mean of 16 patients), the significance of this finding is unknown, especially because these findings had resolved by Day 28, presumably with no intervention. Further it is unclear how many of these patients were male vs. female, how old they were, and how possible co-infection with other parasites may have contributed to the finding of anemia. Further, the timing of these measurements does not match the timing of the recorded related adverse events, e.g. abdominal pain or fever. For example, if the abdominal pain (location unspecified) was due to temporary biliary obstruction due to expulsion of the dying fluke, there may have been a temporary concomitant increase in liver enzymes, specifically AST, ALT, ALP, GGT and bilirubin. Because blood was drawn on Day 5 post-treatment, the time when most patients experienced abdominal pain was not accounted for.*

#### Vital Signs

No information available from this study.

#### ECGs and QT

No ECGs appear to have been done in this study, and QT information is thus unavailable.

### 9.4.2.2. Maco study

A total of 84 children were treated with two different doses of TCBZ in this study. Although 59/84 (70.2%) received Fasinex, the veterinary preparation, the Biopharmaceutics reviewer, Dr. Gerlie Gieser, and Clinical Pharmacology reviewer, Dr. Jason Moore have concluded that bioequivalence between Fasinex and Egaten has been established and that their PK profiles are comparable. Thus, all 84 patients are considered in the safety review of this study.

*Reviewer comment: As in the Keiser study, only the presence or absence of the specific AEs listed in Table 9.7 were evaluated – thus, categorization of AEs by SOC, or PT was not provided. Again, some of this data could not be verified during the OSI audit, and AEs were not recorded beyond 7 days.*

**Table 9.7 Targeted Treatment-emergent AEs on Days 1-7 After Treatment with TCBZ\***

| Adverse effects (%)   | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|-----------------------|-------|-------|-------|-------|-------|-------|-------|
| Abdominal pain        |       |       |       |       |       |       |       |
| Group I               | 11.0  | 21.0  | 7.0   | 7.0   | 11.0  | 0.0   | 0.0   |
| Group II              | 5.0   | 8.0   | 10.0  | 15.0  | 8.0   | 0.0   | 0.0   |
| Nausea and vomiting   |       |       |       |       |       |       |       |
| Group I               | 0.0   | 2.3   | 2.3   | 4.5   | 6.8   | 0.0   | 0.0   |
| Group II              | 0.0   | 2.5   | 0.0   | 0.0   | 0.0   | 2.5   | 0.0   |
| Biliary colic         |       |       |       |       |       |       |       |
| Group I               | 0.0   | 11.4  | 9.1   | 20.5  | 13.6  | 4.5   | 0.0   |
| Group II              | 2.5   | 25.0  | 12.5  | 15.0  | 5.0   | 2.5   | 2.5   |
| Anorexia              |       |       |       |       |       |       |       |
| Group I               | 0.0   | 2.3   | 9.1   | 6.8   | 0.0   | 0.0   | 0.0   |
| Group II              | 0.0   | 2.5   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   |
| Use of antispasmodics |       |       |       |       |       |       |       |
| Group I               | 0.0   | 2.3   | 0.0   | 2.3   | 0.0   | 2.3   | 0.0   |
| Group II              | 0.0   | 0.0   | 2.3   | 0.0   | 2.5   | 0.0   | 0.0   |
| Headaches             |       |       |       |       |       |       |       |
| Group I               | 4.5   | 11.4  | 4.5   | 6.8   | 0.0   | 0.0   | 0.0   |
| Group II              | 10.0  | 10.0  | 10.0  | 10.0  | 0.0   | 0.0   | 0.0   |

Group I (n = 44): 7.5mg triclabendazole administered twice postprandially; Group II (n = 40): single 10-mg/kg triclabendazole dose.

\*59 patients received Fasinex, rather than Egaten®, all in the Asillo region

Source: Maco et al. Efficacy and Tolerability of Two Single-Day regimens of TCBZ for Fascioliasis in Peruvian Children Rev Soc Bras Med Trop 2015; 48(4): 445-453

Maximal occurrence of abdominal pain and biliary colic (the definitions of which were not specified) were reported on Days 2 and 4 post-treatment in the double-dose group, and on Days 4 and 2 post-treatment respectively in the single-dose group. Anti-spasmodic drugs were used in 2 patients each on Days 2, 4, and 6 in Group 1, and in 2 patients each on Days 2 and 5 in Group 2.

*Reviewer comment: Because these findings were not correlated in individual patients, it is not clear whether patients with biliary colic and abdominal pain were the ones who received anti-spasmodics and if so, whether they needed anti-spasmodic medication on more than one day.*

*Further, data on severity was not provided, but the publication states that “While the intensity varied from mild to severe during days 1 to 7, only severe intensity was experienced on days 2 and 4 in 2.5% of Group II. Severe biliary colic occurred in 4.5% of Group 1 on day 2. All of the cases (n=4) with severe biliary colic responded to antispasmodic medication within 2 hours and did not require any further medical or surgical intervention.” (Maco publication, page 448).*

*The publication further states that “A sharp decrease in the occurrence of clinical signs and symptoms was observed in all groups at 7 days post-treatment....no cases of diarrhea, jaundice, pruritus, skin rash, dizziness, dyspnea, cough, or cervical, thoracic, lumbar or muscular pain were reported. None of the participants were withdrawn from the study due to adverse events during the follow-up period. All of the participants completed the study period (60 days in Asillo, 180 days in the remaining sites”.*

The dataset for the Maco study had the following AEs evaluated on Days 1-7: abdominal pain, epigastric pain, right hypochondrium pain, and biliary colic – the definitions of these different events were not provided. No correlation was observed between, for example, right hypochondrium pain and biliary colic. In addition, anorexia and nausea/ vomiting were recorded on all 7 days; most patients had neither.

### **Laboratory Findings**

Laboratory testing included evaluation for eggs in stool, and blood Fas 2 ELISA and eosinophil count. The last two were only done pre-treatment and were not repeated post-treatment.

### **Vital Signs**

No data are available.

### **Electrocardiograms (ECGs)**

No ECGs were done in these studies.

#### **9.4.2.3. CIBA/WHO Studies of Fascioliasis**

As mentioned above, these 6 uncontrolled, open-label studies shared a protocol (Appendix 15.5) with the objective of studying the safety and efficacy of different dosing regimens of TCBZ (5-20 mg/kg given in single or divided doses on Days 1, 2 or 3) in the fasting or post-prandial state in children (Bolivian pediatric study), and adults with *F. hepatica* infection as evidenced by positive fecal egg counts. The TCBZ formulation CGP 23030 was used in all patients except in 6 patients in the Bolivian pediatric study who received Egaten 20 mg/kg for retreatment after failure of a single 10 mg/kg dose of CGP 23030.

Descriptive statistics, comparing pre- and post-therapy assessments were done. The efficacy results of these studies are presented in Section 7 of this review. Table 9.4 depicts the Schedule of Assessments for the CIBA/WHO studies, and Table 9.8 summarizes study details and safety data from them.

**Table 9.8 Selected Details and Overview of Safety in the CIBA/WHO Trials**

| Number/Location/<br>Date                                       | Doses, n                                                                     | Number<br>per Arm    | Age<br>(range)                  | Clinical Findings and lab findings Attributed<br>to Fascioliasis                                                                                                                            |                                                                                                                                                                                          | Imaging                                                      | TEAEs                                                                                                                                                                               | Cure Rate                                                                                                 |
|----------------------------------------------------------------|------------------------------------------------------------------------------|----------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
|                                                                |                                                                              |                      |                                 | Baseline                                                                                                                                                                                    | Day 60                                                                                                                                                                                   |                                                              |                                                                                                                                                                                     |                                                                                                           |
| EGA230B2201,<br>Tehran, Iran.<br>10/1/89-9/14/91               | 5 mg/kg x 3<br>5 mg/kg x 2<br>(fast)<br>10 mg/kg (fast)<br>10 mg/kg (fed)    | 17<br>14<br>17<br>54 | 5-75yrs                         | Abdominal pain: 75%<br>Nausea: 29%<br>Sweating: 71%<br>Hepatomegaly:<br>34/102 (33.3%);<br>Splenomegaly: 15.9%<br>Jaundice: 3 pts<br>Eosinophilia: 44.1%                                    | Abdominal pain:<br>10%<br>Hepatomegaly<br>resolved in 24.5%;<br>improved in 7.8%<br>Splenomegaly<br>resolved in 12.7%<br>Jaundice resolved in<br>100%<br>Eosinophilia<br>persisted 23.5% | Not accurate                                                 | Epigastric pain –<br>88%; urticaria –<br>37%; RUQ pain<br>31%; n/v 28%;<br>abdominal pain<br>22% <sup>3</sup>                                                                       | Total – 76%                                                                                               |
| EGA230B2202,<br>Chile<br>11/14/90-5/15/92                      | 10 mg/kg x 1<br>(fasting)                                                    | 24                   | 11-70 yrs.                      | Abdominal pain:<br>41.7%<br>Any pain in<br>abdomen: 50%<br>Anorexia,<br>constipation,<br>diarrhea: 12.5%                                                                                    | Abdominal pain: 0%<br>Any pain in<br>abdomen: 16.7%<br>Anorexia,<br>constipation: 4.2%                                                                                                   | Not specified                                                | 1 patient (4.2%)<br>each with mild<br>abdominal pain,<br>headache, anorexia,<br>constipation;<br>LFT's normal                                                                       | 79% <sup>6</sup> (17 pts had the<br>Enterotest)                                                           |
| EGA230B2207,<br>Bolivia <sup>1</sup><br>11/24/90-2/17/92       | 10 mg/kg x 1<br>(fed)                                                        | 22                   | 13-63 yrs<br>(mean<br>35.3)     | Hepatic abscesses<br>(100%)<br>Hepatomegaly 9.1%<br>Eosinophilia 68.2%<br>(15pts)<br>Elevated bilirubin<br>(86.3%) but “not<br><i>clinically relevant</i> ”<br>Dilated bile ducts in<br>68% | Hepatic abscesses<br>(100%)<br>Hepatomegaly<br>resolved<br>Eosinophilia<br>resolved in 14 pts<br>No change in<br>hepatic enzymes<br>Dilated bile ducts<br>found in 95.5%                 | Hepatic<br>abscesses<br>(“accuracy is<br>questioned”)        | Right hypochondrial<br>pain – 77.2%<br>Abdominal pain –<br>59.1%<br>Sweating – 54.5%<br>“Wambles” –<br>13.6% <sup>4</sup><br>1 (4.5%) each had<br>severe RUQ pain,<br>n/v, jaundice | 100%                                                                                                      |
| EGA230B2208,<br>Bolivia<br>Pediatric study<br>12/13/91-8/13/92 | 5 mg/kg x 1<br>10 mg/kg x 1<br>5 mg/kg x 2<br>10 mg/kg x 2 (for<br>failures) | 20<br>20<br>20<br>6  | 9.9 yrs,<br>mean wt:<br>25.9 kg | Dilated bile ducts in<br>the combined 10<br>mg/kg grp<br>(8/40=20%)                                                                                                                         | Dilated bile ducts in<br>the combined 10<br>mg/kg grp<br>(5/40=12.5%).<br>Hepatobiliary                                                                                                  | Some<br>reversal of<br>parasite-<br>induced<br>changes at 60 | Abdominal pain in<br>combined 10 mg/kg<br>grp d2-4:<br>17/40=42.5%;<br>2 pts symptomatic                                                                                            | 92.5% (combined 10<br>mg/kg)<br>6 pts (5 from 5 mg/kg,<br>1 from 10 mg/kg failed<br>and were successfully |

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| Number/Location/<br>Date                               | Doses, n                                                                               | Number<br>per Arm | Age<br>(range) | Clinical Findings and lab findings Attributed<br>to Fascioliasis                                                                                                     |                                                                                                                                                                                                                                                    | Imaging                                                                                                   | TEAEs                                                          | Cure Rate                                       |
|--------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------|
|                                                        |                                                                                        |                   |                | Baseline                                                                                                                                                             | Day 60                                                                                                                                                                                                                                             |                                                                                                           |                                                                |                                                 |
|                                                        |                                                                                        |                   |                |                                                                                                                                                                      | changes reversed in the 5 mg/gk x2 gp, and adult flukes were gone.                                                                                                                                                                                 | days <sup>2</sup>                                                                                         | jaundice<br>Sweating (66.7%),<br>vomiting, nausea<br>(<15%)    | retreated with 20 mg/kg                         |
| Havana, Cuba <sup>5</sup><br>8/12/90-2/10/92           | 10 mg/kg (fast)                                                                        | 15                | 15-58 yrs      | Eosinophilia (100%:<br>7-14% eos); normal bile ducts (100%); 11 (79%) had abdominal pain, RUQ or epigastric pain. 50% anorexia; 21.4% urticaria<br>Hepatomegaly: 20% | Eosinophilia resolved in 10/15 (67%), increased in 1 (6.7%), remained unchanged but slightly high in 3 (20%); 6/15 (40%) dilated bile ducts. One patient (6.7%) mild RUQ pain; 6.7% with abdominal discomfort and urticaria; Hepatomegaly resolved | Normal bile ducts at study entry, 7 (46.7%) had dilated ducts at Day 30 which persisted in 6 till Day 60. | 8/15 (53%) with right hypochondrial pain, 1-2 d post-treatment | 86%                                             |
| EGA230B2212,<br>Peru<br>11/4/91-11/25/91<br>(PK Study) | 10 mg/kg fed D1, then 10 mg/kg fasting D3<br>10 mg/kg fasting D1, then 10 mg/kg fed D3 | 12<br><br>10      | 6-62 yrs       | 3/22 has BL symptoms (13.6%).<br>U/S: No hepatic abscesses, but flukes noted in gall bladder of 3 patients                                                           | Final lab assessment at Day 90 – no gross alteration of hematologic parameter or LFTs<br>U/S: 2 fluke infections cleared, parasite present in the GB of the 3 <sup>rd</sup> pt.                                                                    | No hepatic abscesses; flukes present in 3 pts and cleared in 2/3 at EOT                                   | Abdominal pain – 18/22 (82%)                                   | Fasting then fed: 86%<br>Fed then fasting: 100% |

<sup>1</sup>Accurate data recording in this study is questioned” as all patients were recorded as having hepatic abscesses. Source: Module 1, page 10, CSR for EGA230B2207. No patients had signs and symptoms of chronic fascioliasis at study entry. LFTs in all treated patients were normal.

<sup>2</sup>Ultrasound detection was an exploratory endpoint to assess changes to the hepatobiliary system and to confirm that reduction in egg count was associated with disappearance of the adult fluke, not just inhibition of reproduction. Very few blood samples were drawn at Days 30 and 60, so lab assessments are incomplete.

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<sup>3</sup> “Difficult to draw many conclusions from the laboratory values, as many of the samples were either not drawn or the results not recorded”. Page 16, CSR. Unclear if Enterotest was ever done (p. 17). All patients had a raised right liver lobe, pericardial effusion, right-sided pleural effusion both at start and end of study period. “As this is clearly not really possible we must conclude that there was some misunderstanding in the completion of the CRF.” Few U/S examinations were performed so no conclusions are possible.

<sup>4</sup> The CSR notes that the direct translation of “wambles” is uncertain.

<sup>5</sup> These trials were initiated before the European directive 91/507/EEC on Good Clinical Practice came into force. As a result, the following were sometimes inadequately performed, monitored or documented: trial monitoring; drug accountability, patient information document; source data verification; existence of the trial master file; definition of inclusion and exclusion criteria in the Clinical Record Form, and definition of serious adverse events in the Clinical Trial Protocol.

<sup>6</sup> In Section 7.1 of the CSR for the Chilean study (page 11), it says that “All patients were positive for eggs before the administration of study drug”, and designated cure as 19/24 (79%). In Section 7.2 (page 11) of the same CSR, “Unfortunately only 7/24 patients’ samples were positive at baseline.” The cure rate is then designated as 3/7 (43%). There are many such inconsistencies in the performance of these studies. NB. Of the patients who were negative for eggs at baseline (n=17), four became positive on Day 60.

**Table 9.9 Summary of Dosing Regimens in the CIBA/WHO studies**

| Row No. | STUDY ID                       | Treatment (TSARML)                                             | Total n |
|---------|--------------------------------|----------------------------------------------------------------|---------|
| 1       | AH/FH1 Peru                    | A=10 mg/kg on day 1 in the fasting state and 3 post-prandially | 10      |
| 2       |                                | B=10 mg/kg on day 1 post-prandially and 3 in the fasting state | 12      |
| 3       | AH/FH2 Bolivia                 | D=10 mg/kg single dose after food                              | 22      |
| 4       | AH/FH2 Bolivia<br>(paediatric) | I= 5 mg/kg post-prandially on day 1                            | 20      |
| 5       |                                | II= 10 mg/kg post-prandially on day 1                          | 20      |
| 6       |                                | III= 2x5 mg/kg post-prandially on day 1                        | 20      |
| 7       |                                | IV= 2x10 mg/kg on day 1 (human formulation)                    | 6       |
| 8       | AH/FH2 Cuba                    | C= 10 mg/kg single dose fasting                                | 15      |
| 9       | AH/FH2 Iran                    | A=5 mg/kg on days 1, 2, 3, fasting                             | 17      |
| 10      |                                | B=5 mg/kg x2, fasting                                          | 14      |
| 11      |                                | C= 10 mg/kg single dose fasting                                | 17      |
| 12      |                                | D=10 mg/kg single dose after food                              | 54      |
| 13      | AHIFH2 Chile                   | C= 10 mg/kg single dose fasting                                | 24      |

Source: Applicant's submission: Data handling – datasets from 6 CIBA-WHO studies, Table 3.1, p.4

The 6 Bolivian patients retreated with 20 mg/kg in divided doses were counted once; thus, 245 patients were exposed to TCBZ in the CIBA-WHO studies.

### Single-dose TCBZ (10 mg/kg)

#### Combined single-dose analysis

*Reviewer Comment: Analyses of AEs occurring with post-prandial and fasting administration of 10 mg/kg doses (single and divided) were performed by the reviewer (not shown here). Because no major differences in AE occurrences were seen based on the timing of TCBZ administration relative to food consumption, all 10 mg/kg dose groups are considered together in the following analyses.*

The following dose regimens were grouped together – 5 mg/kg x 2 fasting, 10 mg/kg single dose fasting, 10 mg/kg single dose after food, 10 mg/kg post-prandially on day 1, and 2x5 mg/kg post-prandially on day 1, with a total N=186 from 6 studies (see Table 9.9).

However, there was great variability in the manner of coding AEs – some sites recorded Verbatim Terms such as “no adverse event” or “she did not come on Friday” among others. The latter terms were recoded by the Applicant as “unevaluable”. Thus, “no adverse event” and “unevaluable” were excluded from the combined single-dose analysis AE dataset. AEs in the Chilean study, AH/FH2 Chile were provided by the Applicant in a separate dataset as they were derived from the CSR; out of 24 patients, 10 had AEs and were separately included by the reviewer in the AE counts.

*Reviewer Comment: The dose regimens outlined above for single doses were subset from the ae.xpt file for 5 CIBA/WHO studies and concatenated with the aechile.xpt. As noted above, the terms “unevaluable” and “no adverse event” were excluded. In the original ae.xpt dataset for the CIBA-WHO studies submitted to the NDA, treatment-emergent AEs could not be clearly identified. In an IR response (7/23/18), the Applicant corrected errors in the CIBAWHO Data Definition Report and submitted an amended AE dataset on 7/31/18. Further, the Applicant noted that treatment-emergent AEs can be obtained by selecting the calculated visit day (VISDYC)  $\geq 1$  in the dataset. The resubmitted ae.xpt dataset was used by this reviewer in all JMP analyses of AEs along with the Applicant’s recommended method of identifying TEAEs.*

A total of 131/186 (70.4%) patients experienced TEAEs. The following table includes TEAEs that occurred in >1% of the population (2 patients).

**Table 9.10 Treatment-Emergent Adverse Events Occurring in >1% of Patients in the Fasting and Post-Prandial Population Receiving 10 mg/kg (equivalent) x 1 TCBZ in the CIBA-WHO Studies**

| System Organ Class                                   | Preferred Term             | AH/FH2<br>Bolivia,<br>n=22 | %    | AH/FH2<br>Bolivia<br>(pediatric)<br>n=40 | %    | AH/FH2<br>Cuba,<br>n=15 | %    | AH/FH2<br>Iran,<br>n=85 | %    | AH/FH2<br>Chile,<br>n=24 | %   | Total | %, n=186 |
|------------------------------------------------------|----------------------------|----------------------------|------|------------------------------------------|------|-------------------------|------|-------------------------|------|--------------------------|-----|-------|----------|
| Cardiac disorders                                    | Palpitations               | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 2                       | 2.4  | 0                        | 0.0 | 2     | 1.1      |
| Ear and labyrinth disorders                          | Vertigo                    | 3                          | 13.6 | 0                                        | 0    | 0                       | 0.0  | 13                      | 16.5 | 0                        | 0.0 | 16    | 8.6      |
| Gastrointestinal disorders                           | Abdominal pain             | 7                          | 31.9 | 17                                       | 42.5 | 2                       | 13.3 | 17                      | 20   | 2                        | 8.3 | 45    | 24.2     |
|                                                      | Abdominal pain upper       | 13                         | 59.1 | 0                                        | 0    | 4                       | 26.7 | 54                      | 63.5 | 2                        | 8.3 | 73    | 39.2     |
|                                                      | Constipation               | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 0                       | 0.0  | 2                        | 8.3 | 2     | 1.0      |
|                                                      | Diarrhoea                  | 1                          | 4.5  | 0                                        | 0    | 1                       | 6.7  | 1                       | 2.4  | 0                        | 0.0 | 3     | 1.6      |
|                                                      | Nausea                     | 1                          | 4.5  | 1                                        | 2.5  | 0                       | 0.0  | 13                      | 15.3 | 0                        | 0.0 | 15    | 8.1      |
|                                                      | Vomiting                   | 3                          | 13.6 | 3                                        | 7.5  | 0                       | 0.0  | 5                       | 5.9  | 0                        | 0.0 | 11    | 5.9      |
| General disorders and administration site conditions | Asthenia                   | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 7                       | 8.2  | 0                        | 0.0 | 7     | 3.8      |
|                                                      | Chest discomfort           | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 4                       | 4.7  | 0                        | 0.0 | 4     | 2.2      |
|                                                      | Chest pain                 | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 6                       | 7.1  | 0                        | 0.0 | 6     | 3.2      |
|                                                      | Pyrexia                    | 1                          | 4.5  | 0                                        | 0    | 0                       | 0.0  | 3                       | 3.5  | 0                        | 0.0 | 4     | 2.2      |
| Hepatobiliary disorders                              | Biliary colic              | 2                          | 9.1  | 0                                        | 0    | 0                       | 0.0  | 0                       | 0.0  | 0                        | 0.0 | 2     | 1.1      |
|                                                      | Jaundice +Ocular Icterus   | 0                          | 0.0  | 1                                        | 2.5  | 0                       | 0.0  | 3                       | 3.5  | 0                        | 0.0 | 4     | 2.2      |
| Metabolism and nutrition disorders                   | Decreased appetite         | 2                          | 9.1  | 0                                        | 0    | 0                       | 0.0  | 2                       | 2.4  | 2                        | 8.3 | 6     | 3.2      |
| Musculoskeletal and connective tissue disorders      | Arthralgia                 | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 2                       | 2.4  | 0                        | 0.0 | 2     | 1.1      |
|                                                      | Back pain                  | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 3                       | 3.5  | 0                        | 0.0 | 3     | 1.6      |
|                                                      | Musculoskeletal chest pain | 2                          | 9.1  | 0                                        | 0    | 0                       | 0.0  | 5                       | 5.9  | 0                        | 0.0 | 7     | 3.8      |
|                                                      | Musculoskeletal            | 0                          | 0.0  | 0                                        | 0    | 0                       | 0.0  | 2                       | 2.4  | 0                        | 0.0 | 2     | 1.1      |

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| System Organ Class                                     | Preferred Term | AH/FH2<br>Bolivia,<br>n=22 | %    | AH/FH2<br>Bolivia<br>(pediatric)<br>n=40 | %   | AH/FH2<br>Cuba,<br>n=15 | %   | AH/FH2<br>Iran,<br>n=85 | %    | AH/FH2<br>Chile,<br>n=24 | %   | Total | %, n=186 |
|--------------------------------------------------------|----------------|----------------------------|------|------------------------------------------|-----|-------------------------|-----|-------------------------|------|--------------------------|-----|-------|----------|
|                                                        | pain           |                            |      |                                          |     |                         |     |                         |      |                          |     |       |          |
|                                                        | Spinal pain    | 0                          | 0.0  | 0                                        | 0   | 0                       | 0.0 | 2                       | 2.4  | 0                        | 0.0 | 2     | 1.1      |
| <b>Nervous system disorders</b>                        | Headache       | 2                          | 9.1  | 0                                        | 0   | 0                       | 0.0 | 7                       | 8.2  | 2                        | 8.3 | 11    | 5.9      |
| <b>Renal and urinary disorders</b>                     | Chromaturia    | 0                          | 0.0  | 0                                        | 0   | 0                       | 0.0 | 2                       | 2.4  | 0                        | 0.0 | 2     | 1.1      |
| <b>Respiratory, thoracic and mediastinal disorders</b> | Cough          | 0                          | 0.0  | 0                                        | 0   | 0                       | 0.0 | 7                       | 8.2  | 0                        | 0.0 | 7     | 3.8      |
|                                                        | Dyspnoea       | 0                          | 0.0  | 0                                        | 0   | 0                       | 0.0 | 9                       | 10.6 | 0                        | 0.0 | 9     | 4.8      |
| <b>Skin and Subcutaneous Tissue Disorders</b>          | Hyperhidrosis  | 12                         | 54.5 | 20                                       | 50  | 0                       | 0.0 | 10                      | 11.8 | 0                        | 0.0 | 42    | 22.6     |
|                                                        | Pruritus       | 0                          | 0.0  | 0                                        | 0   | 0                       | 0.0 | 8                       | 9.4  | 0                        | 0.0 | 8     | 4.3      |
|                                                        | Urticaria      | 2                          | 9.1  | 1                                        | 2.5 | 1                       | 6.7 | 8                       | 9.4  | 0                        | 0.0 | 12    | 6.5      |

Source: Reviewer analysis of ae2.xpt and aechile.xpt datasets from the CIBA-WHO data submitted by the Applicant.

NB: TEAEs were identified as occurring ≥VISDYC 1 according to clarification obtained from the Applicant by IR.

Several PTs were considered to be synonymous in describing a single condition, and were combined for analysis. The most common were the PTs of “abdominal pain” and “abdominal pain upper”, recorded separately in the datasets – 83 patients (44.6%, including 2 from the Chilean study) had a AE of “abdominal pain upper”, while 48 patients (25.8%, including 2 from the Chilean study) had a AE of “abdominal pain”. Some patients were recorded as experiencing both “abdominal pain” and “abdominal pain upper” at different times. Because the definitions of these two PTs were not provided to explain the difference between them, they were combined together for purposes of analysis; thus, a total of 105 patients (56.5%) – including 4 from the Chilean study – experienced a PT of “abdominal pain”.

Analysis of Abdominal Pain Severity: Fifty-six of the 186 (30.1%) subjects had severe abdominal pain at some point after treatment, but some of those also had moderate (50/186, 26.9%) or mild pain (36/186, 19.4% [including all 4 patients with abdominal pain from the Chilean study who had mild pain]) on other days. Out of 79 occurrences of severe abdominal pain (abdominal pain and abdominal pain upper PTs) in 56 patients, 66 (83.5%) occurred in the first 6 days, with 51 (64.6%) occurring between Days 3 and 5 inclusive. Only 11 episodes of severe abdominal pain (13.9%) occurred between Days 9 and 60 (reviewer’s analysis – not shown).

Out of 67 occurrences of moderate abdominal pain (abdominal pain and abdominal pain upper) in 50 patients, 59 (88.1%) episodes occurred in the first 6 days, and 36 (53.7%) occurred between Days 3 and 5 inclusive. Only 8 (11.9%) episodes occurred between Days 15 and 52 (reviewer’s analysis – not shown).

Reviewer Comment: *The majority of subjects experienced severe and moderate abdominal pain within the first week after treatment with 10 mg TCBZ, with most of those being before day 5. This timing is consistent with abdominal pain related to expulsion of the parasite.*

Almost a quarter (22.6%) of patients who received 10 mg/kg x 1 experienced hyperhidrosis or sweating at various times after treatment; and 6.5% of patients had urticaria. Nausea and vomiting were experienced by 8.1% and 5.9% of enrolled patients, respectively, and an equal percentage (5.9%) experienced headache. Ocular icterus occurred in one patient, but this term, when combined with its synonymous term - jaundice – occurred in a total of 4 patients. Myalgia and pain in extremity occurred in 1 patient each – these terms were considered synonymous for the analysis. Urticaria (16) and urticaria contact (2) were also considered synonymous and were combined.

Dizziness, tremor, alopecia, hemoptysis, hiccups, oropharyngeal discomfort, erythema, night sweats, rash, flushing, peripheral coldness, eye irritation, blurred vision, dyspepsia, toothache, peripheral swelling, flank pain, occurred in 1 patient each, and are therefore not represented in Table 9.10.

## **Other TEAEs Occurring in the 10 mg/kg TCBZ dose group in the CIBA/WHO Studies**

### Skin Disorders

Fifty-nine (31.7%) subjects had TEAEs in the Skin and Subcutaneous Tissue Disorders SOC; of which the most common was hyperhidrosis or sweating reported in 43 (23.1%) patients. Most of those TEAEs occurred in the first 6 days after treatment. Seventeen patients experienced rash, urticaria or pruritus. Rash occurred in a single patient on day 5 after TCBZ and was not characterized further. Twelve patients experienced urticaria – 3 patients on Day 1 after treatment, 3 on Day 2, 1 patient on both Days 3 and 4, 1 on Day 5, 2 on Day 6, 1 on Day 7 and 1 on Day 22. Two patients with early urticaria (Days 1 and 7 post-treatment) also had a second episode recorded on Days 33 and 30 respectively.

*Reviewer comment: Most episodes of urticaria occurred in the first few days following TCBZ treatment suggesting that there may have been a reaction to fluke antigens or possibly to TCBZ itself. These variations in time of occurrence of urticaria suggest that not all episodes were related to TCBZ administration, but may also indicate an atopic predisposition, reaction to other allergens, or to fluke antigens. These studies were done in areas where concomitant parasitic infections or other allergens are expected to be common, so it is possible that some pruritus and urticaria, particularly at later time points, were not related to TCBZ.*

Eight patients (4.3%) experienced pruritus – although the coincidence of pruritus and urticaria might be expected, only 3 patients experienced both together.

### Vertigo

Vertigo occurred in 16 patients (8.6%) among the 6 CIBA-WHO studies. In 8 (50%) of these patients, vertigo occurred on Days 1-2 after treatment with Fasinex, and 14 (87.5%) experienced vertigo within the first 6 days after treatment. The duration of these episodes was not always recorded, but most appear to have lasted 3 mins to 1 hour and 15 mins. Three patients experienced vertigo for 2, 4 and 10 hours, on Days 2 and 3.

Cough and dyspnea occurred in 3.8% and 4.8% of patients respectively. No explanation is offered for these AEs – mechanistically, these AEs could be related to inadvertent “splinting” of the chest due to upper abdominal/RUQ pain leading to the sensation of dyspnea.

### **EGA230B2202 (Chile)**

A separate AE dataset was submitted for the CIBA/WHO study in Chile as it was reconstructed from the CSR. Nine of 24 (37.5%) patients experienced AEs – 4/24 (16.7%) had abdominal pain, and 2 each (8.3%) had headache, decreased appetite and constipation.

### 9.4.3. Exploration of Possible Dose-Response for Safety in the CIBA-WHO Studies

A comparison was made between subjects who received 10 mg/kg x 1 in either the fasting or post-prandial states (n=186) and those who received 5 mg/kg x 1 (n=20 Bolivian pediatric patients) or 10 mg/kg twice on Day 1 (n=6 retreated Bolivian pediatric patients). Patients from the Peruvian study who received a total of 20 mg/kg as 10 mg/kg on Days 1 and 3 were included in the exploration of dose-response, although the treatment regimen was not directly comparable to a total of 20 mg/kg received on one day. Abdominal pain occurred in 100% (20/20) of patients who received 5 mg/kg x 1, and 100% (6/6) of patients who received 20 mg/kg. Of the 186 patients who received 10 mg/kg x 1 TCBZ either fasting, post-prandial, or in divided doses (5 mg/kg x 2), 105 (56.5%), including 4 patients from the Chilean study, had abdominal pain as seen in the analysis shown above.

**Table 9.11 Frequency of TEAEs by SOC and TCBZ Dose**

| System Organ Class                                   | 5 mg/kg fed (N=20) |     | 10 mg/kg fast (N=70) |      | 10 mg/kg fed (N=116) |      | 20 mg/kg (N=6) |     | 10 mg/kg on Days 1 and 3 (N=22) |      |
|------------------------------------------------------|--------------------|-----|----------------------|------|----------------------|------|----------------|-----|---------------------------------|------|
|                                                      | N                  | %   | N                    | %    | N                    | %    | N              | %   | N                               | %    |
| Cardiac disorders                                    | 0                  | 0   | 0                    | 0.0  | 2                    | 1.7  | 0              | 0   | 0                               | 0    |
| Ear and labyrinth disorders                          | 0                  | 0   | 7                    | 10.0 | 9                    | 7.8  | 0              | 0   | 0                               | 0    |
| Eye disorders                                        | 0                  | 0   | 0                    | 0.0  | 1                    | 0.9  | 0              | 0   | 0                               | 0    |
| Gastrointestinal disorders                           | 20                 | 100 | 36                   | 51.4 | 69                   | 59.5 | 6              | 100 | 20                              | 90.9 |
| General disorders and administration site conditions | 0                  | 0   | 10                   | 14.3 | 8                    | 6.9  | 0              | 0   | 2                               | 9.1  |
| Hepatobiliary disorders                              | 1                  | 5   | 1                    | 1.4  | 5                    | 4.3  | 0              | 0   | 0                               | 0    |
| Infections and infestations                          | 0                  | 0   | 0                    | 0.0  | 0                    | 0.0  | 0              | 0   | 3                               | 13.6 |
| Metabolism and nutrition disorders                   | 0                  | 0   | 1                    | 1.4  | 3                    | 2.6  | 0              | 0   | 5                               | 22.7 |
| Musculoskeletal and connective tissue disorders      | 0                  | 0   | 7                    | 10.0 | 6                    | 5.2  | 0              | 0   | 2                               | 9.1  |
| Nervous system disorders                             | 0                  | 0   | 5                    | 7.1  | 5                    | 4.3  | 0              | 0   | 4                               | 18.1 |
| Psychiatric disorders                                | 0                  | 0   | 0                    | 0.0  | 0                    | 0.0  | 0              | 0   | 1                               | 4.5  |
| Renal and urinary disorders                          | 0                  | 0   | 2                    | 2.9  | 1                    | 0.9  | 0              | 0   | 1                               | 4.5  |
| Respiratory, thoracic and mediastinal disorders      | 1                  | 5   | 6                    | 8.6  | 10                   | 8.6  | 0              | 0   | 0                               | 0    |
| Skin and subcutaneous tissue disorders               | 19                 | 95  | 8                    | 11.4 | 51                   | 44.0 | 6              | 100 | 4                               | 18.1 |
| Vascular disorders                                   | 0                  | 0   | 1                    | 1.4  | 1                    | 0.9  | 0              | 0   | 0                               | 0    |

Source: JMP analysis by reviewer using 7.31 AE dataset without unevaluable, after VISDYC 1, using dosing regimens displayed. Dataset with USUBJID, TCBZ dose and L1 text

*Reviewer comment: In this analysis, a clear dose-response for any TEAE could not be discerned.. The occurrences of some AEs in the 5 mg/kg arm, seemed very similar to that occurring in the 20 mg/kg arm – all patients in both arms were pediatric subjects who all seemed to experience abdominal pain; the 6 patients in the 20 mg/kg arm were pediatric patients who were retreated*

with Egaten after initial failure with CGP23030. It is possible that the subjective experience of AEs varies between children and adults, and/or that abdominal pain is more prominent in children due to disproportion between the size of the adult fluke and a child's common bile duct, both of which could contribute to the problems interpreting this post-hoc analysis.

Although half of the patients in the group that received 10 mg/kg on Days 1 and 3 received TCBZ in the fed state on Day 1 and fasted state on Day 3, and vice versa in the other half, the entire cohort of 22 were considered together for the purposes of this analysis. Twenty (91%) of these 22 individuals experienced TEAEs in the Gastrointestinal Disorders SOC; all 91% experienced abdominal pain (PTs of abdominal pain and abdominal pain upper depicted separately in Table 9.12, though both PTs occurred in some patients), while in different SOCs, 5/22 (22.7%) had decreased appetite, 4/22 (18.1%) experienced headache, and 3/22 (13.6%) had urticaria.

**Table 9.12 TEAEs in the Gastrointestinal Disorders SOC by Dose of TCBZ**

| Preferred Term                   | TCBZ Dose          |     |                      |      |                      |      |                          |       |                                 |      |
|----------------------------------|--------------------|-----|----------------------|------|----------------------|------|--------------------------|-------|---------------------------------|------|
|                                  | 5 mg/kg fed (N=20) | %   | 10 mg/kg fast (N=70) | %    | 10 mg/kg fed (N=116) | %    | 10 mg/kg q6-8h x 2 (N=6) | %     | 10 mg/kg on Days 1 and 3 (N=22) | %    |
| Abdominal pain*                  | 20                 | 100 | 8                    | 11.4 | 35                   | 30.2 | 6                        | 100.0 | 18                              | 81.8 |
| Abdominal pain upper*            | 0                  | 0   | 33                   | 47.1 | 38                   | 32.8 | 0                        | 0.0   | 12                              | 54.5 |
| Diarrhoea                        | 0                  | 0   | 2                    | 2.9  | 1                    | 0.9  | 0                        | 0.0   | 2                               | 9.1  |
| Dyspepsia                        | 0                  | 0   | 0                    | 0.0  | 1                    | 0.9  | 0                        | 0.0   | 0                               | 0    |
| Flatulence                       | 0                  | 0   | 0                    | 0.0  | 0                    | 0.0  | 0                        | 0.0   | 1                               | 4.5  |
| Gastrointestinal sounds abnormal | 0                  | 0   | 0                    | 0.0  | 0                    | 0.0  | 0                        | 0.0   | 2                               | 9.1  |
| Nausea                           | 3                  | 15  | 6                    | 8.6  | 9                    | 7.8  | 0                        | 0.0   | 5                               | 22.7 |
| Toothache                        | 0                  | 0   | 0                    | 0.0  | 1                    | 0.9  | 0                        | 0.0   | 1                               | 4.5  |
| Vomiting                         | 1                  | 5   | 4                    | 5.7  | 7                    | 6.0  | 1                        | 16.7  | 1                               | 4.5  |

Source: JMP analysis by reviewer using 7.31 AE dataset without unevaluable, after VISDYC 1, using dosing regimens displayed. Dataset with USUBJID, TCBZ dose, L1 and L4 text

\*These 2 PTs were sometimes recorded in the same patient. When both PTs were combined together as abdominal pain, a total of 20/22 patients (91%) who received 10 mg/kg on Days 1 and 3 experienced this AE.

Although the percent occurrence of abdominal pain (combined abdominal pain and abdominal pain upper PTs) in the 10 mg/kg on Days 1 and 3 treatment arm (91%) seemed larger than the occurrence of the same AE in the 10 mg/kg x 1 arm (56.5%), it also occurred in 100% of patients in both the 5 mg/kg and the 10 mg/kg q6-8h x 2 (Bolivian pediatric study) arms. Both the disparate numbers of patients in various treatment arms as well as potential differences in AE occurrence and recognition in adults vs. children could have skewed the results.

However, if patients in the two total 20 mg/kg regimens (10 mg/kg on Days 1 and 3, n=22; and 10 mg/kg q6-8h x 2, n=6) are combined for an exploratory analysis of AE occurrence vs. the 186 patients in the combined 10 mg/kg arm, 26/28 (92.9%) and 105/186 (56.5%) patients who received 20 mg/kg and 10 mg/kg TCBZ respectively experienced abdominal pain. In addition, 5/28 (17.9%) and 2/28 (7.1%) experienced nausea and vomiting respectively in the higher dose

group, compared with 8.1% and 5.9% for these AEs in the 10 mg/kg group. An imbalance was also seen in occurrence of headache and urticaria – 4/28 (14.3%) and 3/28 (10.7%) patients respectively in the 20 mg/kg TCBZ group vs. 5.9% and 6.5% respectively in the 10 mg/kg group. Thus, with the caveat of the noted data shortcomings and limitations of post-hoc analysis, a dose-response for AEs between the 20 mg/kg and 10 mg/kg TCBZ groups for fascioliasis treatment seems to be discernible.

TEAEs in the Skin and Subcutaneous Tissue Disorders SOC were examined by dose of TCBZ, and are summarized in Table 9.13.

**Table 9.13 TEAEs in the Skin and Subcutaneous Tissue Disorders SOC by TCBZ Dose**

| Preferred Terms     | TCBZ Dose          |      |                      |     |                      |      |                          |       | 10 mg/kg on Days 1 and 3 (N=22) | %    |
|---------------------|--------------------|------|----------------------|-----|----------------------|------|--------------------------|-------|---------------------------------|------|
|                     | 5 mg/kg fed (N=20) | %    | 10 mg/kg fast (N=70) | %   | 10 mg/kg fed (N=116) | %    | 10 mg/kg q6-8h x 2 (N=6) | %     |                                 |      |
| Alopecia            | 0                  | 0.0  | 0                    | 0.0 | 1                    | 0.9  | 0                        | 0.0   | 0                               | 0    |
| Hyperhidrosis       | 19                 | 95.0 | 5                    | 7.1 | 38                   | 32.8 | 6                        | 100.0 | 1                               | 4.5  |
| Night sweats        | 0                  | 0.0  | 0                    | 0.0 | 1                    | 0.9  | 0                        | 0.0   | 0                               | 0    |
| Pruritus            | 0                  | 0.0  | 2                    | 2.9 | 6                    | 5.2  | 0                        | 0.0   | 1                               | 4.5  |
| Rash                | 0                  | 0.0  | 0                    | 0.0 | 1                    | 0.9  | 0                        | 0.0   | 0                               | 0    |
| Rash maculo-papular | 0                  | 0.0  | 0                    | 0.0 | 0                    | 0.0  | 0                        | 0.0   | 0                               | 0    |
| Urticaria           | 0                  | 0.0  | 2                    | 2.9 | 10                   | 8.6  | 0                        | 0.0   | 3                               | 13.6 |

Source: JMP analysis by reviewer using 7.31 AE dataset without unevaluable, after VISDYC 1, using dosing regimens displayed. Dataset with USUBJID, TCBZ dose, L1 and L4 text

NB. These analyses do not include the 17 patients in EGA230B2201 in Iran who received 5 mg/kg once a day for 3 days.

The most common AE in the Skin and Subcutaneous Tissue Disorders SOC was hyperhidrosis – virtually 100% of children in both the 5mg/kg and 20 mg/kg retreated arms experienced this AE, while 7.1% and 32.8% of subjects in the 10 mg/kg fasting arm and 10 mg/kg post-prandial arm, respectively, experienced it. Interestingly, the occurrence of hyperhidrosis in patients who received 10 mg/kg on Days 1 and 3 was very low – 4.5% - the reasons for this are unclear.

### Laboratory Findings from the Primary Safety Population and Supportive Studies

Laboratory assessments differed among the studies submitted to this NDA, were not standardized, and normal/abnormal ranges and categories were not defined. Thus, only broad trends in the studies submitted to this NDA can be discerned; these findings are summarized below:

- 1) Maco study – Baseline serology (ELISA to detect IgG against the 25 kDa excretory/secretory antigen Fas 2) and evaluation of eosinophilia (defined as eosinophils >500/μL) were performed “to evaluate subgroup heterogeneity” prior to treatment allocation. Mean eosinophil count in Group 1 (7.5 mg/kg Fasinex q12h x 2)

using 37 available serum samples from the Asillo site, was 745 cells/mL with a range of 0-5,125 cells/mL; in Group 2 (10 mg/kg Fasinex x 1 – using 48 serum samples from Asillo), the mean was 1049 cells/mL, with a range of 0-7,150 cells/mL). The mean Fas 2 ELISA OD between the two groups at the Asillo site was 0.35 (range 0.01-0.53). No other laboratory measurements were done, and no results are available for the remaining 25 subjects at other sites. No post-treatment measurements were done.

- 2) Keiser study – Baseline blood sample was taken to evaluate hematologic parameters (WBC, hemoglobin, eosinophil count) and liver (ALT, AST, ALP, GGT, total bilirubin) and kidney (blood urea and serum creatinine) function; these were repeated 5 and 28 days post-treatment, both in the artemether-treated patients and in the 16 patients who received rescue TCBZ therapy. In the 16 TCBZ patients, no significant differences were seen in laboratory parameters pre- and post-treatment (both 10 mg/kg and 20 mg/kg TCBZ groups) aside from slight variations in the bilirubin and hemoglobin levels. Alkaline phosphatase remained slightly elevated in the 16 patients treated with 10 mg/kg TCBZ, but were normal in the 4 patients who required retreatment with 20 mg/kg.

**Table 9.14 Liver, Renal and Hematological Parameters Pre- and Post-Treatment with TCBZ**

| Parameter                                  | Reference range | 10 mg/kg triclabendazole (n = 16) |                                  |                                   | 20 mg/kg triclabendazole (n = 4) |                                  |                                   |
|--------------------------------------------|-----------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|----------------------------------|-----------------------------------|
|                                            |                 | Day of analysis                   |                                  |                                   | Day of analysis                  |                                  |                                   |
|                                            |                 | Pretreatment day 0 (mean ± SD)    | Post-treatment day 5 (mean ± SD) | Post-treatment day 28 (mean ± SD) | Pretreatment day 0 (mean ± SD)   | Post-treatment day 5 (mean ± SD) | Post-treatment day 28 (mean ± SD) |
| Alkaline phosphatase (ALP) (IU/l)          | 30–120          | 133.7 (38.8)                      | 137.3 (39.9)                     | 135.8 (37.7)                      | 111.0 (65.1)                     | 106.4 (59.2)                     | 99.5 (32.2)                       |
| Alanine transaminase (ALT) (IU/l)          | 9–60            | 10.9 (2.3)                        | 16.0 (11.4)                      | 11.9 (2.5)                        | 18.3 (3.2)                       | 19.3 (8.1)                       | 20.5 (9.3)                        |
| Aspartate transaminase (AST) (IU/l)        | 10–40           | 10.6 (3.9)                        | 19.6 (23.2)                      | 13.1 (3.0)                        | 23.5 (10.4)                      | 29.3 (13.7)                      | 29.3 (8.7)                        |
| Gamma glutamyl transpeptidase (GGT) (IU/l) | 0–51            | 7.0 (1.4)                         | 8.3 (2.6)                        | 7.7 (1.8)                         | 7.2 (1.1)                        | 9.4 (3.3)                        | 9.4 (3.3)                         |
| Bilirubin (mg/dl)                          | 0.2–1.2         | 0.6 (0.2)                         | 0.4 (0.3)*                       | 0.6 (0.2)**                       | 0.4 (0.1)                        | 0.6 (0.3)                        | 0.6 (0.1)                         |
| Urea (mg/dl)                               | 12–48           | 37.9 (11–0)                       | 35.2 (12.6)                      | 34.7 (6.6)                        | 23.8 (2.0)                       | 18.1 (6.3)                       | 22.2 (2.7)                        |
| Creatinine (mg/dl)                         | 0.6–1.3         | 0.8 (0.2)                         | 0.7 (0.2)                        | 0.8 (0.1)                         | 0.9 (0.3)                        | 1.1 (0.4)                        | 0.9 (0.2)                         |
| Eosinophils (%)                            | 0–6             | 4.5 (2.5)                         | 3.3 (1.5)                        | 3.5 (1.2)                         | 3.8 (1.0)                        | 3.5 (1.0)                        | 4.0 (0.8)                         |
| Hemoglobin (g/dl)                          | 11.5–17.5       | 12.8 (1.8)                        | 11.3 (1.1)*                      | 12.5 (1.3)**                      | 13.5 (0.6)                       | 13.3 (0.8)                       | 12.9 (0.6)                        |
| Total leucocytes (mm <sup>3</sup> )        | 3900–10,000     | 6356 (951)                        | 5950 (1074)                      | 6707 (918)                        | 5300 (902)                       | 5900 (1320)                      | 6350 (661)                        |

\*Statistically significant difference from baseline (p<0.05).

\*\*Statistically significant difference between first and second follow-up survey.

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Source: Table 4 [4]

- 3) CIBA/WHO Studies of Fascioliasis: Detailed interpretation of laboratory results was limited as laboratory parameters were not standardized and normal/abnormal values and ranges were not defined. In many cases, laboratory evaluations were not performed as scheduled, resulting in missing data. In general, many patients were noted to have hematological and biochemical abnormalities at baseline, reflective of fascioliasis, and in general, most of these abnormalities improved over the follow-up period. Overall, there

were no substantial changes in eosinophil or hemoglobin levels over the study periods (Days 0-90) in all dose groups. Mean levels of creatinine, AST and ALT remained relatively stable during the study period for all dose groups.

- 4) CIBA/WHO Paragonimiasis Studies: Clinical laboratory evaluations were made on Days 0, 6 and 90. The categories of change of liver enzymes or other biochemical or hematological parameters were not specified or standardized so these data are of limited utility. The study report notes that most patients had values within the normal range, or “higher than normal but not clinically relevant” – actual values were not provided. Anemia and leukocytosis were noted in some patients, with variations during the study.
- 5) Egyptian Fascioliasis Studies: Laboratory data was presented as mean values for the study population at various time points, so while trends can be discerned, it was not possible to provide a detailed analysis of the potential effect of TCBZ treatment on these values.
  - a) EGA230B2209 (Hassan study) – Hematological and biochemical tests were done at baseline and at months 1, 2 and 3 after treatment. At baseline, anemia was found in 47/60 (78.3%) patients, and eosinophilia was noted in 71.6%. Alkaline phosphatase was elevated in 61.7% of patients, while ALT and AST were elevated in 40%. Post-treatment, anemia improved, eosinophil count and ALP levels decreased and dilatation of the common bile duct improved. No effect was seen on renal function. Patient-level data were not available.
  - b) EGA230B2210 (Elsahly study) – Hematological and biochemical tests were done at baseline, Days 4, 6, 30 and 60 post-treatment. Mean eosinophil count at baseline was  $957 \times 10^9/L$  (range 106-6600); 64% (16/25) of patients had eosinophilia  $> 440/mm^3$ , while 40% had anemia at baseline. Mean total bilirubin, ALT, AST and ALP were within normal limits. Post-treatment, eosinophilia declined but did not normalize by 2 months after treatment in the 16 patients who had baseline eosinophilia. Anemia resolved post-treatment in 20% of patients who had baseline anemia. Liver enzyme values remained within normal limits post-treatment. Renal function remained normal pre- and post-treatment.
  - c) EGA230B2211 (Frag study) – Mean eosinophil count at baseline was  $748/mm^3$ ; 36.7% of patients had eosinophilia. One week after treatment, the number of patients with eosinophilia rose slightly but dropped thereafter; 2 months after treatment, 20% of patients had persistent eosinophilia. At baseline, 50% of patients were anemic, but 2 months after treatment, 38% were persistently anemic. Mean ALP value was above normal prior to treatment but improved significantly and normalized by 2 months post-treatment. No significant changes were seen in ALT, AST, bilirubin, urea or creatinine values.

#### **Vital Signs from the Studies with Patient-Level Data and Supportive Studies**

- 1) Maco study - No vital signs measurements were reported.

- 2) Keiser study – No vital signs measurements were reported.
- 3) CIBA-WHO Studies – No vital signs data are available.
- 4) Egyptian Fascioliasis Studies – no major changes in vital signs were noted.

### **Electrocardiograms (ECGs)**

No ECGs were done in the studies with patient-level data, the Egyptian fascioliasis studies or the CIBA/WHO paragonimiasis studies.

## **9.5. Analysis of Submission-Specific Safety Issues**

### **Immunogenicity**

Not applicable.

### **QT Prolongation**

Dietary administration of TCBZ doses of 39 mg/kg/day (1.1-times the MRHD based on body surface area comparison) was associated with a transient prolongation of the QT and QTc intervals in some dogs at weeks 5 and 9 of a 13-week nonclinical study. Mean QT (QTc) intervals of 212 - 227 (318 – 338 msec) were observed in the TCBZ group compared to 190-193 (280 – 297) msec in controls; QT intervals normalized by week 13. Additionally, when dogs were administered 40 or 100 mg/kg triclabendazole as a single dose, prolongation of the mean QTc ranging from 217-247 msec compared to a normal (historical control) range of 212±19 msec was observed. Plasma levels of the sulfone metabolite in dogs (which is thought to mediate QTc prolongation) were about 100-500 times the plasma level of the sulfone metabolite measured in human plasma (Dr. Tessie Alapatt, Section 5).

ECGs were not done in any of the studies submitted with patient-level data to this NDA, but no deaths or serious adverse events involving collapse or syncope suggestive of a cardiac or arrhythmic event occurred in enrolled subjects. ECG data were also scant in the reviewed literature; thus, the risk of QT prolongation with TCBZ administration cannot be adequately assessed in humans based on existing clinical data. The Applicant notes that, based on worldwide use of TCBZ, there have not been any reports of syncope, collapse or sudden death in the literature or in the Novartis Global Safety Database, and further contends that the likelihood of QT prolongation is small given the generally utilized single or two-dose TCBZ regimens.

A TQT study to characterize the risk of QT prolongation in humans has not been conducted by the Applicant. Nonetheless, the proposed product labeling contains a Warning regarding potential for QT prolongation with Egaten, especially if administered with other QT-prolonging agents, seemingly based solely on the nonclinical studies. However, other than avoidance of QT-prolonging concomitant medications, there are no recommendations to screen patients for a prolonged QT interval prior to, during, or after treatment with TCBZ.

Reviewer comment: A consult was requested from the FDA QT-IRT team during the review cycle – after review, their conclusion was as follows:

“The sponsor did not submit clinical ECG data to inform the label. We recommend that the sponsor conducts a TQT study as per the ICH E14 guideline for characterization of QTc effects. We do not accept nonclinical data alone as a replacement for a TQT study.”

*Thus, the Applicant will conduct a thorough QT study as a PMR. This was communicated to the Applicant during the Late-Cycle Meeting.*

### **G6PD Deficiency**

In the study report of EGA230B2209 – Hassan Study (submitted by the Applicant to this NDA), two siblings were noted to have experienced jaundice presumed due to hemolysis (reticulocytosis, negative Coombs test) following administration of TCBZ; one “recovered” in 2 weeks, while another took several weeks. No further information or characterization was available; it is also unclear whether G6PD deficiency in these 2 subjects was known prior to treatment or was found during post-treatment investigations.

[REDACTED] (b) (4)

Reviewer Comment: [REDACTED] (b) (4)  
[REDACTED]. During the Late-Cycle meeting, the Applicant verified that no individuals with G6PD deficiency have been identified in their development program other than the Egyptian siblings mentioned above, and further acknowledged that the information from those siblings was incomplete at best. [REDACTED] (b) (4)

### **Liver Enzyme Elevations**

[REDACTED] (b) (4)  
Increases in ALT, AST, ALP and bilirubin are seen in some patients as part of their *Fasciola* infection and are also seen post-treatment in some, potentially related to expulsion of the dead or dying fluke. However, patients with pre-existing hepatic or biliary impairment unrelated to fascioliasis were not specifically studied in the studies submitted to the NDA; [REDACTED] (b) (4)

Reviewer comment: The review team recommended [REDACTED] (b) (4)

## 9.6. Safety Analyses by Demographic Subgroups

**Keiser:** Because there were only 16 patients in the TCBZ arm of the study, a demographic subgroup analysis was not deemed appropriate or meaningful.

### Maco

All 84 subjects in the Maco trial were between the ages of 2 and 16 years. In section 9.1.4, the TEAE analysis indicated that abdominal pain and biliary colic were the two most commonly-occurring TEAEs, and that the frequency was highest on Days 2 and 4 post-treatment. The following table depicts occurrence of these two TEAEs on Days 2 and 4 by gender and dosing regimen.

**Table 9.15 Occurrence of Abdominal Pain and Biliary Colic on Days 2 and 4 Post-Treatment in the Maco Study Population**

|                             | Dose               |                  |                    |                   |
|-----------------------------|--------------------|------------------|--------------------|-------------------|
|                             | 10 mg/kg x 1       |                  | 7.5 mg/kg x 2      |                   |
|                             | Female<br>N=20 (%) | Male<br>N=20 (%) | Female<br>N=26 (%) | Male,<br>N=18 (%) |
| <b>Abdominal pain Day 2</b> |                    |                  |                    |                   |
| none                        | 18 (90)            | 19 (95)          | 19 (73.1)          | 16 (88.9)         |
| mild                        | 0                  | 1 (5)            | 6 (23.1)           | 2 (11.1)          |
| moderate                    | 2 (10)             | 0                | 1 (3.8)            | 0                 |
| <b>Biliary Colic Day 2</b>  |                    |                  |                    |                   |
| none                        | 16 (80)            | 14 (70)          | 23 (88.5)          | 16 (88.9)         |
| mild                        | 4 (20)             | 4 (20)           | 0                  | 1 (5.6)           |
| moderate                    | 0                  | 1 (5)            | 2 (7.7)            | 0                 |
| severe                      | 0                  | 1 (5)            | 1 (3.8)            | 1 (5.6)           |
| <b>Abdominal pain Day 4</b> |                    |                  |                    |                   |
| none                        | 17 (85)            | 17 (85)          | 23 (88.5)          | 18 (100)          |
| mild                        | 0                  | 3 (15)           | 1 (3.8)            | 0                 |
| moderate                    | 3 (15)             | 0                | 2 (7.7)            | 0                 |
| <b>Biliary Colic Day 4</b>  |                    |                  |                    |                   |
| none                        | 17 (85)            | 17 (85)          | 23 (88.5)          | 12 (66.7)         |
| mild                        | 0                  | 1 (5)            | 1 (3.8)            | 4 (22.2)          |
| moderate                    | 3 (15)             | 1 (5)            | 2 (7.7)            | 2 (11.1)          |
| severe                      | 0                  | 1 (5)            | 0                  | 0                 |

Source: alldata.xpt dataset provided by the Applicant, analyzed by the reviewer in JMP

These retrospective analyses are problematic as the specific definitions of “abdominal pain” and “biliary colic” were not provided; thus, the difference between the 2 was not clear. Further, because these patients are all children, the assessment of pain is likely to be very subjective. Given these limitations, the small numbers of individuals, and the noted problems with the OSI audit of the Maco trial, very little can be discerned from this data other than to note that the majority of patients did not experience either abdominal pain or biliary colic on Days 2 or 4.

*Reviewer comment:* No real trends were detected in this safety analysis by gender; potential issues in collection of data as outlined above affect the reliability of this data.

**Table 9.16 Distribution of Baseline Egg Count Categories in the Treatment Arms - Maco**

| Baseline Egg Count/gm stool | 7.5 mg/kg x 2 | 10 mg/kg x 1 |
|-----------------------------|---------------|--------------|
| 24-96                       | 9             | 8            |
| 97-144                      | 10            | 6            |
| 145-216                     | 10            | 12           |
| 217-288                     | 10            | 7            |
| 289-528                     | 5             | 6            |

Source: alldata.xpt dataset; reviewer analysis in JMP

**Reviewer Comment:** *This reviewer analyzed the occurrence of abdominal pain by baseline egg count (analyses not shown) - 40% of patients with the highest baseline egg count in the 7.5 mg/kg arm had abdominal pain at Day 2 post-treatment, but none did at Day 4. In the 10 mg/kg arm, 0 patients had abdominal pain at Day 2, but 33.3% did at Day 4. Overall, the numbers are too small for a meaningful comparison to be made. A similar analysis was attempted for patients with biliary colic; again, the numbers were too small for meaningful comparison.*

**CIBA/WHO Trials:** See Table 7.14 for a demographic analysis of the population in the CIBA/WHO trials by dose regimen; an analysis of TEAE occurring in various SOCs by dose regimen is provided in Table 9.11. A further demographic analysis of distribution of SOCs by dosing regimen is depicted in Table 9.17.

**Table 9.17 Distribution of SOCs of TEAEs Occurring in the CIBA/WHO Studies by Gender and Dosing Regimen Administered in the Fasting or Post-Prandial State**

| System Organ Class                                   | Dosing Regimen and Administration in Relationship to Food |            |                  |            |              |            |              |           |
|------------------------------------------------------|-----------------------------------------------------------|------------|------------------|------------|--------------|------------|--------------|-----------|
|                                                      | 5 mg/kg fed                                               |            | 10 mg/kg fasting |            | 10 mg/kg fed |            | 20 mg/kg fed |           |
|                                                      | Female, n=7                                               | Male, n=13 | Female, n=45     | Male, n=25 | Female, n=64 | Male, n=52 | Female, n=4  | Male, n=2 |
| Cardiac disorders                                    | 0                                                         | 0          | 0                | 0          | 2 (3.1)      | 0          | 0            | 0         |
| Ear and labyrinth disorders                          | 0                                                         | 0          | 7 (15.6)         | 0          | 9 (14.1)     | 0          | 0            | 0         |
| Eye disorders                                        | 0                                                         | 0          | 0                | 0          | 1 (1.6)      | 0          | 0            | 0         |
| Gastrointestinal disorders                           | 7 (100)                                                   | 13 (100)   | 28 (62.2)        | 8 (32)     | 41 (64.1)    | 28 (53.8)  | 4 (100)      | 2 (100)   |
| General disorders and administration site conditions | 0                                                         | 0          | 8 (17.8)         | 2 (8.0)    | 6 (9.4)      | 2 (3.8)    | 0            | 0         |
| Hepatobiliary disorders                              | 1 (14.3)                                                  | 0          | 0                | 1 (4.0)    | 3 (4.7)      | 2 (3.8)    | 0            | 0         |
| Metabolism and nutrition disorders                   | 0                                                         | 0          | 0                | 1 (4.0)    | 2 (3.1)      | 1 (1.9)    | 0            | 0         |
| Musculoskeletal and connective tissue disorders      | 0                                                         | 0          | 6 (13.3)         | 1 (4.0)    | 4 (6.3)      | 2 (3.8)    | 0            | 0         |
| Nervous system disorders                             | 0                                                         | 0          | 5 (11.1)         | 0          | 5 (7.8)      | 0          | 0            | 0         |
| Renal and urinary disorders                          | 0                                                         | 0          | 0                | 2 (8.0)    | 1 (1.6)      | 0          | 0            | 0         |
| Respiratory, thoracic and mediastinal disorders      | 0                                                         | 1 (7.7)    | 5 (11.1)         | 1 (4.0)    | 7 (10.9)     | 3 (5.8)    | 0            | 0         |
| Skin and subcutaneous tissue disorders               | 7 (100)                                                   | 12 (92.3)  | 5 (11.1)         | 3 (12.0)   | 29 (45.3)    | 22 (42.3)  | 4 (100)      | 2 (100)   |
| Vascular disorders                                   | 0                                                         | 0          | 1 (2.2)          | 0          | 1 (1.6)      | 0          | 0            | 0         |

Source: Reviewer analysis in JMP Version 11. An ADSL dataset was not provided so the patient's age and gender from PTHIST.xpt was joined with a AE dataset prepared by the reviewer from the dataset resubmitted by the Applicant on 7/31/18. The dataset contained many unevaluable terms as previously detailed in Section 9.1.3 – these were removed. Entries (listings) that did not have a VISDYC ≥ 1 (treatment-emergent flag) were removed

Numerically more TEAEs occurred in females compared with males in the 10 mg/kg dosing group, whether TCBZ was administered in the fasted or post-prandial state. These differences appeared most marked in the Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Nervous System Disorders and Musculoskeletal and Connective Tissue Disorders SOCs (see Table 9.17); these were also the SOCs in which the greatest number of TEAEs occurred. There was little gender disparity in the Skin and Subcutaneous Tissue Disorders SOC despite occurrence of multiple TEAEs. A small gender disparity was observed in the Respiratory, Thoracic and Mediastinal Disorders SOC, but represented few AEs.

**Table 9.18 Occurrence of TEAEs in Specific SOCs in the Other Dosing Regimens in the CIBA/WHO Studies**

| System Organ Class                                   | A=10 mg/kg on day 1 in the fasting state and 3 post-prandially, N=10 | B=10 mg/kg on day 1 post-prandially and 3 in the fasting state, N=12 | A=5 mg/kg on days 1, 2, 3, fasting, N=17 |
|------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------|
| Ear and labyrinth disorders                          | 0                                                                    | 0                                                                    | 6 (35.3)                                 |
| Gastrointestinal disorders                           | 10 (100)                                                             | 10 (83.3)                                                            | 15 (88.2)                                |
| General disorders and administration site conditions | 2 (20)                                                               | 0                                                                    | 5 (29.4)                                 |
| Hepatobiliary disorders                              | 0                                                                    | 0                                                                    | 1 (5.9)                                  |
| Infections and infestations                          | 1 (10)                                                               | 2 (16.7)                                                             | 0                                        |
| Metabolism and nutrition disorders                   | 4 (40)                                                               | 1 (8.3)                                                              | 1 (5.9)                                  |
| Musculoskeletal and connective tissue disorders      | 0                                                                    | 2 (16.7)                                                             | 4 (23.5)                                 |
| Nervous system disorders                             | 2 (20)                                                               | 2 (16.7)                                                             | 4 (23.5)                                 |

| System Organ Class                              | A=10 mg/kg on day 1 in the fasting state and 3 post-prandially, N=10 | B=10 mg/kg on day 1 post-prandially and 3 in the fasting state, N=12 | A=5 mg/kg on days 1, 2, 3, fasting, N=17 |
|-------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------|
| Psychiatric disorders                           | 1 (10)                                                               | 0                                                                    | 0                                        |
| Renal and urinary disorders                     | 1 (10)                                                               | 0                                                                    | 2 (11.8)                                 |
| Respiratory, thoracic and mediastinal disorders | 0                                                                    | 0                                                                    | 5 (29.4)                                 |
| Skin and subcutaneous tissue disorders          | 3 (30)                                                               | 1 (8.3)                                                              | 9 (52.9)                                 |
| Vascular disorders                              | 0                                                                    | 0                                                                    | 1 (5.9)                                  |

*Reviewer comment: The incidence of TEAEs in multiple SOCs – e.g Gastrointestinal, Ear and Labyrinth Disorders, General Disorders and Administration Site Conditions, Respiratory, Thoracic and Mediastinal Disorders, and Skin and Subcutaneous Tissue Disorders – appeared to be more common in the group receiving 5 mg/kg on Days 1, 2, and 3 compared with the 10 mg/kg arms. If AEs are related to C<sub>max</sub> as may be expected, this result is surprising. However, because there were only 17 subjects who received this dosing regimen, it is difficult to draw any conclusions. There was a trend to increased occurrence of TEAEs in the 10 mg/kg D1 fasting/D3 fed group vs. the 10 mg/kg D1 fed/D3 fasting group; again, the very small number of subjects doesn't allow for reliable conclusions.*

## 9.7. Specific Safety Studies

### 9.7.1. CIBA/WHO Studies of Paragonimiasis

Study reports of 3 CIBA/WHO studies of TCBZ for paragonimiasis were submitted in this Application and culled for supportive safety information; none had datasets for independent analysis. The pathogenesis of paragonimiasis is distinct from that of fascioliasis as the adult flukes of *Paragonimus* spp. live in the lung rather than the liver; thus, adverse event frequencies from these studies were especially important in understanding the causality of the abdominal pain frequently seen with TCBZ use for fascioliasis, i.e, differentiating between a possible drug toxicity vs. the expulsion of the dead fluke through the biliary tree. The following discussion focuses only on TCBZ safety information from these studies; efficacy of TCBZ for paragonimiasis is not relevant to this review.

Two of these 3 studies were done in Ecuador and 1 in Cameroon; as with the CIBA/WHO trials for fascioliasis, the 3 studies shared a common protocol and were open-label, comparative, Phase 2 dose-finding trials conducted between 1989 and 1993. The trial plan and core protocol for TCBZ in human paragonimiasis was approved in 1990 by WHO SCRIHS, and the study was carried out in accordance with the recommendations of the Declaration of Helsinki. The study was not conducted in accordance with GCP as it started before the Directive on GCP came into force on 1/1/92.

All studies used the intermediate TCBZ formulation, CGP 23030.

Patients with eggs of *Paragonimus* spp. in sputum were enrolled, treated with TCBZ (or praziquantel in 2 studies), monitored in hospital for 7 days, and then followed as outpatients at Days 30 and 60. Endpoints included the assessment of clearance of parasite eggs from the sputum, global assessment by the investigator of adequate or inadequate resolution/failure of therapy, findings on chest X-ray, evaluation of clinical signs and symptoms, and hematologic and liver function parameters.

**Table 9.19 Overview of CIBA/WHO Trials of TCBZ for Paragonimiasis**

| Study                           | Drug/Dose                          | Number exposed to TCBZ | Age/Gender             | Adverse Events                                                                                                                        |
|---------------------------------|------------------------------------|------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <b>Cameroon<br/>EGA230B2213</b> | TCBZ 5 mg/kg q24h x 3              | 11                     | 5-54 yrs,<br>26M, 19F  | Total TCBZ N: 35<br>Headache 5.7%, abdominal pain 5.7%,<br>vomiting 2.9%, diarrhea 2.9%                                               |
|                                 | TCBZ 10 mg/kg q6-8h x 2            | 12                     |                        |                                                                                                                                       |
|                                 | TCBZ 10 mg/kg x1                   | 12                     |                        |                                                                                                                                       |
|                                 | PZQ <sup>1</sup> 25 mg/kg tid x 3d | 10                     |                        |                                                                                                                                       |
| <b>Ecuador<br/>EGA230B2205</b>  | TCBZ 10 mg/kg x1                   | 77                     | 4-68 yrs,<br>74M, 90F  | Total TCBZ N: 154<br>Dizziness 5.4%, abdominal pain 1.3%,<br>diarrhea 1.3%, fever 1.9%                                                |
|                                 | TCBZ 10 mg/kg q6-8h x 2            | 77                     |                        |                                                                                                                                       |
| <b>Ecuador<br/>EGA230B2206</b>  | TCBZ 5 mg/kg x 3                   | 16                     | 12-60 yrs,<br>25M, 37F | Total TCBZ N: 47<br>abdominal pain 17% (6.4% were thought to<br>be drug-related); headache 10.6%, dizziness<br>4.3%,<br>jaundice 2.1% |
|                                 | TCBZ 10 mg/kg q6-8h x 2            | 15                     |                        |                                                                                                                                       |
|                                 | TCBZ 10 mg/kg x1                   | 16                     |                        |                                                                                                                                       |
|                                 | PZQ 25 mg/kg tid x 3d              | 15                     |                        |                                                                                                                                       |

Source: Table constructed by reviewer from the CSRs for the Paragonimiasis studies submitted in the NDA

<sup>1</sup>Praziquantel

No SAES, deaths or discontinuations due to adverse events occurred in any of the 3 studies.

In Study 2213, 9 AEs occurred in the 3 TCBZ dosage groups, of which 6/35 (1.7%) - headaches in 2 individuals, abdominal pain in 2 individuals, and vomiting and diarrhea each in 1 subject - were thought by the investigators to be related to TCBZ treatment. In the PZQ group, 1 patient each (10%) had AEs related to therapy: abdominal pain, urticaria, and icterus. No major changes in hematological or chemical parameters could be discerned from the study report. In particular, most ALT, AST, alkaline phosphatase and bilirubin values were within the normal range, or higher than normal “but not clinically relevant” at Day 0, and most remained relatively constant or declined at the subsequent time points of Day 6 and Day 90.

*Reviewer comment: Summarized tabulated laboratory data were provided, and it was unclear why certain values were designated “upper clinically relevant limit” for each enzyme [see page 97 of the cgp23030ahp2.cameroon Study Report]. Nonetheless, no significant elevations in liver enzymes appear to have occurred.*

In Study 2205, dizziness was the most common AE, occurring in 4/77 (5.2%) of the total 20 mg/kg group, and 5/77 (6.5%) individuals of the 10 mg/kg dose group. Transaminase levels remained within the normal range for all but one of the study subjects – this patient had elevated AST and ALT at baseline which remained elevated during the study period. No

individual had jaundice; renal function tests and hematological parameters remained normal throughout the study period.

In Study 2206, AEs occurred with approximately equal frequency in all 3 TCBZ dosing groups together (49%) compared with the PZQ group (51%). Two subjects in the TCBZ groups had headaches, 2 experienced dizziness, 3 had abdominal pain – none of which were listed as severe. There were 2 patients with jaundice, one in group A (TCBZ 5 mg/kg x 3) on Day 30 and another in Group C (TCBZ 10 mg/kg x 1) on Day 6. According to the study report, ALT and AST were “above central normal, were never high enough to be considered clinically relevant at any time throughout the study period, bilirubin values remained unchanged throughout treatment...”

*Reviewer comment: Both episodes of jaundice in Study 2206 were noted to be “transient” but no further details were provided regarding possible etiology or patient course. Further, the study report section on changes in laboratory values did not note elevated bilirubin in any patient in Group C, although 1 patient in each of the first two TCBZ groups (5 mg/kg x 3 and 10 mg/kg x 2) and the PZQ group were identified as having bilirubin values that “were higher than normal but not clinically relevant”; thus, some inaccuracy was noted. In this study, abdominal pain occurred in more patients (17%) than in the other 2 paragonimiasis studies, but was still much lower than the 56.5% and 92.9% frequency of abdominal pain seen in the combined 10 mg/kg arms and 20 mg/kg arms respectively, in the CIBA/WHO fascioliasis studies. Further, no dose-response for AEs was seen in the paragonimiasis studies.*

*Overall, the 3 studies of TCBZ for treatment of paragonimiasis are useful as sources of safety information, especially for the higher dose of 20 mg/kg. Human infection with lung flukes, most commonly *Paragonimus westermanii*, and liver flukes, *Fasciola* spp, share the same initial pathogenesis with ingestion of metacercariae (from contaminated watercress or other leafy vegetables in fascioliasis and infected crabs/crayfish in paragonimiasis), which then excyst in the duodenum, and penetrate through the intestinal wall into the peritoneal cavity. Thus, the initial symptoms of abdominal pain, fever, malaise, anorexia are common to both infections. Subsequently, while *Fasciola* spp migrate through the liver and grow to maturity in the biliary tree, *Paragonimus* spp migrate through the diaphragm and mature in the lungs – thus, symptomatology in the intermediate and chronic stages differs between the two infections, reflecting the site of chronicity. Eggs produced by adult *Paragonimus* flukes are found in the sputum (though some can be found in the stool if the egg-laden sputum is swallowed), while eggs produced by *Fasciola* spp flukes are found in stool.*

*In the 3 paragonimiasis studies summarized above, a total of 105 and 104 subjects were given a dose of 10 mg/kg or 20 mg/kg TCBZ respectively. Overall, abdominal pain occurred in 5 (4.8%) patients in the 10 mg/kg cohort and 4 (3.8%) in the 20 mg/kg cohort - much lower frequencies compared with the 56.5% and 92.9% of patients that experienced abdominal pain in the 10 mg/kg and 20 mg/kg groups respectively in the CIBA/WHO fascioliasis studies. This underscores the impression that the AE of abdominal pain post-treatment in fascioliasis is very likely related to the expulsion of the dead/dying fluke, rather than to TCBZ itself. In addition, and unlike in the*

*fascioliasis studies, no dose-response for abdominal pain or any other AE was noted in the paragonimiasis studies.*

*Note: During the Late-Cycle Meeting, the Applicant was asked to provide data from the paragonimiasis studies in .xpt format to allow independent analysis by the clinical reviewer; these datasets were submitted late in the review cycle. The occurrence of abdominal pain at rates of 4.8% and 3.8% in the 10 mg/kg and 20 mg/kg TCBZ groups was verified. Other AEs that occurred with >2% frequency in the 10 mg/kg and 20 mg/kg groups respectively were: pyrexia (4.8% and 0.9%), dizziness (4.8% and 3.8%), headache (1.9% and 2.9%), and diarrhea (0.9% and 3.8%) [see Table 15.31, Section 15.5]. Overall, adverse event occurrence was verified to be low; in particular, abdominal pain occurred much less frequently after TCBZ treatment for paragonimiasis compared with fascioliasis and is thus more likely associated with pathobiology of the disease, rather than the drug. Further, triclabendazole at 10 mg/kg and 20mg/kg doses exhibited the same safety profile without an apparent dose-response for safety.*

### 9.7.2. Egyptian Studies of TCBZ for Fascioliasis

These studies conducted by the Egyptian government between 1995 and 1996, were open-label, non-randomized studies that used Fasinex in doses of 10 mg/kg x 1, or 10 mg/kg divided into 2 equal doses of 5 mg/kg 6 hours apart. These studies enrolled symptomatic and asymptomatic subjects with chronic fascioliasis as judged by the presence of eggs in stool. The primary efficacy endpoint was presence or absence of *Fasciola* eggs in stool on Days 4, 6, 7, 30 and 60. Standard laboratory evaluations included complete blood counts, liver and kidney function tests, abdominal ultrasonography, stool examinations for *Fasciola* eggs by the Kato-Katz method, and in some patients, anti-*Fasciola* IgG titers. ECG and Xrays were done in the Hassan study. Patients were admitted to hospital for one week following treatment for clinical and laboratory evaluations and returned for follow-up on Days 30 and 60.

**Table 9.20 Selected Details, Efficacy and Safety Information from the Egyptian Government Studies of TCBZ for Fascioliasis**

| Name of Study/Design                                                                             | Study Population                                                                                                                                                             | Efficacy                                                                                                                                                           | Safety                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <sup>1</sup> Hassan<br>EGA230B2209<br><br>10 mg/kg x 1 (n=30)<br>5 mg/kg x 2, 6 hr apart (n=30). | N=60. 14 males, 24 females < 15 years; 2 males, 20 females > 15 years                                                                                                        | *Cure=100% after 1 week; 91.6% after 1 month.<br>*Split dose cure rate: 86.6%;<br>*Single dose: 80%<br>*No significant decrease in anti- <i>Fasciola</i> IgG at 3m | *Abdominal pain: 58.3% <sup>2</sup> on Day 4 after treatment<br>*Vomiting: 1.7%<br>*Jaundice: 5% (2 of 3 had G6PD deficiency)                                  |
| Elsahly<br>EGA230B2210<br><br>Dose=10 mg/kg                                                      | N=25. 12 males; 13 females, age 10-55 yrs. 64% had eosinophilia before trt. Dropped gradually to 758/mL 2m post-treatment. 68% (1 additional pt) had eosinophilia after trt. | *Cure=100% at 1 week; 88% at 1m and 2m.                                                                                                                            | No change in LFTs or renal function; 32% with nausea and vomiting Days 1 and 2. Most patients had abdominal pain at baseline, this declined from day 4 onward. |
| Farag                                                                                            | N=50. Single dose: 60%                                                                                                                                                       | *Cure (absence of eggs in stool):                                                                                                                                  | *Slight increase from baseline in right                                                                                                                        |

| Name of Study/Design                                                               | Study Population                                                                                                  | Efficacy                                                                                                                                                                                                                                                                            | Safety                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>EGA230B2211</b><br><br>10 mg/kg x 1 (n=25);<br>5 mg/kg x 2, 6hr apart<br>(n=25) | male, 10-49 yrs. Split dose: 36% male, 10-55 yrs.<br>36.7% had eosinophilia before trt; 20% still had it 2m later | 88% in single dose and 72% with split dose at 1 week; 88% and 96% respectively at 1m; 92% and 96% at 2m<br><br>*Cure (absence of eggs in stool and absence of flukes on U/S): 48% and 40% respectively with single and split doses at 1 week; 76% and 84% at 1m; 84% and 92% at 2m. | hypochondrial pain (64%), abdominal colic (52%) and dyspepsia/nausea/vomiting (42%) on Day 1 after treatment. Significant decline at all other timepoints – 2%, 6% and 4% respectively at 2m.<br><br>*VS all normal, mild increases in AST/ALT post-trt; all normal by 1 and 2m. |

<sup>1</sup>CGP 23030 is the interim human formulation first developed for use in humans – Egaten® was subsequently developed. Prior to CGP 23030, only Fasinx was used.

<sup>2</sup>The text indicates abdominal pain occurred in 58.3%; the table on page 19 of the study report says 66.7%. The jaundice and vomiting numbers from the text (used here) are also different from those in Table 6 of the study report (p.19).

G6PD – glucose-6-phosphatase deficiency; LFTs – liver function tests; U/S – ultrasound; VS – vital signs; AST – aspartate aminotransferase; ALT – alanine aminotransferase; trt – treatment; m – months.

**Reviewer Comment:** *These 3 Egyptian studies had similar study design, administered the CGP 23030 at a dose of 10 mg/kg either singly or split as two 5 mg/kg doses 6 hr apart, and enrolled subjects with chronic fascioliasis as defined by the presence of Fasciola eggs in stool. As with many of the historical studies, children were a significant subgroup. Many of the study subjects had abdominal pain at baseline, some had fever, anorexia, malaise, anemia, and eosinophilia. Cure rates (absence of eggs in stool) were consistently ≥80%, except in the Farag study, in which the split dose resulted in cure in 72% of subjects at 1 week. However, by 1 month, both dose groups achieved cures in excess of 85%. In addition, abdominal pain or right hypochondrial pain occurred in >50% of patients in all 3 studies soon after treatment, but declined steadily thereafter and in most cases, resolved by 2 months. All authors mentioned that symptoms only persisted in subjects who failed treatment as evidenced by reappearance of eggs in stool. These results are consistent with those obtained from the 2 IITs for which safety information is available, as well as those from the 6 CIBA/WHO studies.*

### 9.7.3. Selected Supportive Studies from Literature

References provided by the Applicant as well as literature references independently identified by the reviewer were reviewed. Meaningful cross-study comparisons are challenging because study populations, study designs, and methodology of data collection among other parameters, were different. These studies can potentially provide limited supportive evidence to the Applicant’s conclusions of TCBZ safety and effectiveness for the treatment of fascioliasis. Much of the extensive existing literature on the use of TCBZ for fascioliasis consists of case reports or case series; for the most part, these were reviewed but are not mentioned further in this review. Details of selected randomized or open-label studies are summarized in Table 9.21.

**Table 9.21 Selected Studies from Literature**

| First author, Type of Study, Date and Location, Adult vs. Pediatric | # Pts                                                    | Brief Description                                                                                                                                                                                                                                                                        | Treatment                                                                                                                      | End-Points                                                                                                                                                                                                                                                                                  | Efficacy                                                                                                                                                                                                                                                                                                                                                                                                                                | Safety Concerns                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Talaie, 2004 [28] Iran                                              | 165 pts; 13 D/C'd; Evaluable: Chronic 33; Suggestive 119 | Ages 10-65. Divided into cases ( <b>chronic</b> ) (stool Fasciola egg+) and suggestive cases ( <b>acute</b> ) (3 of fever, shoulder pain, abdo pain, pruritus, urticaria, hepatomegaly, serum IgG>128, >5% eosinophilia)                                                                 | Random allocation TBZ 10mg/kg x 1, or q24h for 2d, or 3d (Egaten®)<br><br>Single dose: 51<br>Double dose:52<br>Triple dose: 49 | Cases - cure was complete absence of eggs after trt. Suggestive cases: combination of egg- stool, decrease or disappearance of clinical symptoms and IgG levels < 128 after trt.                                                                                                            | Abdominal pain(AP) in 90% at baseline in all groups; fever in 50%. One week later, AP in 20%. Ova disappeared in single- and double-dose groups on days(D) 14, 30 and 60. 2 pts in the triple-dose group were egg+ on D14 and 30 - cleared with another 10mg/kg. Number of patients with falling IgG titer increased in all groups to D60 (all were cured on D60). Cure rates were not significantly different among the 3 dose groups. | Mild nausea, vomiting, pruritus, epigastric pain, hepatomegaly in 10% of single-dose, 15% of double-dose and 10% triple-dose arm.<br><br>Elevation in AST and/or ALT seen in 7 (14%) patients in triple-dose group but normalized in 4 of them by Day 60. No jaundice was seen.                                                                                                                                                                            |
| Millan, 2000 [24] Cuba                                              | 82                                                       | ages 15-81 with <b>chronic latent fascioliasis</b> who failed previous therapy - PRZ (59), metronidazole (26), thiabendazole (7), mebendazole (5), emetine (3), bithionol (3). 60 days open non-comparative. Not ethical to use placebo as one pt infected died as a result of infection | Pts with eggs in stool who failed one round of therapy >30d prior to enrollment. TCBZ 10mg/kg x 2 (Egaten?)                    | Primary - clearance of eggs, decrease of Fas E/S antigens in stool below cut-off, absence of parasites at US. Secondary: decrease in ab levels, disappearance of eosinophilia, intercurrent biliary colic. Trt failure: persistent egg excretion and moving parasites in the biliary system | Hospitalized for 7 days. Blood work D0,3,7,15,30, 60. Stool D0, 3, 7, 30 and 60. Ab/Ag testing D0, 30, 60. US exam D0, daily d1-7, 15, 30, 60. At study entry, all had eggs, 44% had S/S. at D60, 8 of 79 (10%) had S/S. 4 pts continued to excrete ova; all responded to another dose                                                                                                                                                  | 54/82 (66%) had AEs. 40/82 (49%) had biliary colic on (median) Day 5 post-therapy, 35 (42.7%) had epigastric pain; 41/82 (40%) had increased ALP c/w parasite expulsion (confirmed by ultrasound) on days 4-7. Three patients with biliary colic had obstructive jaundice. Low to moderate transient fever in 7 patients. Most AEs (53) were mild, 20 were moderate, 1 had severe abdominal pain on Day 6, which resolved in 2 hours after anti-spasmodic. |
| El-                                                                 | 134                                                      | Pts with <b>chronic</b>                                                                                                                                                                                                                                                                  | Group 1: 10                                                                                                                    | Stool egg                                                                                                                                                                                                                                                                                   | 79.4% of gp 1 and 94% gp                                                                                                                                                                                                                                                                                                                                                                                                                | Mild, colicky                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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| First author, Type of Study, Date and Location, Adult vs. Pediatric        | # Pts | Brief Description                                                                                                       | Treatment                                       | End-Points                       | Efficacy                                                                                                                                                                                                                                                                                                                                                              | Safety Concerns                                                                                                               |
|----------------------------------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Morshed y, 1999 [23] Egypt                                                 |       | <b>fascioliasis (eggs)</b> randomly divided into 2 gps – Group 1, N=68; Group 2, N=66 (groups had both adults/children) | mg/kg x 1<br>Group 2: 10 mg/kg q12h x 2         | count at 5 weeks, lab parameters | 2 cured at 5 weeks                                                                                                                                                                                                                                                                                                                                                    | abdominal pain in some. One patient had jaundice                                                                              |
| Saba; 2004 [86] Turkey                                                     | 53    | Mean age: 42 (9-75). 28 pts with acute, 19 with chronic, 6 latent                                                       | TBZ 10 mg/kg x 1 - 37pts;<br>10mg/kg x 2 -13pts | Case Series                      | Baseline: epigastric pain 55%; RUQ pain 38%, malaise 38%.<br>30 pts eventually assessed (13 did not return, 5 had surgery, 2 treated with PZQ.<br>Treatment successful in 30 patients - 78% cure with one dose;<br>7 non-responders: 4 successful with 2 <sup>nd</sup> course, 2 with 3 more courses, 1 did not respond to TCBZ, treated with albendazole. 90% with 2 | “Well-tolerated...only moderate side effects” (not specified)                                                                 |
| El-Karasky, 1999 [87] Egypt                                                | 40    | 40 children, ages 4-15. Dx by fever, eggs, eosinophilia, IHAT, U/S, Path                                                | TBZ 10mg/kg                                     |                                  | 77.5% (31 cases) cured at 2 months, 9 pts required a second dose                                                                                                                                                                                                                                                                                                      | None major; transient fever, RUQ discomfort in 4pts, 4 days after trt.                                                        |
| Farag; 1998 Egypt                                                          | 50    | Chronic fascioliasis, >10 years                                                                                         | TBZ 10mg/kg x 1 (25pts); 5mg/kg x 2 q6h (25)    |                                  | 94% cure at 2 m (no eggs in stool) vs. 88% with no eggs in stool and neg US                                                                                                                                                                                                                                                                                           | mild RUQ pain, transient jaundice in one pt, transient elevation in LFT's                                                     |
| <b>Interventional non-randomized, open-label, proof-of-concept studies</b> |       |                                                                                                                         |                                                 |                                  |                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                               |
| Apt; 1995 [17] Chile                                                       | 24    | Chronic hepatic fascioliasis in adults                                                                                  | TBZ 10 mg/kg x 1                                |                                  | 79.2% cured (no eggs in stool) after single dose. 3/5 left took another dose - all cleared, 2 refused.                                                                                                                                                                                                                                                                | None                                                                                                                          |
| Villegas; 2012 [1] Bolivia                                                 | 90    | 90 children, ages 5-14 y in the Altiplano, Bolivia - a highly endemic area. All children had a stool test -             | TBZ 10 mg/kg x 1                                |                                  | 21.7% prevalence of infection at baseline. 77.8% parasitological cure with single dose TBZ. 20 children were re-treated and cure was 97.8% from                                                                                                                                                                                                                       | Headache (5), nausea (1) and abdo pain (2) were reported on day of trt. Only 3 had abdo pain one week later, one child with a |

NDA Multi-Disciplinary Review and Evaluation – NDA

| First author, Type of Study, Date and Location, Adult vs. Pediatric | # Pts | Brief Description                                                                                                                                                              | Treatment                                                                                                                                 | End-Points | Efficacy                                                                                                                                                                                                                                                                                | Safety Concerns                                                                                                                              |
|---------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                     |       | positivity ID's by Kato-Katz. If >300 epg, they were hosp'd. All were treated with 10mg/kg TBZ. 3 m later, all had repeat stool exam. If positive, they received another dose. |                                                                                                                                           |            | baseline - only 2 still positive.                                                                                                                                                                                                                                                       | high-intensity infection had abdo pain at one week. No meds needed except anti-pyretics.                                                     |
| Kaya, 2011 [13] Turkey                                              | 30    | Clinical fascioliasis in adults: 22/30 with hepatic phase, 5 with biliary phase, and 3 with biliary phase associated with acute pancreatitis                                   | TBZ 10mg/kg x 1 (formulation not specified – likely Egaten)                                                                               |            | Abdo pain (100%), fever (59%), nausea in 3, chills, weight loss in 4 (18%), urticaria, asthenia. RUQ tenderness (68%), hepatomegaly (27%). Eosinophilia present in 100% pts in hepatic phase, 50% pts in biliary phase anemia in 27%, ALT/AST/ALP increase in 9-50%. IHA very positive. | TBZ x 1 dose results in complete clinical and lab recovery in all pts 3 m after treatment.                                                   |
| El-Tantawy, 2007 [27] Egypt                                         | 12    | Open-label, non-randomized study of Fasinex PK in infected pts and healthy controls. Ages 16-45                                                                                | TBZ 10mg/kg x 1 in 12 infected pts, and 12 healthy volunteers. Pts were hosp'd for 3 months, PK studies done. <b>All received Fasinex</b> |            | 100% cure in patients                                                                                                                                                                                                                                                                   | “Several patients complained of RUQ pain post drug administration”                                                                           |
| Barduagni, 2008 [88] Egypt                                          | 10    | Age 8-58 yrs, half were children. Fecal excretion of eggs of both species was examined.                                                                                        | TBZ 10 mg/kg x 1                                                                                                                          |            |                                                                                                                                                                                                                                                                                         | 6 weeks from single TBZ dose, 7 pts still in the study were still excreting eggs of <i>S. mansoni</i> , but none of <i>Fasciola</i> ie. 100% |

NDA Multi-Disciplinary Review and Evaluation – NDA

| First author, Type of Study, Date and Location, Adult vs. Pediatric | # Pts | Brief Description                                                          | Treatment                                                                             | End-Points | Efficacy                                                                                                                                                  | Safety Concerns                                                           |
|---------------------------------------------------------------------|-------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
|                                                                     |       | Co-infected with <i>Schistosoma mansoni</i> and <i>Fasciola spp</i>        |                                                                                       |            |                                                                                                                                                           | cure. After 3 months, 4/5 remaining pts still had <i>S. mansoni</i> eggs. |
| Hammou da, 1995 [89] Egypt                                          | 10    | Chronic fascioliasis, only 4 had eggs in stool. Followed after TBZ, adults | TBZ 10 mg/kg x 1 (formulation unspecified)                                            |            | Egg neg gp were cured with one dose with decrease in eo's and nl lft's. The egg-pos group required a second dose 2 weeks after the first. All were cured. | Mild jaundice, fever, RUQ pain in one pt.                                 |
| Dauchy, 2006 [90] France                                            | 8     | Clinical cases of fascioliasis in adults                                   | TBZ 10mg/kg x 1. 6 pts failed and were retreated with 20 mg/kg TBZ with cure (Egaten) |            | 6/8 pts failed one dose of TBZ - all these 6 were cured with the second dose                                                                              | 2 pts with dyspepsia and epigastric pain - transient.                     |
| Lopez-Velez; 1999 Spain                                             | 6     | 3 adult subjects were initially treated with PRZ and failed.               | TBZ 10 mg/kg x 1, then repeated 2 days later                                          |            | 100% cure?                                                                                                                                                | Mild RUQ pain in one pt.                                                  |

## 9.8. Additional Safety Explorations

### Human Carcinogenicity or Tumor Development

Not applicable

### Pediatrics and Assessment of Effects on Growth

The Hien and Keiser studies included some children (see Demographics Table in Section 7), while the Maco study focused solely on children between the ages of 2 to 16 years. The CIBA-WHO studies included a significant number of children <18 years and the Bolivian pediatric study only enrolled children. Because treatment with TCBZ is short-term, no effects on growth related to TCBZ treatment are anticipated or were recorded in these studies. Indeed, growth stunting and anemia are known to be associated with fascioliasis itself [93].

### Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

## 9.9. Safety in the Postmarket Setting

Both Fasinex and Egaten have been used extensively in humans worldwide for treatment of fascioliasis starting in the late 1980's; since 2006, the Applicant has donated more than 2 million treatment courses of TCBZ worldwide through WHO. Egaten is registered in Egypt and France and was put on the WHO list of essential drugs in 1997. Over these decades of use, TCBZ appears to have been well-tolerated - commonly-reported AEs in the literature are similar to those described in Section 9.4.2. In this section, various sources of information regarding postmarket safety of TCBZ are reviewed.

### 9.9.1. Named Patient Use of Triclabendazole

Following initial reports of good tolerability of Fasinex in humans, it was made available for some patients worldwide on a named patient basis. Two study reports reporting this data were submitted to NDA 208711 and safety information from them is covered in this section.

- a) EGA230B2204 – Open-label study in European patients conducted between 1986 and 1994. Monitoring and documentation of patients and drug usage are inadequate in some cases and data are missing. The recommended doses of Fasinex or CGP23030 were 10 mg/kg q24h x 2 or 10 mg/kg x 1, though regimens could be modified by the investigator. The intended duration of follow-up was 60 days with patients hospitalized for 7 days and assessments on Days 0, 1, 2, 3, 4, 6, 30 and 60. A total of 33 patients with *Fasciola* eggs in their stool were included, of which 23 (69.7%) received 10 mg/kg q24h x 2, 5 (15.2%) received 2 doses separated by >24 hours or not recorded, 3 (9.1%) received 10 mg/kg x 1 and 4 (12.1%) patients received a different regimen modified by the investigator. "Data with respect to individual patient regimens is inadequate and

therefore all regimens are considered together in this report.” (EGA230B2204 Study Report, page 5). Of this population overall, 63.6% of patients were female and median age was 51 years (range 10-78). At study entry, 13 (39.4%) patients had right hypochondrial pain, 33.3% had abdominal pain, and 6 (18.1%) had anorexia, nausea or vomiting.

Serious adverse events were not defined in the study, but there were no hospitalizations due to adverse events or abnormal clinical findings, and no deaths. The following adverse events occurred: abdominal pain in 45.5% of patients, right hypochondrium pain in 39.4%, fever in 15.2%, pruritus in 12.1% and neck pain in 9.1%.

*Reviewer comment: From the report, it was not possible to delineate which patients had abdominal pain alone, right hypochondrium pain alone or the two combined.*

All AEs were reported within the first 30 days with the majority within the first 8 days after treatment. The majority of AEs lasted <120 minutes with 22 events lasting >120 minutes.

- b) EGA230B2301 – Open-label study of CGP 23030 conducted between 1994 and 1998 for treatment of human fascioliasis in patients in Europe, Australia, Canada and the U.S. Eight-two patients with chronic fascioliasis as evidenced by *Fasciola* eggs in the stool were enrolled and treated with 10 mg/kg x 1, or 10 mg/kg q12h x 2 for severe or persistent infections. Recording of study data and adverse events were often unclear or missing – for example, 9 (11%) patients appeared to receive a single dose of TCBZ, 17 (21%) received 2 doses between 10h and 24h apart, but for 56 (68%) patients, the treatment schedule was either ambiguous or not recorded at all.

There were no deaths attributed to TCBZ, although a French patient thought to have cholangitis related to fascioliasis died 11 days after receiving TCBZ. On autopsy, he was found to have cholangiocarcinoma, not fascioliasis. Two patients experienced SAEs defined as needing hospitalization. Basic details of these patients are provided in the following table:

**Table 9.22 Serious Adverse Events in EGA230B2301**

| Patient | Adverse event                     | Severity | Relationship to treatment | Action taken    | Outcome             |
|---------|-----------------------------------|----------|---------------------------|-----------------|---------------------|
| (b) (6) | Abdominal pain                    | Severe   | Highly probable           | Hospitalization | Complete recovery   |
|         | Jaundice (icterica)               | Moderate | Highly probable           | Hospitalization | Complete recovery   |
|         | Jaundice                          | Mild     | probable                  | Hospitalization | Complete recovery   |
|         | Serum Aminotransferases increased | Mild     | probable                  | Hospitalization | Condition improving |
|         | Serum bilirubin increased         | Mild     | probable                  | Hospitalization | Condition improving |
|         | Eosinophilia                      | Moderate | probable                  | Hospitalization | Condition improving |

Adverse events reported as serious or which led to death or hospitalization are listed

Source: Study Report of EGA230B2301, page 28

Both patients recovered completely; the German patient had persistently elevated transaminases, bilirubin and eosinophil counts at the end of the study (Day 60) however, although all parameters had improved.

*Reviewer comment: Scant details are provided about the 2 patients with SAEs and the patient who died. Demographic data is redacted on the CRF forms, and laboratory measurements are not available, so a full evaluation of the clinical scenarios and relatedness to TCBZ is not possible.*

The following adverse events were recorded in 15 (18.3%) patients in EGA230B2301– 9 (10.2%) had abdominal pain, while 3.6% had jaundice, and 2.4% each had nausea, fever and pruritus. All other AEs occurred with a frequency <2%.

*Reviewer comment: Although at least 40 patients (and probably more) between the 2 studies received 2 doses of TCBZ 12-24h or more apart, and several received a single 10 mg/kg dose, information on them is so limited that very little can be concluded aside from the fact that the AEs recorded seemed to be consistent with AEs recorded in other TCBZ-treated fascioliasis patients in the NDA studies with patient-level data or in the literature.*

### 9.9.2. Report of the WHO Informal Meeting on use of TCBZ in Fascioliasis Control (2007)

A meeting between WHO and selected member countries with a high fascioliasis burden, was held in 2006 to discuss large-scale provision of TCBZ to them by the Applicant through WHO, with the intent of scaling up treatment at the community level and instituting systematic monitoring and reporting. The document of the Meeting Proceedings noted that TCBZ was not used widely in large community-based control programmes at that time due to limited availability. During this meeting, a surveillance protocol for evaluation of TCBZ tolerability in a community setting was discussed and agreed upon.

A summary of adverse events following treatment in endemic countries was provided:

- a) Vietnam - A hospital-based survey in Vietnam found a low incidence of AEs in 51 individuals > 10 years (most 20-49 years) with acute fascioliasis treated with 10 mg/kg x 1 or 10 mg/kg q6-8h x 2. "Liver pain" was found in 17.6% of the patients, other abdominal pain in 15.7%, fatigue in 11.8%, skin rash in 5.9%, vomiting in 2%, and headache and dizziness in 2% each. TCBZ was not registered for human use at that time.
- b) Cuba – Eighty-two patients (mean age 42 years) with mixed acute and chronic fascioliasis were treated with a single dose of 20 mg/kg; biliary colic occurred post-treatment in 48.8% of patients, nausea, vomiting, anorexia in 8.5% each, pruritus in 6.1%, and jaundice in 3.6%. Most reactions were mild (71.6%) or moderate (27%). TCBZ was not registered for human use at that time.
- c) Egypt – "TCBZ has been widely used to treat fascioliasis since 1998 without any single report of adverse reactions."

*Reviewer comment: This latter statement raises questions about the mechanism of reporting – whether passive or active – and seems surprising given the thousands of doses of TCBZ administered in Egypt. Further, in 3 Egyptian government-sponsored studies between 1995 and 1996, AEs were certainly seen, as discussed in Section 9.4.*

Additional information regarding the safety of TCBZ administration in Egypt was culled from the WHO report: At the time of this report, Egypt was the only country that had actively implemented control activities against human fascioliasis. From 1998 to 2002, the National Control Program (NCP) of the Ministry of Health screened almost 36,000 children, and detected and treated 1280 cases of human fascioliasis. A decrease in prevalence of fascioliasis infection from 6% in 1996 to 1% in 2003 was documented. Decreases in intensity of infection were also found. No adverse reactions were observed in treated children.

*Reviewer comment: It is unclear whether or how completely safety information was collected on the Egyptian children. During the Mid-Cycle meeting, the Applicant was requested to obtain and provide information from WHO on the safety of TCBZ in mass screening and treatment programs, and on implementation of the surveillance protocol discussed during the 2006 WHO meeting.*

In response to an IR dated November 30<sup>th</sup>, 2018, the Applicant summarized written and verbal replies to FDA questions provided by the officer responsible for Preventive Chemotherapy and Transmission Control (PCT) within the Department of Control of Neglected Tropical Disease (NTD) at the WHO, and also by the relevant Neglected Infectious Diseases Specialist responsible for fascioliasis control within the Pan American Health Organization/WHO (PAHO/WHO). According to this information, the 2006 surveillance protocol was made available to any country's Ministry of Health requesting Egaten via the Novartis donation program administered by WHO and was implemented in 2 countries – Bolivia and Peru – carrying out mass treatment in targeted areas with high-burden populations. No significant adverse events were reported to

WHO. After an initial successful pilot study [1] the Bolivian government apparently intended to “implement distribution on a large scale”, potentially without individual diagnosis.

*Reviewer comment: Further in their response, the Applicant noted that no formal reports have been shared by the Bolivian or Peruvian Ministries of Health after implementation of mass treatment programs, even after they were contacted by an officer from PAHO. They were able to ascertain however, that no serious AEs from these programs have been reported.*

### Expectations on Safety in the Postmarket Setting

Between 2006 (when the TCBZ donation program started) and 2018, an estimated 2.6 million treatment courses of TCBZ have been dispensed across 34 countries. Since 2015, approximately 300,000 treatment courses have been distributed annually. No major safety concerns have emerged. Both WHO and CDC continue to recommend TCBZ as the drug of choice for treatment of fascioliasis.

*Reviewer comment: In their response to the IR dated November 30<sup>th</sup>, 2018 the Applicant reported that, per information from WHO, no cases of hemolysis or fatal arrhythmias related to TCBZ administration have been reported to WHO. The Applicant also checked the WHO safety database (Vigibase) in Uppsala Sweden and found a total of 9 cases for TCBZ reported through the 3<sup>rd</sup> quarter of 2018. Details of these patients are outlined in the table below:*

| Report ID/<br>Report type        | Age group<br>(in years)/<br>Gender | Preferred term<br>(PT)                                                                        | Case seriousness/<br>Other concomitant<br>medications and<br>co-suspects (as<br>reported) | Triclabendazole<br>Suspect/<br>concomitant |
|----------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------|
| (b) (6)<br>Spontaneous<br>report | 65- 74/<br>Female                  | Wrong patient<br>received<br>medication, Drug<br>ineffective, Blood<br>pressure<br>increased, | Non serious/<br>Biotin, Glucosamine,<br>Ciclosporin,<br>Minoxidil, Calcium,<br>Fish oil,  | Concomitant                                |
| (b) (6)<br>Spontaneous<br>report | Unknown/<br>Unknown                | Drug resistance,<br>Fascioliasis                                                              | Serious/<br>Not applicable                                                                | Suspect                                    |
| (b) (6)                          | 2-11/<br>Female                    | Dyspepsia,<br>Abdominal pain                                                                  | Non serious/<br>Metronidazole                                                             | Suspect                                    |

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|                               |                         |                                    |                                                                                                                               |             |
|-------------------------------|-------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------|
| (b) (6)<br>Spontaneous report | 2-11/<br>Male           | Abdominal pain                     | Non serious/<br>Not applicable                                                                                                | Suspect     |
| (b) (6)<br>Spontaneous report | 12-17/<br>Female        | Abdominal pain                     | Non serious/<br>Not applicable                                                                                                | Suspect     |
| (b) (6)<br>Spontaneous report | 18-44/<br>Male          | Gynaecomastia                      | Unknown/<br>Not applicable                                                                                                    | Suspect     |
| (b) (6)<br>Spontaneous report | 45-64/<br>Female        | Jaundice, Hepatic enzyme increased | Unknown/<br>Not applicable                                                                                                    | Suspect     |
| (b) (6)<br>Spontaneous report | 75 and above/<br>Female | Psoriasis, Eczema                  | Non serious/<br>Adalimumab,<br>Calcium Gluconate,<br>Hydrochlorothiazide,<br>Leflunomide,<br>Hydroxychloroquine,<br>Verapamil | Concomitant |
| (b) (6)<br>Spontaneous report | Unknown/<br>Female      | Psychotic disorder, Vomiting       | Unknown/<br>Not applicable                                                                                                    | Suspect     |

Source: Information contained in the Applicant's response to an IR, dated November 30, 2018

*Reviewer comment: Most of these reports note AEs such as abdominal pain which are commonly associated with TCBZ for fascioliasis treatment. From the information provided, it was not possible for this reviewer to adjudicate these cases further.*

### 9.9.3. Periodic Safety Update Report (2012-2017)

The Applicant submitted a PSUR for the period indicated. Egaten is registered in Egypt (1997) and France (2002). It was registered in both Ecuador and Venezuela in 2001 but has been de-registered in both countries for unknown reasons. No safety-related changes to the Core Data Sheet (CDS) were made in the PSUR over the 5-year interval. A signal of drug resistance was identified based on post-marketing case reports in the Novartis Global Safety Database as reported by health care professionals and culled from the literature, and the CDS was updated to incorporate this as follows:

Section 7: Adverse Drug Reactions (ADR): One new ADR was added in Table 7-2

a. "Drug Resistance (frequency unknown)" under general disorders and administration site conditions.

## Resistance to TCBZ

TCBZ-resistant fascioliasis appears to be of increasing concern worldwide. The drug has been used extensively in the livestock industry to prevent losses in production, which has led to widespread resistance in cattle and sheep in Ireland, Spain, Australia, Peru, and Argentina. Because fascioliasis is a zoonosis, there is concern for transmission of resistant infection to humans [91]. Cases of resistant fascioliasis have been reported from Netherlands [69] Turkey, Chile [92] and Peru [25] where a case series of 7 patients non-responsive to TCBZ was reported. Notably, all 7 patients received at least 3, and some received 4 courses of Egaten (each consisting of 10 mg/kg q12h x 2, though one patient received 10 mg/kg q12h x 3); 5 of these patients continued to excrete *Fasciola* eggs in their stool. There was no mention in the publication [24] of adverse events following administration of multiple courses of TCBZ.

### 9.9.4. Clinical Safety Experience with 20 mg/kg TCBZ

Evidence for safety of 20 mg/kg TCBZ is specifically addressed in this section, with reference to relevant discussion in Section 9.4 (i.e. the Keiser study and discussion around Tables 9.11, 9.12, and 9.13 which explores the comparative safety of various dosing regimens of TCBZ in the CIBA/WHO studies). Forty-four patients in the Maco trial received a total of 15 mg/kg in 1 day (7.5 mg/kg q12h x 2), but none received 20 mg/kg; these patients are therefore not considered further here.

In addition to the studies with patient-level data submitted to this NDA, important safety data for a TCBZ dose of 20 mg/kg was culled from the CIBA/WHO paragonimiasis studies (as discussed in Section 9.7) as well as selected supportive literature studies; the combined safety database of 356 patients is tabulated in Table 9.23.

**Table 9.23 Patients Treated with 20 mg/kg (10 mg q6-8h, q12h or q24h x 2) TCBZ from the NDA Studies with Patient-Level Data, Paragonimiasis Studies and Selected Literature Studies**

| Study                                  | Number of exposed patients | Dose regimen             |
|----------------------------------------|----------------------------|--------------------------|
| <b>Primary Safety Population</b>       |                            |                          |
| Keiser                                 | 4                          | 10 mg/kg q24h x 2        |
| CIBA/WHO trials                        | 6                          | 10 mg/kg q12h x 2        |
| CIBA/WHO trials                        | 22                         | 10 mg/kg on Days 1 and 3 |
| <b>CIBA/WHO Paragonimiasis Studies</b> |                            |                          |
| Cameroon EGA230B2213                   | 12                         | 10 mg/kg q6-8h x 2       |
| Ecuador EGA230B2205                    | 77                         | 10 mg/kg q6-8h x 2       |
| Ecuador EGA230B2206                    | 15                         | 10 mg/kg q6-8h x 2       |
| <b>Selected Literature Studies</b>     |                            |                          |
| Talaie                                 | 52                         | 10 mg/kg q24h x 2        |
| Millan                                 | 82                         | 10 mg/kg q12h x 2        |
| El-Morshedy                            | 66                         | 10 mg/kg q12h x 2        |

| Study        | Number of exposed patients | Dose regimen                   |
|--------------|----------------------------|--------------------------------|
| Saba         | 13                         | 10 mg/kg q24h x 2              |
| Cabada       | 7                          | 10 mg/kg q12h x 2 <sup>1</sup> |
| <b>Total</b> | <b>356</b>                 |                                |

<sup>1</sup>All 7 patients received at least 3 courses of 10 mg/kg q12h x 2, one patient received 3 courses. The time between courses is not specified

*Reviewer comment: Although drawn from disparate studies with differing study designs, this group of 356 individuals provides important safety information to support the 20 mg/kg TCBZ q12h x 2 dose.*

All of these studies are listed and/or discussed in the relevant sections above. In the Keiser trial, 16 patients received the single dose of 10 mg/kg, and 4/16 were retreated with 20 mg/kg (10 mg/kg q24h x 2) after failing treatment with 10 mg/kg; adverse events were documented over 72 hours. Mild abdominal pain occurred in 4/4 (100%) of the patients who received the 20 mg/kg dose vs. 50% (8/16) of the 10 mg/kg dose, but 0% in the former group and 6.3% of patients in the 10 mg/kg dose had moderate pain. Nausea occurred in 3/4 (75%) patients and 1 person each (25%) had diarrhea, vomiting and fever at 48 hours in the higher-dose group; by contrast, these AEs occurred in 0%, 0%, 12.5% and 12.5%, respectively, in the 10 mg/kg group. Dizziness was more prominent in the 10 mg/kg group (62.5%) vs. the higher-dose group (50%) at 48 hours. No differences between the dose groups were seen with regard to biochemical and hematological parameters.

*Reviewer comment: The very small numbers makes it difficult to do more than comment on trends.*

The 6 patients from the CIBA/WHO trials who received 10 mg/kg q6-8h x 2 were all pediatric patients who failed the single dose of CGP23030; they were retreated with Egaten, and 100% of them had moderate abdominal pain and hyperhidrosis on Days 3, 4, and 6. All recovered with no intervention other than anti-spasmodic medication and all were cured of *Fasciola* infection. The 22 patients who received 10 mg/kg TCBZ on Days 1 and 3 experienced a somewhat higher incidence of AEs compared to those who received 10 mg/kg either as a single dose or divided doses of 5 mg/kg. As discussed in Section 9.4, AEs occurring in the 28 patients who received a total TCBZ dose of 20 mg/kg were compared with those occurring in the 186 patients who received 10 mg/kg TCBZ (regardless of exact dosing regimen or whether received in the fed or fasted state) and listed in Table 9.24.

**Table 9.24 Adverse Events Occurring in ≥2% of Patients Who Received a Total of 10 mg/kg or 20 mg/kg TCBZ in the CIBA/WHO Studies**

| Adverse Events              | 10 mg/kg<br>N=186, n (%) | 20 mg/kg in two divided doses <sup>1</sup><br>N=28, n (%) |
|-----------------------------|--------------------------|-----------------------------------------------------------|
| Abdominal pain <sup>2</sup> | 111 (60)                 | 24 (86)                                                   |
| Hyperhidrosis               | 42 (23)                  | 7 (25)                                                    |
| Vertigo                     | 16 (9)                   | 0                                                         |
| Nausea                      | 15 (8)                   | 5 (18)                                                    |
| Urticaria                   | 12 (7)                   | 3 (11)                                                    |
| Vomiting                    | 11 (6)                   | 2 (7)                                                     |
| Headache                    | 11 (6)                   | 4 (14)                                                    |
| Dyspnea                     | 9 (5)                    | 0                                                         |
| Pruritus                    | 8 (4)                    | 1 (4)                                                     |
| Asthenia                    | 7 (4)                    | 0                                                         |
| Musculoskeletal chest pain  | 7 (4)                    | 1 (4)                                                     |
| Cough                       | 7 (4)                    | 0                                                         |
| Decreased appetite          | 6 (3)                    | 5 (18)                                                    |
| Chest pain                  | 6 (3)                    | 0                                                         |
| Pyrexia                     | 4 (2)                    | 0                                                         |
| Jaundice <sup>3</sup>       | 4 (2)                    | 0                                                         |
| Chest discomfort            | 4 (2)                    | 0                                                         |
| Palpitations                | 2 (1)                    | 0                                                         |
| Diarrhea                    | 0                        | 2 (7)                                                     |

<sup>1</sup> Divided doses were given 6-48 hours apart

<sup>2</sup> Includes PTs of abdominal pain upper and abdominal pain

<sup>3</sup> Includes PTs of jaundice and ocular icterus

*Reviewer comment: In the CIBA/WHO studies, the most common AEs of abdominal pain, hyperhidrosis, nausea, urticaria, headache and decreased appetite all occurred more frequently in the 20 mg/kg group compared with the 10 mg/kg group. Vertigo was the exception, occurring more frequently in the 10 mg/kg group. These observations do not account for the intensity of infection, or the age group, weight or height of the individuals in each group which may relate to possible disproportion between the size of the adult fluke and the size of the biliary tract. Given the mechanism of action of TCBZ, and the dose-response for efficacy seen in the CIBA/WHO fascioliasis studies, it is biologically plausible that the 20 mg/kg dosing regimen was associated with increased or more efficient killing of the adult fluke(s) when compared with the 10 mg/kg dose, resulting in increased release of antigens and consequently greater incidence of urticaria and headache. Similarly, because the post-treatment abdominal pain is generally thought to be related to expulsion of the dying/dead fluke via the common bile duct, enhanced killing, especially with a larger fluke burden, may account for a higher incidence of abdominal pain. However, the disparate numbers of patients in each dose arm and the identified issues with adverse event recording in the CIBA/WHO studies, preclude firm conclusions.*

In the 3 paragonimiasis studies, a total of 105 subjects were given a single dose of 10 mg/kg TCBZ, while 104 received 20 mg/kg (10 mg/kg q6-8h x 2) and 27 received 5 mg/kg q24h x 3;

abdominal pain occurred in 5 (4.8%), 4 (3.8%) and 3 (11.1%) of those subjects respectively. Thus, there did not appear to be a dose-response for this AE, and the frequencies seen were much lower than the 56.5% and 92.9% occurrence in the 10 mg/kg and 20 mg/kg TCBZ groups in the CIBA/WHO fascioliasis studies.

Study EGA230B2205 of TCBZ for paragonimiasis in Ecuador made a head-to-head comparison of 10 mg/kg x 1 vs. 10 mg/kg q6-8h x 2 TCBZ. Adverse events in the 2 arms are tabulated below:

**Table 9.25 Adverse Events Occurring in the Treatment Arms of EGA230B2205**

| Adverse Effect     | Regimen       |               |
|--------------------|---------------|---------------|
|                    | B<br>(N = 77) | C<br>(N = 77) |
|                    | N             | %             |
| DIZZINESS          | 4             | ( 5.2)        |
| FEVER              | 1             | ( 1.3)        |
| ABDOMINAL PAIN     | 2             | ( 2.6)        |
| DIARRHOEA          | 2             | ( 2.6)        |
| CHILLS             | 1             | ( 1.3)        |
| DIARROHEA          | 1             | ( 1.3)        |
| FEVER AND CEPHALEA | 0             | 1 ( 1.3)      |
| JOINTS PAIN        | 1             | ( 1.3)        |
| PAIN IN JOINTS     | 1             | ( 1.3)        |

B: Triclabendazole 10 mg/kg twice daily for one day, postprandially.

C: Triclabendazole 10 mg/kg single dose, postprandially.

Source: Applicant's CSR EGA230B2205, p.49

*Reviewer comment: Although there is a slight numerical difference in occurrence of abdominal pain and diarrhea, the incidence of dizziness and fever was actually less in the double-dose arm (B) than in the single-dose arm (C). It is unclear why diarrhea is represented twice in the table above, but when counted together, occurred in 3.9% of patients in the higher dose group compared to 0% in the 10 mg/kg group. Based on this direct comparison, the type and frequency of AEs with 20 mg/kg does not seem significantly different than their occurrence in the 10 mg/kg dose group. This again is in contrast to the dose comparison in the CIBA/WHO studies (Table 9.23) and suggests that some of the imbalance in AEs noted there was due more to enhanced killing of both mature and immature flukes.*

Recording of AEs in the selected publications listed in Table 9.22 lacked detail and varied widely – however, the available information is summarized below:

- **Talaie [27]** – Abdominal pain occurred in 15% of patients in the 10 mg/kg q24h x 2 group, compared with 10% each in the 10 mg/kg x 1 and 10 mg/kg q24h x 3 groups; thus, no dose-response for this AE was noted.
- **Millan [23]**– AEs are summarized in the table below:

**Table 9.26 Adverse Events Recorded in the Millan Study in Patients Treated with TCBZ 10 mg/kg q12h x 2**

| Event                      | No. | Day of onset post-therapy median (range)* |
|----------------------------|-----|-------------------------------------------|
| Biliary colic              | 40  | 5 (2–30)                                  |
| Associated with jaundice*  | 3   | 5, 9                                      |
| Epigastric pain            | 35  | 4 (1–60)                                  |
| Nausea, anorexia, vomiting | 7   | 4 (2–30)                                  |
| Fever                      | 7   | 3 (2–60)                                  |
| Pruritus                   | 5   | 5 (1–60)                                  |
| Associated with urticaria* | 2   | 1, 60                                     |
| Associated with jaundice*  | 3   | 5, 9                                      |
| Intensity of events        |     |                                           |
| Mild                       | 53  |                                           |
| Moderate                   | 20  |                                           |
| Severe†                    | 1   |                                           |
| Total events‡              | 74  |                                           |
| Total patients‡            | 54  |                                           |

\* When events occurred sporadically, the single days of onset in each patient are given.

† Biliary colic responding to spasmolytics within two hours.

‡ More than one event may have occurred in a single patient.

Source: Millan et al, 2000.

In addition, 50% of patients had alkaline phosphatase (ALP) > ULN, while 2/3rds had ALT and AST above ULN at Day 7 post-treatment; of significance, 17.7%, 40.2% and 50% of patients had ALP, ALT and AST > ULN at baseline.

- **El-Morshedy** [2] – 66 individuals (mean age 14.2 years) received TCBZ 10 mg/kg q24h x 2, while 68 patients (mean age 16.1 years) received 10 mg/kg x 1. The drug was very well-tolerated with mild colicky abdominal pain being the only reported complaint; jaundice with a distended inflamed gall bladder occurred in 1 patient 3 days post-treatment, but the patient recovered without medical intervention – this AE was thought to be related to TCBZ. There were no post-treatment changes in LFTs and no mention of a possible dose-response for abdominal pain.
- **Saba** [92] – Thirteen patients received TCBZ 20 mg/kg in “divided doses” (interval was not specified) with “only moderate side effects” (no other details were provided). Two non-responders were treated with 3 additional courses of TCBZ, with no mention of additional AEs.
- **Cabada** [24]– Seven patients with TCBZ-resistant fascioliasis received at least 3 and some 4 courses of Egaten (each consisting of 10 mg/kg q12h x 2, though one patient received 10 mg/kg q12h x 3); adverse events were not mentioned in the publication.

The evidence from the NDA studies with patient-level data, the paragonimiasis studies and the literature support the safety of TCBZ in 356 patients who received 20 mg/kg TCBZ (or more) for the treatment of human fascioliasis. No deaths or unexpected adverse events were reported. However, evaluation of TCBZ safety at this dose from these studies suffers from the heterogeneity of disease characteristics and stage, study design and AE collection as well as the incompleteness of AE recording. Thus, the Applicant will conduct a (b) (4)

enrolling at least (b) (4) treated with the currently recommended dose of 10 mg/kg q12h x 2 as a PMC.

### 9.10. Integrated Assessment of Safety

Evidence of safety of TCBZ for fascioliasis treatment was obtained from several sources; although data from all studies had shortcomings, the combined weight of evidence supports TCBZ's safety at both the 10 mg/kg x 1 and 10 mg/kg x 2 dosing regimens. Summary safety assessments from the disparate studies in the safety database for NDA 208711 are provided below:

- a) **CIBA/WHO studies:** Cure rates were high (70-100%) across all 6 studies. Abdominal pain was the most common adverse event seen, occurring in 56.5% of 186 patients treated with 10 mg/kg x 1 TCBZ and 92.9% of 28 patients treated with 20 mg/kg in divided doses. This AE seems more related to the pathobiology of the disease, i.e., related to expulsion of the dead/dying fluke through the common bile duct rather than to the drug per se, as evidenced by the much lower frequency of abdominal pain in the CIBA/WHO studies of TCBZ for paragonimiasis discussed below. There appeared to be a consistent dose-response for other adverse events as well, with a higher incidence of hyperhidrosis (25%), nausea (17.9%), decreased appetite (17.9%), headache (14.3%) and urticaria (10.7%) with the 20 mg/kg dose compared with the 10 mg/kg dose (22.6%, 8.1%, 3.2%, 5.9% and 6.5% respectively). Other AEs that occurred in ≤5% of patients in either dose group included dyspnea, asthenia, pruritus, musculoskeletal pain, cough, pyrexia, diarrhea and chest pain. However, no correlation was provided between treatment dose and infection burden or pre-treatment symptoms, these studies were not designed specifically to assess dose-response, the numbers of patients in each dosage arm were disparate and the conduct of these studies and adverse event collection suffered from the limitations discussed in previous sections.
- b) **IITs:**
- **Maco [5]** – This open-label, Phase 2 study in 5 rural areas of Peru was conducted with 2 different doses of TCBZ - 7.5 mg/kg q12h x 2 (Group 1) vs. 10 mg/kg x 1 (Group 2) - for treatment of chronic fascioliasis in children age 2-16 years. The most common adverse event was biliary colic which occurred in 11.4% of Group 1 and 25% of Group 2 subjects on Day 2 post-treatment, and in 20.5% and 15% respectively, on Day 4, but complete AE collection could not be verified.
  - **Keiser [4]** – In this open-label, non-randomized trial designed to study artemether treatment for chronic fascioliasis, 16 patients received 10 mg/kg TCBZ as rescue treatment after failing artemether; 4 of them were subsequently retreated with 20 mg/kg in divided doses. Abdominal pain occurred in 56.3% and 68.8% of patients at 48h and 72h respectively in the 10 mg/kg group, and in 100% and 50% of the 4 patients who received 20 mg/kg at the same time points respectively. At 48h post-treatment, other adverse events commonly reported in the 10 mg/kg and 20 mg/kg groups respectively were headache (31.3% and 50%), dizziness (62.5% and 50%), diarrhea (0 and 25%), vomiting (12.5% and

25%) and fever (12.5% and 25%). AEs were only monitored for 72 hours although all patients recovered and none had SAEs; in addition, the very small numbers preclude firm conclusions.

c) **Selected Literature Studies**

In general, AE information in these studies lacked detail but provide supportive safety information.

- **Millan [24]** – Eighty-two patients with chronic fascioliasis who failed previous therapy with praziquantel, metronidazole, thiabendazole, mebendazole, emetine and bithionol were treated with 20 mg/kg TCBZ q12h x 2 and monitored in hospital for 7 days. AEs included biliary colic in 49% of patients, increased alkaline phosphatase in 40%, and obstructive jaundice in 3.7%. Most AEs were mild, 20 were classified as moderate, and 1 severe (abdominal pain on Day 6 which resolved in 2 hours after administration of an anti-spasmodic medication).
  - **El-Morshedy [23]** – This randomized study of 2 different dosing regimens of TCBZ – 10 mg/kg x 1 vs. 10 mg/kg q24h x 2 - in 134 Egyptian adult and pediatric patients with chronic fascioliasis included very little safety information other than that mild colicky abdominal pain was the only complaint recorded, and that one patient developed jaundice 3 days post-treatment with elevated AST, ALT, and bilirubin. This patient’s gall bladder was inflamed and distended on ultrasound; the work-up was not specified. All markers returned to normal within 2 months.
  - **Talaie [28]** – In this randomized study of 3 dosing regimens of TCBZ (10 mg/kg q24h x 1, 2, or 3) in 165 adult and pediatric patients with “suggestive” (presumably acute) or confirmed (chronic) fascioliasis, AEs were generally mild. Occurrence of any AE, including nausea, vomiting, weakness, pruritus, epigastric pain, and hepatomegaly (without change in liver enzymes) was reported in 10%, 15% and 10% of patients in the 3 treatment groups respectively.
  - **Villegas [1]** – Ninety Bolivian children, ages 5-14 yrs with chronic fascioliasis, were given a single dose of 10 mg/kg TCBZ. AEs were mild and consisted of headache in 5 (5.6%) patients, nausea in 2 (2.2%), and abdominal pain in 2 (2.2%) patients on the day of treatment. Three patients (3.3%) had abdominal pain 1 week later which resolved quickly, no medications other than antipyretics were required.
- d) **Egyptian government-sponsored studies**- Studies B2209 (Hassan), B2210 (El-Sahly) and B2211 (Frag) enrolled a total of 135 adults and pediatric patients with chronic fascioliasis and treated them with CGP 23030 at a dose of 10 mg/kg as a single dose, or two 5 mg/kg doses 6 hours apart. Abdominal pain occurred frequently – in 58.3% of patients in the Hassan study, and 52% of patients in the Farag study - but was transient. About 1/3<sup>rd</sup> of patients had nausea and vomiting on Days 1 and 2 after treatment.
- e) **Named Patient Program conducted by CIBA/Novartis**– a total of 115 patients were administered CGP 23030 worldwide through the compassionate use program between 1986 and 1998. Adverse events consisted mostly of abdominal pain and biliary colic, but these all occurred within the first few days after treatment and were transient, but details were scant.

- f) **Paragonimiasis Studies** – In 3 CIBA/WHO-sponsored studies conducted in Cameroon and Ecuador between 1991 and 1993, 3 doses of TCBZ for paragonimiasis were studied - 5 mg/kg x 3 q24h x 3, 10 mg/kg q6-8h x 2, and 10 mg/kg x 1). In these studies, 105 subjects were treated with a single dose of 10 mg/kg, and 104 subjects received 10 mg/kg q6-8h x 2. Abdominal pain occurred in 5 (4.8%) and 4 (3.8%) subjects in the 10 and 20 mg/kg cohorts respectively - a much lower frequency than in subjects who received a single dose (56.5%) or two doses (92.9%) of TCBZ for fascioliasis in the CIBA/WHO studies. In contrast to the CIBA/WHO studies of fascioliasis, no dose-response for this or any other AE were noted. This supports the idea that abdominal pain occurring post-treatment of fascioliasis is more likely related to the expulsion of the dead/dying fluke, rather than an adverse event related to the drug itself.
- g) **Post-market Data** - Egaten was first registered in Egypt in 1997, and then in France in 2002. It was also registered in 2001 in both Ecuador and Venezuela but has subsequently been de-registered in both countries, although the reason for this was not explained in the NDA documentation. Between 2006 and 2018, an estimated 2.6 million treatment courses (single dose of 10 mg/kg) had been distributed worldwide. The Periodic Safety Update Report (PSUR) submitted by the Applicant for the most recent review period of November 1, 2012 to March 31, 2017, did not demonstrate new or significant safety signals, but did note a new signal for drug resistance, which has been added to the Core Data Sheet (CDS). This signal was based on 18 cases in the Novartis Global Safety Database and literature reports, in which patients failed to respond to multiple treatment courses with recommended doses of Egaten. No new adverse reports or concerns regarding QT prolongation or were found.

Because none of these data were collected as part of registrational trials, they do not fit the standards of adequate and well-controlled trials that FDA normally requires in an NDA. In addition, because many of the common post-treatment adverse events such as abdominal pain, nausea, fever, anorexia, and elevations in liver enzymes are also part of the symptom complex of fascioliasis and are present at baseline in a significant proportion of patients, it was not always possible to separate pre- and post-treatment symptoms and signs in these studies. Because TCBZ has been used widely for decades, a robust literature exists— of which some of the main studies were reviewed previously. These disparate studies with patient-level data, post-market data, and literature reports together consistently support the safety of TCBZ for treatment of fascioliasis. In addition, TCBZ has the advantage of very high efficacy with 1-2 doses, which lessens concern regarding drug-drug interactions and patient non-compliance, further adding to its favorable safety profile. As anecdotal reports and small case series of resistance to TCBZ in human fascioliasis infections have emerged, it has been shown to be well-tolerated even in patients who have received repeated courses [64].

(b) (4) in the proposed label were not found to be substantiated by clinical evidence; the review team thus recommended removal of the (b) (4) (b) (4) for reasons discussed in the review. The Warning regarding (b) (4) was removed after analysis by the Clinical Pharmacology reviewer, Dr. Jason

Moore. The Applicant is required to conduct a TQT study as a PMR to resolve the remaining Warning of risk of QT prolongation.

Finally, though the majority of efficacy data for treatment of fascioliasis is for a single 10 mg/kg dose [REDACTED] (b) (4) the team concluded over the course of the review, that the most appropriate recommended dose should be 10 mg/kg q12h x 2. The Applicant agreed to this recommendation. After a detailed review of safety in patients exposed to the higher dose, a possible dose-response for safety was seen in the CIBA/WHO studies of fascioliasis but was not borne out in the CIBA/WHO studies of paragonimiasis, suggesting that the imbalance in the former may be more related to the pathobiology of the disease itself, rather than to TCBZ. The safety database is considered sufficient to support approval; however, as discussed through this review, the problems inherent in comparing outcomes in dosing arms with disparate numbers, combining patients from studies with different study designs, different thresholds, different schedule of assessments, and incomplete characterization of adverse events impede our ability to be fully confident of TCBZ's safety profile at the higher dose. Thus, a PMC for a [REDACTED] (b) (4) study enrolling [REDACTED] (b) (4) patients treated with 10 mg/kg q12h x 2 has been requested from the Applicant.

Summary: The overall evidence provided in the application supports the safety of TCBZ (Egaten) for the treatment of fascioliasis at 20 mg/kg PO in two divided doses given 12 hours apart.

## **10 Advisory Committee Meeting and Other External Consultations**

There was no Advisory Committee meeting was held as there were no issues that needed input from the committee.

## 11 Pediatrics

TCBZ has Orphan Drug Designation and is therefore exempt from PREA requirements. In the proposed labeling, TCBZ is recommended for adults and children (b) (4).

Fascioliasis is a disease that affects children disproportionately in some endemic countries such as Peru, and TCBZ has been used in children as young as 2 years, including in the Maco study.

The following table summarizes the age ranges included in the studies submitted to this NDA; highlighted in red are details of patients who received the suggested dose of 20 mg/kg in divided doses.

**Table 11.1 Age Ranges Represented in the Studies Submitted to NDA 208711**

| Study, N                               | Dosing Regimen                                | Male | Female | Age Range (y)<br>(mean) | Subjects <<br>18y (N) | Weight range<br>(kg)<br>(mean) |
|----------------------------------------|-----------------------------------------------|------|--------|-------------------------|-----------------------|--------------------------------|
| <b>CIBA/WHO Fascioliasis Studies</b>   |                                               |      |        |                         |                       |                                |
| <b>Peru, 22</b>                        | 10 mg/kg x 2 D1 fasting, D3 fed               | 5    | 5      | 13-62 (39.1)            | 2                     | 27-60 (48.1)                   |
|                                        | 10 mg/kg x 2 D1 fed, D3 fasting               | 6    | 6      | 6-50 (18)               | 7                     | 17-51 (33.3)                   |
| <b>Bolivia, 22 (adult)</b>             | 10 mg/kg fed                                  | 12   | 10     | 13-63 (35.3)            | 5                     | 35-79 (51.8)                   |
| <b>Bolivia, 60 (Pediatric)</b>         | 5 mg/kg D1 fed (n=20)                         | 13   | 7      | 8-12 (9.7)              | 20                    | 20-35 (26.4)                   |
|                                        | 10 mg/kg D1 fed (n=20)                        | 15   | 5      | 8-12 (10.5)             | 20                    | 19-36 (27.4)                   |
|                                        | 2 x 5 mg/kg D1 fed (n=20)                     | 14   | 6      | 7-12 (9.7)              | 20                    | 17-33 (23.8)                   |
|                                        | 10 mg/kg x 2, D1 and 2 fed (retreatment, n=6) | 2    | 4      | 8-13 (10.7)             | 6 <sup>1</sup>        | 20-37 (26.7)                   |
| <b>Chile, 24</b>                       | 10 mg/kg fasting                              | 12   | 12     | 11-70 (26.8)            | 15                    | 42-82 (59.2)                   |
| <b>Cuba, 15</b>                        | 10 mg/kg fasting                              | 7    | 8      | 15-58 (36.8)            | 1                     | 51-91.4 (71.5)                 |
| <b>Iran, 102</b>                       | 5 mg/kg D 1,2,3 fasting (n=17)                | 1    | 16     | 10-60 (34)              | 1                     | 35-85 (62.1)                   |
|                                        | 5 mg/kg x 2 D1 fasting (n=14)                 | 0    | 14     | 12-63 (37.2)            | 2                     | 30-83 (58.7)                   |
|                                        | 10 mg/kg fasting (n=17)                       | 6    | 11     | 14-60 (36.2)            | 1                     | 45-73 (58.7)                   |
|                                        | 10 mg/kg fed (n=54)                           | 11   | 43     | 5-75 (40.8)             | 4                     | 18-91 (57)                     |
| <b>Maco Study<sup>2</sup></b>          |                                               |      |        |                         |                       |                                |
|                                        | 7.5 mg/kg q12h x 2                            | 15   | 16     | 6-15 (9.7)              | 31                    |                                |
|                                        | 10 mg/kg x 1                                  | 14   | 14     | 2-13 (9.2)              | 28                    |                                |
| <b>Keiser Study</b>                    |                                               |      |        |                         |                       |                                |
|                                        | 10 mg/kg x 1                                  | 6    | 10     | Mean 14.4 (SD 5.8)      |                       | Mean 55.4 (SD 26.2)            |
|                                        | 10 mg/kg q24h x 2                             | 2    | 2      | Mean 16.3 (SD 2.5)      | unknown               | Mean 66.3 (SD 19.8)            |
| <b>CIBA/WHO Paragonimiasis Studies</b> |                                               |      |        |                         |                       |                                |
| <b>EGA230B2213</b>                     | 5 mg/kg q24h x 3 (fed)                        | 7    | 4      | 9-20 (11.9)             | 10                    | 20-60 (34.9)                   |
|                                        | 10 mg/kg q12h x 2 (fed)                       | 5    | 7      | 6-26 (12.7)             | 9                     | 20-66 (37.5)                   |

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| Study, N                             | Dosing Regimen          | Male | Female | Age Range (y)<br>(mean)            | Subjects <<br>18y (N) | Weight range<br>(kg)<br>(mean) |
|--------------------------------------|-------------------------|------|--------|------------------------------------|-----------------------|--------------------------------|
|                                      | 10 mg/kg x 1 (fed)      | 9    | 3      | 5-54 (14.1)                        | 11                    | 13-52 (33.4)                   |
| <b>EGA230B2205</b>                   | 10 mg/kg x 2 (fed)      | 34   | 43     | 6-58 (17.3)                        | 52                    | 14-70 (41)                     |
|                                      | 10 mg/kg x 1 (fed)      | 30   | 47     | 4-52 (16.3)                        | 53                    | 18-67 (39.4)                   |
| <b>EGA230B2206</b>                   | 5 mg/kg q24h x 3 (fed)  | 9    | 7      | 12-52 (24.1)                       | 8                     | 23-67 (49.1)                   |
|                                      | 10 mg/kg q12h x 2 (fed) | 4    | 11     | 12-54 (22.4)                       | 8                     | 21-72 (45.9)                   |
|                                      | 10 mg/kg x 1 (fed)      | 6    | 10     | 12-57 (19.4)                       | 10                    | 27-60 (41.1)                   |
| <b>Egyptian Fascioliasis Studies</b> |                         |      |        |                                    |                       |                                |
| <b>EGA230B2209<sup>3</sup></b>       | 10 mg/kg x 1 (N=30)     | 16   | 44     | 14 Males <15 y; 24<br>Females <15y | <15y: 38              | unknown                        |
|                                      | 5 mg/kg q6h x 2 (N=30)  |      |        |                                    |                       |                                |
| <b>EGA230B2210</b>                   | 10 mg/kg x 1 (fed)      | 12   | 13     | 10-55 (26)                         | unknown               | unknown                        |
| <b>EGA230B2211</b>                   | 10 mg/kg x 1 (fed)      | 15   | 10     | 10-49 (22.8)                       | unknown               | unknown                        |
|                                      | 5 mg/kg q6h x 2 (fed)   | 9    | 16     | 10-55 (19.9)                       | unknown               | unknown                        |

<sup>1</sup>These 6 patients were retreated with Egaten 20 mg/kg total dose

<sup>2</sup>These demographics represent the 59 subjects seen at the Asillo site who received Fasinex®. Age and gender breakdown was not provided for the remaining 25 subjects, although the mean age of all 84 subjects was 9.3 years.

<sup>3</sup>At baseline, abdominal pain was found in 50/60 (83.3%) of patients, hepatomegaly in 42 (70%) patients, splenomegaly in 25% of patients. Abdominal was also seen as an adverse event, occurring in 35 (58.3%) patients on the 4<sup>th</sup> day, mainly among children.

Specifically, as seen in Table 11.1, a total of 136 patients among these studies (highlighted in red) received 20 mg/kg of TCBZ in divided doses, although the dosing intervals differed among studies; 84 (61.8%) of those patients were under 18 years, with the youngest being 6 years of age.

Although the CIBA/WHO studies in both fascioliasis and paragonimiasis were not conducted under GCP, the bulk of data in children comes from these studies. The adverse event profile has been discussed previously. Thus, the indication in the Applicant's proposed label for treatment of adults and children ≥6 years of age seems reasonable. Insufficient data exists for treatment of children younger than 6 years of age.

## 12 Labeling Recommendations

### 12.1. Prescribing Information

| Summary of Significant Labeling Changes (High level changes and not direct quotations) |                                                 |                                                                                                    |
|----------------------------------------------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Section                                                                                | Proposed Labeling                               | Approved Labeling                                                                                  |
| #1. Indications and Usage                                                              | Indicated for treatment of fascioliasis (b) (4) | Indicated for treatment of fascioliasis                                                            |
| #2. Dosage and Administration                                                          | (b) (4)                                         | 20mg/kg in two divided doses 12 hours apart                                                        |
| #5. Warnings and Precautions                                                           | (b) (4)                                         | Removed                                                                                            |
|                                                                                        | (b) (4) QT Prolongation                         | Language modified                                                                                  |
|                                                                                        | (b) (4)                                         | Removed                                                                                            |
|                                                                                        |                                                 | Removed                                                                                            |
| #6. Adverse Reactions                                                                  | Text and AE Table                               | Revised, discussed AR profile with 10 and 20 mg/kg doses separately; Liver Enzyme Elevations added |
| #7 Drug Interactions                                                                   | (b) (4)                                         | Removed; text modified                                                                             |
| #8 Use in Specific Populations                                                         | Pregnancy                                       | Multiples of exposure specified                                                                    |
| #8.4 Pediatric Use                                                                     | (b) (4)                                         | Removed                                                                                            |
| #12 Clinical Pharmacology                                                              | PK                                              | Updated to include exposures with food;<br>Text in all sections modified                           |
| #13 Nonclinical Toxicology                                                             | (b) (4)                                         | Removed<br>Other text modified                                                                     |
| #14 Clinical Studies                                                                   | Text (b) (4)                                    | Extensively modified to include IIT study results.                                                 |
| #17 Patient Counseling Information                                                     | Administration Instructions                     | Instructions modified<br>QT Prolongation information added                                         |

### **13 Risk Evaluation and Mitigation Strategies (REMS)**

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None recommended.

#### **13.1. Safety Issue(s) that Warrant Consideration of a REMS**

None.

#### **13.2. Conditions of Use to Address Safety Issue(s)**

None.

#### **13.3. Recommendations on REMS**

None.

## 14 Postmarketing Requirements and Commitments

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1. PMR 3556-1 Conduct a thorough QT/QTc trial of Egaten.

Draft Protocol Submission: 06/2019  
Final Protocol Submission: 10/2019  
Study Completion: 04/2020  
Final Report Submission: 10/2020

2. PMC 3556-2 Conduct an open-label, single-arm study to assess outcomes of treatment with Egaten 20 mg/kg in patients with fascioliasis.

Draft Protocol Submission: 05/2019  
Final Protocol Submission: 10/2019  
Interim Report Submissions: 06/2021  
06/2022  
06/2023  
06/2024  
Study/Trial Completion: 06/2025  
Final Report Submission: 12/2025

## 15 Appendices

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### 15.1. References

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## 15.2. Financial Disclosure

Financial disclosure information was sought by Novartis from investigators involved in the 3 investigator-initiated trials (IITs) and the 6 non-randomized, open-label trials conducted by CIBA/WHO under a single protocol in epidemic situations (2 in Bolivia, 1 each in Chile, Peru, Cuba and Iran) between October 1989 and August 1992. None of these studies were conducted under a US IND, but the trial plan and core protocol for triclabendazole in human fascioliasis was approved in 1990 by the Scientific Committee for Research in Human Subjects (SCRIHS) of WHO. Novartis presumes “to the best of our knowledge” (under Financial Certification and Disclosure, page 3), that these trials were conducted per regulatory standards followed by WHO at the time.

Over the course of the Rolling Review, financial disclosures were obtained from 4 investigators in the Hien 2008 study, 4 from Keiser 2011, 2 from Maco 2015, and 1 from EGA230B2202; none of them were/are full or part-time employees of Novartis, and no disclosable financial information was reported by any of them.

### Covered Clinical Study (Name and/or Number):

**Table -15.1 Hien 2008 (EGA230B2401)**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                         |                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)    |
| Total number of investigators identified: <u>11</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                              |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                              |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                              |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <b>N/A</b></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p> |                                         |                                                              |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant) |

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|                                                                                             |                                         |                                                                  |
|---------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Is a description of the steps taken to minimize potential bias provided:                    | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>7</u> |                                         |                                                                  |
| Is an attachment provided with the reason:                                                  | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

**Table -15.2 Keiser 2011 (EGA230B2402)**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: <u>4</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <b>N/A</b></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S _____</p> <p>Sponsor of covered study: _____</p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

**Table -15.3 Maco 2015 (EGA230B2403)**

|                                                |                                         |                                                |
|------------------------------------------------|-----------------------------------------|------------------------------------------------|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from |
|------------------------------------------------|-----------------------------------------|------------------------------------------------|

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         | Applicant)                                                       |
| Total number of investigators identified: <u>6</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <b>N/A</b></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S _____</p> <p>Sponsor of covered study: _____</p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>4</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

**Table -15.4 CIBA/WHO Studies (EGA230B2201, 2202, 2203, 2207, 2208, 2212)**

|                                                                                                                                                                                              |                                         |                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                               | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>12</u>                                                                                                                                          |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                               |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                          |                                         |                                                           |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR</p> |                                         |                                                           |

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|                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| <p>54.2(a), (b), (c) and (f): <b>N/A</b></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S<br/>Sponsor of covered study: _____</p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                           | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                              | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>11</u>                                                                                                                                                                                                                                                                                                                          |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                            | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

### 15.3. OCP Appendices (Technical documents supporting OCP recommendations)

#### 15.3.1. Summary of Bioanalytical Method Validation and Performance

Multiple validated high-performance liquid chromatography (HPLC) assays using UV detection were used for the quantification of triclabendazole (TCBZ) and its sulfoxide (TCBZ-SO) and sulfone (TCBZ-SO<sub>2</sub>) metabolites as shown in Table -15.5.. The most relevant bioanalytical assay is C.R.B. R21/1991 as it was used for Studies B2101 and B2212, which were chosen for further review. As this assay was validated in 1991, it does not meet current standards for bioanalytical assays outlined in the Agency's Bioanalytical Method Validation guidance. For instance, no incurred sample reanalysis was performed. However, the main standards for sensitivity, specificity, accuracy, and precision were met. The diluted plasma or urine samples spiked with the internal standard solution were stable for at least 10 hours at room temperature. The performance of the method is summarized in Table -15.5 and Table -15.6.

**Table -15.5. Summary of Bioanalytical Assay Methods. Adapted from Table 1-1 of the Summary of Biopharmaceutical Studies.**

| Analyte(s)                             | Matrix           | LLOQ (Lower Limit of Quantification)                            | Method validation report | Clinical studies which used this method                                     |
|----------------------------------------|------------------|-----------------------------------------------------------------|--------------------------|-----------------------------------------------------------------------------|
| TCBZ, TCBZ-SO and TCBZ-SO <sub>2</sub> | Plasma and Urine | TCBZ: 30 nmol/L<br>TCBZ-SO and TCBZ-SO <sub>2</sub> : 50 nmol/L | C.R.B. R21/1991          | Study B2101;<br>Study B2212-C.R.B. R 1/1992;<br>Study B2216;<br>Study B2218 |
| TCBZ, TCBZ-SO and TCBZ-SO <sub>2</sub> | Urine            | 50 nmol/L for the three compounds                               | C.R.B. R21/1991          | Not used in any clinical study                                              |
| TCBZ, TCBZ-SO and TCBZ-SO <sub>2</sub> | Plasma           | Not reported                                                    | Embedded in Study B2214  | Study B2214                                                                 |
| TCBZ, TCBZ-SO and TCBZ-SO <sub>2</sub> | Plasma           | Not reported                                                    | Embedded in Study B2215  | Study B2215                                                                 |

Novartis Codes: Triclabendazole (TCBZ): EGA230 or CGP 23030; Triclabendazole sulphoxide (TCBZ-SO): CGP 23031 or CGA 110 752; Triclabendazole sulfone (TCBZ-SO<sub>2</sub>): CGA274204 or CGA 110 753

**Table -15.6. Intra-Day and Inter-Day Reproducibility of the Method in Plasma and Urine. Adapted from Figure 1-5 of the Summary of Biopharmaceutic Studies.**

| Biological fluid |                 | Intra-day/<br>Inter-day | Parameter*                | TCBZ        | TCBZ-SO   | TCBZ-SO2  |
|------------------|-----------------|-------------------------|---------------------------|-------------|-----------|-----------|
| Plasma           | Reproducibility | Within-day              | Mean Recovery (Range) (%) | 96-104      | 96-102    | 96-105    |
|                  |                 |                         | CV (Range) %              | 1-5         | 1-9       | 2-9       |
|                  |                 | Day-to-day              | Mean Recovery (Range) (%) | 99-106      | 98-105    | 99-107    |
|                  |                 |                         | CV (Range)%               | 2-5         | 2-7       | 2-11      |
|                  | LOQ             |                         |                           | 27.8 nmol/L | 50 nmol/L | 50 nmol/L |
| Urine            | Reproducibility | Within-day              | Mean Recovery (Range) (%) | 99-101      | 95-104    | 95-104    |
|                  |                 |                         | CV (Range)%               | 1-5         | 1-8       | 1-5       |
|                  |                 | Day-to-day              | Mean Recovery (Range) (%) | 102-107     | 100-108   | 98-104    |
|                  |                 |                         | CV (Range)%               | 2-8         | 5-8       | 2-11      |
|                  | LOQ             |                         |                           | 50 nmol/L   | 50 nmol/L | 50 nmol/L |

\* Represented as range based on estimation at different concentrations

15.3.2. **Individual Study Reviews**

| <b>In Vitro Studies</b>                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DMPK R00-1279: Plasma Protein Binding of Triclabendazole and Its Major Metabolites (Sulfoxide and Sulfone) in Human Plasma                                                                                              |
| DMPK R1600737: Triclabendazole: Metabolic Profile in Human Liver Microsomes, Contributions of Cytochrome P450 and Flavin-Containing Monooxygenase (FMO) Enzymes to Metabolism, and Potential for Drug-Drug Interactions |
| DMPK R1700972: Sulfoxide Metabolite: Metabolic Profile in Human Liver Microsomes, and Contributions of Cytochrome P450 Enzymes to Metabolism                                                                            |
| DMPK R1600656-01: Evaluation of Triclabendazole and Its Sulfoxide and Sulfone Metabolites, as Inhibitors of Human Cytochrome P450 <b>Enzymes</b>                                                                        |
| DMPK R1600691: In Vitro Assessment of Cytochrome P450 Enzyme Time Dependent Inhibition (TDI) by Triclabendazole and its Sulfoxide and Sulfone Metabolites                                                               |
| DMPK R1700893-01: Supplemental In Vitro Assessment of Cytochrome P450 Enzyme Inhibition by Triclabendazole, Sulfoxide and Sulfone: Ki and Microsomal Protein Binding Determinations                                     |
| DMPK R1700971-01: In Vitro Assessment of Fluvoxamine and Rofecoxib as Inhibitors of Triclabendazole S-oxidation Metabolism                                                                                              |
| <b>Clinical Studies</b>                                                                                                                                                                                                 |
| EGA2302-B2101: Comparison of Triclabendazole Bioavailability from 250 mg Veterinary and New Pharmaceutical Tablets after Single Oral Postprandial Administration of 750 mg (3 Tablets) to Twelve Healthy Volunteers     |
| EGA230-B2212: Combined Clinico-pharmacokinetic Trial with Triclabendazole (CGP 23030) in Peruvian Patients Infected <i>with</i> Fasciola hepatica ( <b>liver fluke</b> )                                                |

**DMPK(CH) R00-1279: Plasma Protein Binding of Triclabendazole and Its Major Metabolites (Sulfoxide and Sulfone) in Human Plasma**

Date: June 6, 2000

Sponsor: Novartis Pharma AG

Test Site: 2 sites in Switzerland and France

**METHODS**

Protein binding was determined by adding TCBZ and its sulfoxide and sulfone metabolites each to heparinized human plasma where it was incubated for 20 minutes at 37°C. After ultracentrifugation, the concentrations of TCBZ and its metabolites were determined in the plasma water fraction.

**RESULTS**

Plasma binding was high for each species of TCBZ as shown in Table -15.7. Quantification of unchanged TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> was done by HPLC-UV. The LOQ for TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> in supernatant were 0.028, 0.053, and 0.025 µM, respectively.

**Table -15.7. Fraction Unbound of TCBZ and Its Major Metabolites. Adapted from Pg 5 of the Study Report.**

| Conc.<br>[µM] | Fraction of drug unbound<br>[% of total] |          |           |
|---------------|------------------------------------------|----------|-----------|
|               | EGA230                                   | CGP23031 | CGA274204 |
| 50            | n.d.                                     | 1.6      | n.d.      |
| 20            | n.d.                                     | 1.6      | n.d.      |
| 5             | n.d.                                     | 1        | n.d.      |
| 2             | 3.3                                      | < 0.3    | < 0.15    |
| 0.2           | 2.5                                      | n.d.     | n.d.      |

n.d.: not done, EGA230: TCBZ, CGP23031: TCBZ-SO, CGA274204: TCBZ-SO<sub>2</sub>

Reviewer Comment: The fraction recovered was below the limit of quantification when the total TCBZ concentration was lower than 2 µM and when the total TCBZ-SO and TCBZ-SO<sub>2</sub> concentrations were lower than 20 µM. Thus, 1.6% is the most reliable estimate of fraction of drug unbound for TCBZ-SO, and 3.3% is the most reliable estimate of fraction of drug unbound for TCBZ. Due to the analytical issues, there is no precise estimate of fraction unbound of TCBZ-SO<sub>2</sub>. However, if the LOQ value is used, the upper bound (most conservative value) of the fraction unbound can be estimated for TCBZ-SO<sub>2</sub>: 1.25%.

**Reviewer Assessment:** The plasma protein binding of TCBZ and TCBZ-SO is high: 96.7% and 98.4%, respectively. The plasma protein binding of TCBZ-SO<sub>2</sub> also appears to be high, but this experiment was not able to find a precise estimate of the protein binding due to analytical issues.

**DMPK R1600737: Triclabendazole: Metabolic Profile in Human Liver Microsomes, Contributions of Cytochrome P450 and Flavin-Containing Monooxygenase (FMO) Enzymes to Metabolism, and Potential for Drug-Drug Interactions**

Date(s): Nov 2016 – Mar 2017

Sponsor: Novartis

Testing site: DDI and Induction/In Vitro ADME/PKS, Novartis, East Hanover, New Jersey, USA

**METHODS**

The metabolism of TCBZ was studied using human liver microsomes (HLM); cryopreserved hepatocytes; recombinant human (rh) CYP, FMO, and (UDP-glucuronosyltransferase) UGT enzymes. In order to determine the relative contribution of CYP and FMO enzymes responsible for metabolism, TCBZ was incubated with HLM and an inhibitor for each CYP of interest. The contribution of specific enzyme to the TCBZ oxidative metabolism was estimated by comparing TCBZ clearance value in HLM with or without specific inhibition, corrected with inhibitor cross-reactivity for CYPs and normalized to a total 100%.

**RESULTS**

The hepatic metabolism of TCBZ was found to be mediated mostly by CYP1A2 (64%). Estimated values of intrinsic clearance and percent fraction metabolized are shown in Table -15.8. All of the proposed metabolites of TCBZ and potential pathways based on the data collected are shown in Figure 15-1.

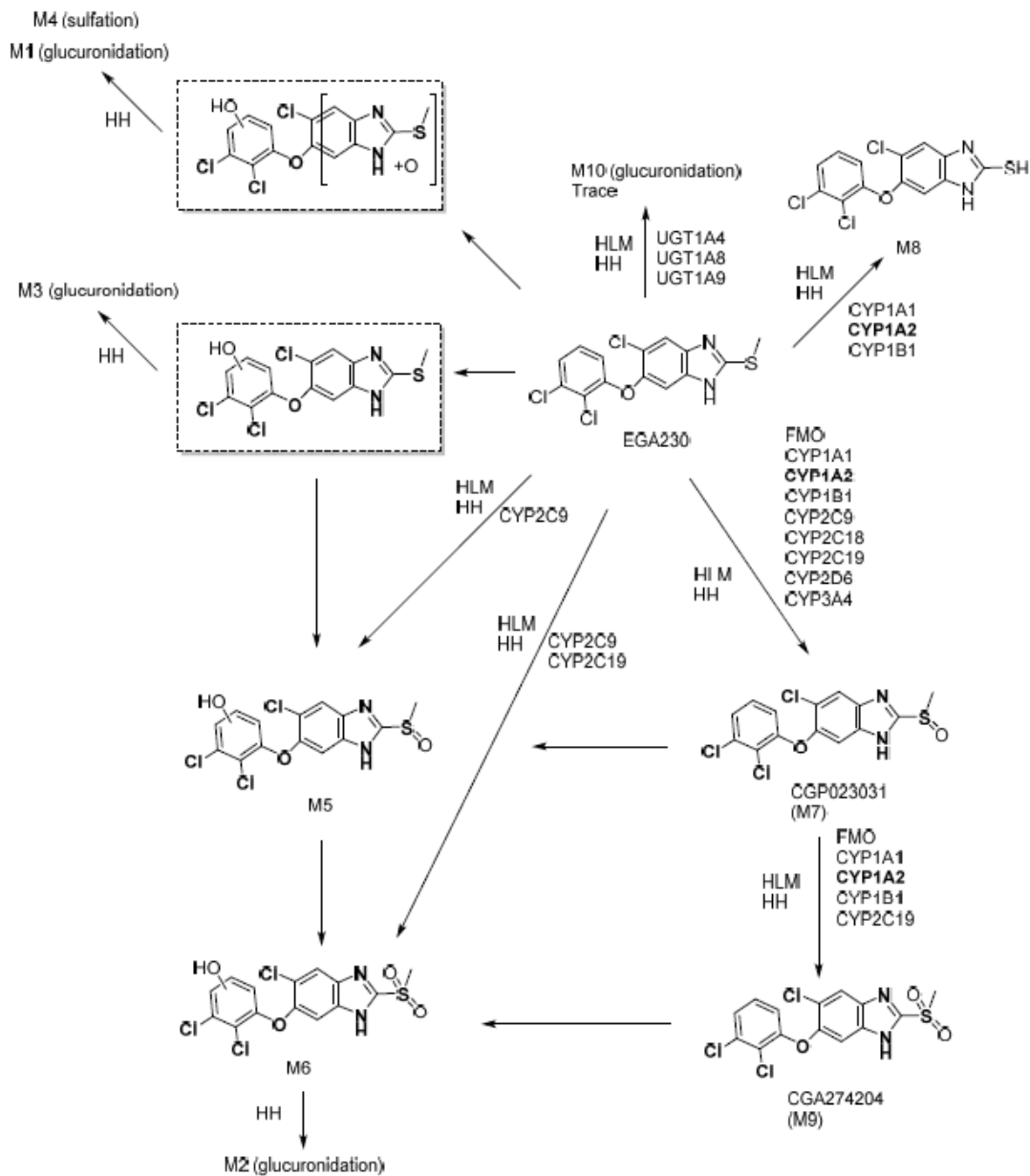
**Table -15.8. Intrinsic Clearance of Enzymes Involved in TCBZ Metabolism. Adapted from Table 6-9 of the Study Report.**

| Enzyme  | Inhibition                 |    | CL <sub>int</sub><br>(mL/h/mg<br>protein) | Median<br>reported<br>K <sub>i</sub> or IC <sub>50</sub><br>( $\mu$ M) <sup>a</sup> | Experimental<br><i>fm</i> (%) | Corrected<br><i>fm</i> <sub>CYP</sub> (%) <sup>b</sup> | Normalized<br><i>fm</i> <sub>CYP</sub> (%) <sup>c</sup> |
|---------|----------------------------|----|-------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------|---------------------------------------------------------|
|         | No inhibition              |    | 57.3                                      |                                                                                     |                               |                                                        |                                                         |
| CYP1A2  | Furafylline,<br>$\mu$ M    | 10 | 7.89                                      | 2.00                                                                                | 86.2                          | 94.2                                                   | 64.1                                                    |
| CYP2C9  | Sulfaphenazole,<br>$\mu$ M | 5  | 43.6                                      | 0.510                                                                               | 24.1                          | 13.1                                                   | 8.89                                                    |
| CYP2C19 | Ticlopidine,<br>$\mu$ M    | 10 | 21.4                                      | 1.70                                                                                | 62.6                          | -12.4                                                  | 0.00 <sup>d</sup>                                       |
| CYP2D6  | Quinidine,<br>$\mu$ M      | 2  | 50.4                                      | 0.0605                                                                              | 12.0                          | 14.8                                                   | 10.0                                                    |
| CYP3A   | Ketoconazole,<br>$\mu$ M   | 1  | 42.6                                      | 0.100                                                                               | 25.8                          | 10.5                                                   | 7.14                                                    |
| FMO     | Heat 45°C for<br>min       | 3  | 51.7                                      | n.a. <sup>e</sup>                                                                   | 9.84                          |                                                        |                                                         |

<sup>a</sup> Median values were calculated from DMPK R0400785. If a range of values was reported for a study an average value was taken. The K<sub>i</sub> or IC<sub>50</sub> values that were used in the calculations corresponded to inhibition of one enzyme (or subfamily, in the case of CYP3A); <sup>b</sup> Experimental *fm*<sub>CYP</sub> was corrected with inhibitor crossreactivity; <sup>c</sup> Corrected

$fm_{CYP}$  was normalized to a total of 90.2% so the sum of  $fm_{CYP}$  and  $fm_{FMO}$  reached 100%; <sup>d</sup> negative  $fm_{CYP}$  value after correction were considered to be analytical artifacts and set as 0; <sup>e</sup> not applicable

**Figure 15-1. Proposed Hepatic Metabolic Pathway of TCBZ. Adapted from Figure 7-4 of the Study Report.**



**Reviewer Assessment:** This study appears appropriately designed to assess the metabolic pathway of TCBZ.

**DMPK R1700972: Sulfoxide Metabolite: Metabolic Profile in Human Liver Microsomes, and Contributions of Cytochrome P450 Enzymes to Metabolism**

Date(s): February-May 2017

Sponsor: Novartis

Testing Site: DDI and Induction/In Vitro ADME/PKS, Novartis, East Hanover, New Jersey, USA

**METHODS**

The metabolism of triclabendazole sulfoxide (TCBZ-SO) was studied using human liver microsomes (HLM) and recombinant human (rh) CYP and FMO enzymes. To determine the relative contribution of CYP and enzymes responsible for metabolism, TCBZ was incubated with HLM and an inhibitor for each CYP of interest. The contribution of specific enzyme to the TCBZ-SO oxidative metabolism was estimated by comparing TCBZ-SO clearance value in HLM with or without specific inhibition, corrected with inhibitor cross-reactivity for CYPs and normalized to a total 100%.

**RESULTS**

The hepatic metabolism of TCBZ-SO was found to be mediated mostly by CYP2C9 (84%). Estimated values of intrinsic clearance and percent fraction metabolized are shown in Table -15.9.. The proposed metabolic pathways of TCBZ-SO based on the data collected is shown in Figure 15-2.

**Table -15.9. Intrinsic Clearance of Enzymes Involved in TCBZ-SO Metabolism. Adapted from Table 6-4 of the Study Report.**

| Enzyme  | Inhibitor, concentration | CL <sub>int</sub> (mL/h/mg protein) | Median reported K <sub>i</sub> or IC <sub>50</sub> (μM) <sup>a</sup> | Experimental fm (%) | Corrected fm <sub>CYP</sub> (%) <sup>b</sup> | Normalized fm <sub>CYP</sub> (%) <sup>c</sup> |
|---------|--------------------------|-------------------------------------|----------------------------------------------------------------------|---------------------|----------------------------------------------|-----------------------------------------------|
|         | <b>No inhibition</b>     | <b>0.442</b>                        |                                                                      |                     |                                              |                                               |
| CYP1A2  | Furafylline, 10 μM       | 0.499                               | 2.00                                                                 | -12.9               | 0 <sup>d</sup>                               |                                               |
| CYP2C8  | Montelukast, 2 μM        | 0.439                               | 0.0140 (0.71) <sup>d</sup>                                           | 0.661               | -65.4                                        | 0 <sup>d</sup>                                |
| CYP2C9  | Sulfaphenazole, 5 μM     | 0.0201                              | 0.510                                                                | 95.4                | 112                                          | 84.0                                          |
| CYP2C19 | Ticlopidine, 10 μM       | 0.354                               | 1.70                                                                 | 20.0                | 14.5                                         | 10.9                                          |
| CYP2D6  | Quinidine, 2 μM          | 0.435                               | 0.0605                                                               | 1.60                | 0.352                                        | 0.264                                         |
| CYP3A   | Ketoconazole, 1 μM       | 0.412                               | 0.100                                                                | 6.66                | 6.54                                         | 4.90                                          |

<sup>a</sup> Median values were calculated from (DMPK R0400785). If a range of values was reported for a study an average value was taken. The K<sub>i</sub> or IC<sub>50</sub> values that were used in the calculations corresponded to inhibition of one enzyme (or subfamily, in the case of CYP3A);

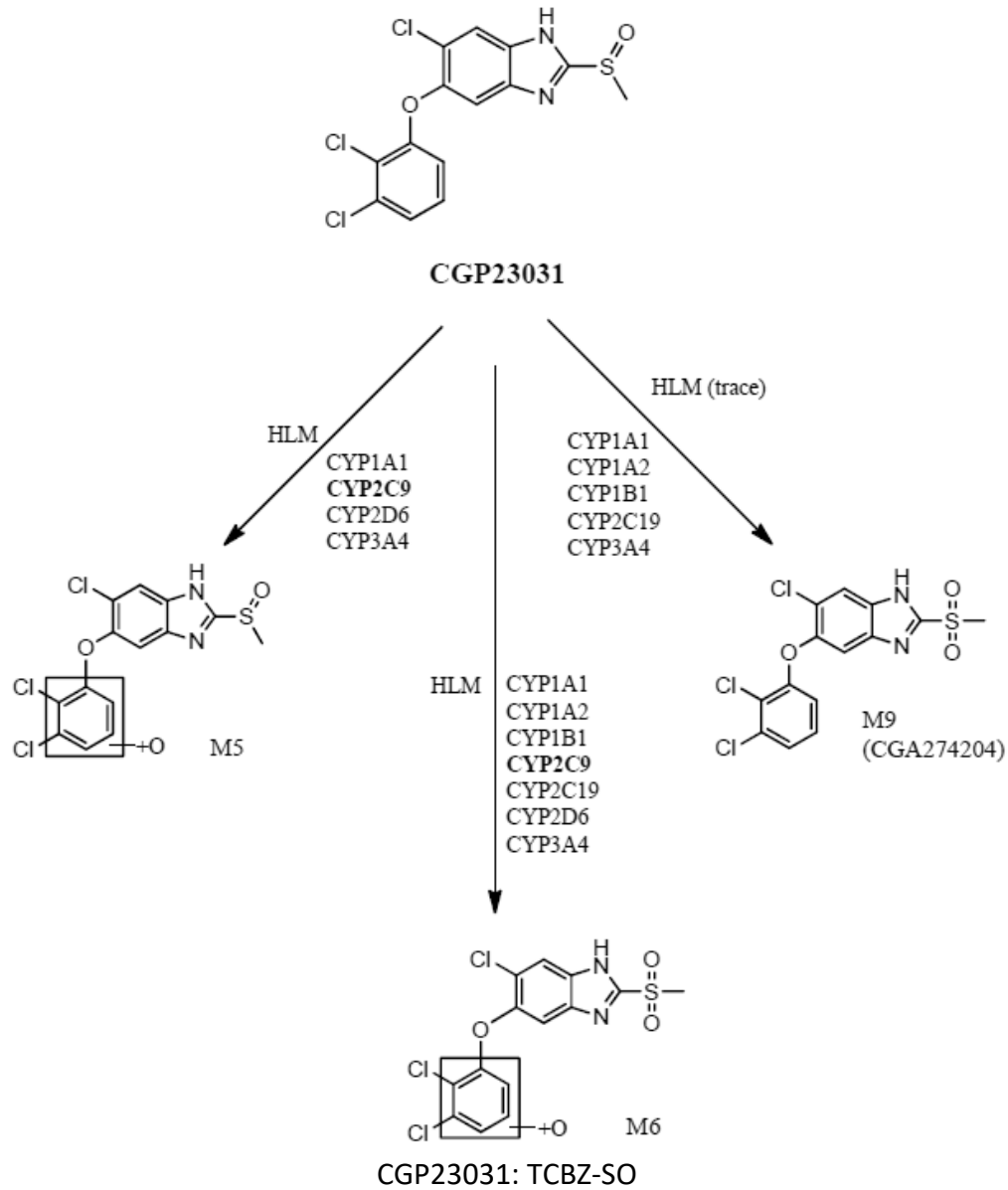
<sup>b</sup> Experimental fm<sub>CYP</sub> was corrected with inhibitor cross-reactivity;

<sup>c</sup> Corrected fm<sub>CYP</sub> was normalized to a total of 100%;

<sup>d</sup> negative fm<sub>CYP</sub> value were considered to be analytical artifacts and set as 0. No further analysis was conducted.

<sup>e</sup> The value in parenthesis is the IC<sub>50</sub> for CYP2C8 inhibition using a human liver microsomal concentration of 1.0 mg/mL. Due to the non-specific microsomal protein binding of montelukast, the IC<sub>50</sub> value varies with protein concentration. The microsomal protein concentration used in this study was 1.0 mg/mL

**Figure 15-2. Proposed Metabolic Pathway of TCBZ-SO. Adapted from Figure 7-3 of the Study Report.**



**Reviewer Assessment:** This study appears appropriately designed to assess the metabolic pathway of TCBZ-SO.

**DMPK R1600656-01: Evaluation of Triclabendazole and Its Sulfoxide and Sulfone Metabolites, as Inhibitors of Human Cytochrome P450 Enzymes**

Date(s): November 2016 – February 2017

Sponsor: Novartis

Testing Site: (b) (4)**METHODS**

This study was designed to evaluate the potential for triclabendazole (TCBZ, CGP023030) and its sulfoxide (TCBZ-SO, CGP023031) and sulfone (TCBZ-SO<sub>2</sub>, CGA274204) metabolites to inhibit human CYP enzymes. TCBZ and its metabolites in pooled human liver microsomes at concentrations from 0 to 100 μM were each incubated with CYP-selective probe substrates with the experimental condition described in Table -15.10. Probe substrate concentrations used were less than or approximately equal to their K<sub>m</sub> values reported in the literature.

**Table -15.10. Probe Substrates and Incubation Time for Determination of CYP Inhibition Potential. Adapted from Table 2-2 of the Study Report.**

| Probe substrate  | CYP Enzyme | Concentration (μM) | Protein (mg/mL) | Incubation time (min) | Literature K <sub>m</sub> value (μM) <sup>1</sup> |
|------------------|------------|--------------------|-----------------|-----------------------|---------------------------------------------------|
| Phenacetin       | CYP1A2     | 40                 | 0.2             | 10                    | 27                                                |
| Coumarin         | CYP2A6     | 1.5                | 0.05            | 5                     | 1.3 <sup>2</sup>                                  |
| Bupropion        | CYP2B6     | 80                 | 0.1             | 5                     | 97                                                |
| Amodiaquine      | CYP2C8     | 1.5                | 0.02            | 5                     | 1.6                                               |
| Diclofenac       | CYP2C9     | 5                  | 0.05            | 5                     | 3.7                                               |
| S-mephenytoin    | CYP2C19    | 40                 | 0.3             | 10                    | 32                                                |
| Dextromethorphan | CYP2D6     | 5                  | 0.1             | 5                     | 4.9                                               |
| Chlorzoxazone    | CYP2E1     | 60                 | 0.1             | 5                     | 60 <sup>3</sup>                                   |
| Midazolam        | CYP3A4/5   | 3                  | 0.02            | 5                     | 2.2                                               |
| Testosterone     | CYP3A4/5   | 50                 | 0.05            | 10                    | 65                                                |

**RESULTS**

The positive control for each enzyme inhibited enzyme activity in each scenario. TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> each had the potential to inhibit most CYP enzymes, with the relevant values of IC<sub>50</sub> shown in Table -15.11..

**Table -15.11. Inhibitory Effect of CGP023030 (TCBZ), CGP023031 (TCBZ-SO), and CGA274204 (TCBZ-SO2) on CYP Enzymes. Adapted from Table 6-2 of the Study Report.**

| CYP enzyme | Probe reaction                   | IC <sub>50</sub> (μM) <sup>a</sup> ± Standard error |              |              |
|------------|----------------------------------|-----------------------------------------------------|--------------|--------------|
|            |                                  | CGP023030                                           | CGP023031    | CGA274204    |
| CYP1A2     | phenacetin O-deethylation        | 4.0 ± 0.24                                          | 9.5 ± 0.37   | 96 ± 5.1     |
| CYP2A6     | coumarin 7-hydroxylation         | 7.8 ± 0.57                                          | 17 ± 0.79    | 43 ± 6.6     |
| CYP2B6     | bupropion hydroxylation          | 2.6 ± 0.12                                          | 7.4 ± 0.35   | 5.6 ± 0.22   |
| CYP2C8     | amodiaquine N-deethylation       | 1.2 ± 0.076                                         | 3.1 ± 0.088  | 0.71 ± 0.016 |
| CYP2C9     | diclofenac 4'-hydroxylation      | 1.7 ± 0.083                                         | 2.2 ± 0.062  | 0.65 ± 0.010 |
| CYP2C19    | S-mephenytoin 4'-hydroxylation   | 1.7 ± 0.12                                          | 0.48 ± 0.016 | 31 ± 3.9     |
| CYP2D6     | dextromethorphan O-demethylation | 15 ± 0.87                                           | 31 ± 1.9     | 57 ± 2.3     |
| CYP2E1     | chlorzoxazone 6-hydroxylation    | >100                                                | >100         | >100         |
| CYP3A4/5   | midazolam 1'-hydroxylation       | NC                                                  | NC           | NC           |
| CYP3A4/5   | testosterone 6'-hydroxylation    | 3.4 ± 0.16                                          | 11 ± 0.64    | 31 ± 2.0     |

<sup>a</sup> total (bound + unbound) Mean IC<sub>50</sub> value (n=3)

NC – Not calculated, due to enhancement of CYP3A4 activity detected with all three test articles

**Reviewer Assessment:** This study was appropriately designed to assess the inhibitory potential of TCBZ and its metabolites. A suitable range of concentrations was used as it correlated with relevant clinical exposure and captured the IC<sub>50</sub> in most cases. In addition, the probe substrates agreed with those recommended by the Agency.

**DMPK R1600691: In Vitro Assessment of Cytochrome P450 Enzyme Time Dependent Inhibition (TDI) by Triclabendazole and its Sulfoxide and Sulfone Metabolites**

Date(s): November 2016 – February 2017

Sponsor: Novartis

Testing Site: DDI and Induction/In Vitro ADME/PKS, Novartis, East Hanover, New Jersey, USA

**METHODS**

This study was designed to evaluate the potential for triclabendazole (TCBZ, CGP023030) and its sulfoxide (TCBZ-SO, CGP023031) and sulfone (TCBZ-SO<sub>2</sub>, CGA274204) metabolites to act as time-dependent inhibitors of CYP enzymes using pooled human liver microsomes. The probe substrates and reaction conditions are shown in Table -15.12. TCBZ and its metabolites were incubated at concentrations between 0 and 100  $\mu$ M.

**Table -15.12. Probe Substrates and Incubation Time for Determination of Time-Dependent CYP Inhibition Potential. Adapted from Table 2-2 of the Study Report.**

| Probe substrate | CYP      | Concentration ( $\mu$ M) | [Protein] (mg/mL) | Incubation time (min) |
|-----------------|----------|--------------------------|-------------------|-----------------------|
| Phenacetin      | CYP1A2   | 100                      | 0.05              | 6                     |
| Bupropion       | CYP2B6   | 1500                     | 0.02              | 6                     |
| Amodiaquine     | CYP2C8   | 20                       | 0.025             | 6                     |
| Diclofenac      | CYP2C9   | 50                       | 0.025             | 6                     |
| S-mephenytoin   | CYP2C19  | 300                      | 0.05              | 6                     |
| Bufuralol       | CYP2D6   | 50                       | 0.025             | 6                     |
| Midazolam       | CYP3A4/5 | 20                       | 0.025             | 6                     |

**RESULTS**

TCBZ and its metabolites did not act as time-dependent mediators of CYP enzymes, but the positive controls all successfully inhibited CYP enzymes as shown in Table -15.13..

**Table -15.13. Time-dependent Inhibitor Effect of CGP023030 (TCBZ), CGP023031 (TCBZ-SO), and CGA274204 (TCBZ-SO2) on CYP Enzyme-selective Probe Substrates. Adapted from Table 6-1 of the Study Report.**

| CYP enzyme | Probe reaction                 | Test compound                        | K <sub>i</sub> (μM)<br>Total <sup>a</sup> | k <sub>inact</sub><br>(1/min) |
|------------|--------------------------------|--------------------------------------|-------------------------------------------|-------------------------------|
|            |                                | Furafylline <sup>b</sup>             | 0.687 ± 0.148                             | 0.0324 ± 0.00222              |
| CYP1A2     | phenacetin O-deethylation      | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
|            |                                | Ticlopidine <sup>b</sup>             | 0.393 ± 0.236 <sup>c</sup>                | 0.0430 ± 0.00530 <sup>c</sup> |
| CYP2B6     | bupropion hydroxylation        | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
|            |                                | Gemfibrozil glucuronide <sup>b</sup> | 10.5 ± 0.933                              | 0.0647 ± 0.00143              |
| CYP2C8     | amodiaquine N-deethylation     | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
|            |                                | Tienilic acid <sup>b</sup>           | 1.81 ± 0.439                              | 0.0875 ± 0.00895              |
| CYP2C9     | diclofenac 4'-hydroxylation    | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
|            |                                | Ticlopidine <sup>b</sup>             | 2.17 ± 1.24                               | 0.0256 ± 0.00526              |
| CYP2C19    | S-mephenytoin 4'-hydroxylation | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
|            |                                | Paroxetine <sup>b</sup>              | 0.157 ± 0.0442                            | 0.0333 ± 0.00202              |
| CYP2D6     | bufuralol 1'-hydroxylation     | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |
| CYP3A4/5   | midazolam 1'-hydroxylation     | Troleandomycin <sup>b</sup>          | 0.233 ± 0.0549                            | 0.0496 ± 0.00281              |
|            |                                | CGP023030                            | n.t.                                      | n.t.                          |
|            |                                | CGP023031                            | n.t.                                      | n.t.                          |
|            |                                | CGA274204                            | n.t.                                      | n.t.                          |

n.t.: no time-dependent inhibition observed

<sup>a</sup>total (bound + unbound) K<sub>i</sub> value<sup>b</sup>positive control<sup>c</sup>parameters were determined using 100-fold dilution method.

**Reviewer Assessment:** This study was appropriately designed to assess the time-dependent inhibition potential of TCBZ and its metabolites. The probe substrates agreed with those recommended by the Agency. A suitable range of concentrations was used as it correlated with relevant clinical exposure.

### DMPK R1700893-01: Supplemental In Vitro Assessment of Cytochrome P450 Enzyme Inhibition by Triclabendazole, Sulfoxide and Sulfone: $K_i$ and Microsomal Protein Binding Determinations

Date(s): March-May 2017

Sponsor: Novartis

Testing Site: (b) (4)

#### METHODS

This study was designed to determine the inhibition constant ( $K_i$ ) for triclabendazole (TCBZ, CGP023030) and its sulfoxide (TCBZ-SO, CGP023031) and sulfone (TCBZ-SO<sub>2</sub>, CGA274204) metabolites in human liver microsomes against human CYP enzymes. Probe substrate concentrations and incubation conditions are shown in Table -15.14., and the concentrations of TCBZ and its metabolites tested against each enzyme are shown in Table -15.15..The microsomal binding ability of TCBZ and its metabolites, sulfoxide and sulfone was also evaluated using equilibrium dialysis

**Table -15.14. Probe Substrates and Incubation Time for Determination of Time-Dependent CYP Inhibition Potential. Adapted from Table 2-2 of the Study Report.**

| Probe substrate | CYP Enzyme | Protein (mg/mL) | Incubation time (min) | Concentrations ( $\mu$ M)                 |
|-----------------|------------|-----------------|-----------------------|-------------------------------------------|
| Phenacetin      | CYP1A2     | 0.2             | 10                    | 12, 18, 26, 40, 59, 89, 133, 200          |
| Coumarin        | CYP2A6     | 0.05            | 5                     | 0.35, 0.53, 0.79, 1.2, 1.8, 2.7, 4.0, 6.0 |
| Bupropion       | CYP2B6     | 0.1             | 5                     | 19, 28, 42, 63, 95, 142, 213, 320         |
| Amodiaquine     | CYP2C8     | 0.02            | 5                     | 0.35, 0.53, 0.79, 1.2, 1.8, 2.7, 4.0, 6.0 |
| Diclofenac      | CYP2C9     | 0.05            | 5                     | 0.94, 1.4, 2.1, 3.2, 4.7, 7.1, 11, 16     |
| S-mephenytoin   | CYP2C19    | 0.3             | 10                    | 7.0, 11, 16, 24, 36, 53, 80, 120          |
| Testosterone    | CYP3A4/5   | 0.05            | 10                    | 16, 20, 25, 31, 38, 48, 60, 75            |

**Table -15.15. Concentrations of TCBZ and Its Metabolites Analyzed. Adapted from Figure 2-3 of the Study Report.**

| Test compound | CYP Enzyme | IC <sub>50</sub> ( $\mu$ M) | Concentrations ( $\mu$ M)      |
|---------------|------------|-----------------------------|--------------------------------|
| CGP023030     | CYP1A2     | 4.0                         | 0, 1.0, 2.0, 4.0, 8.0, 16      |
|               | CYP2A6     | 7.8                         | 0, 2.0, 3.9, 7.8, 16, 31       |
|               | CYP2B6     | 2.6                         | 0, 0.65, 1.3, 2.6, 5.2, 10     |
|               | CYP2C8     | 1.2                         | 0, 0.30, 0.60, 1.2, 2.4, 4.8   |
|               | CYP2C9     | 1.7                         | 0, 0.43, 0.85, 1.7, 3.4, 6.8   |
|               | CYP2C19    | 1.7                         | 0, 0.43, 0.85, 1.7, 3.4, 6.8   |
|               | CYP3A4/5   | 3.4                         | 0, 0.85, 1.7, 3.4, 6.8, 14     |
| CGP023031     | CYP2C8     | 3.1                         | 0, 0.78, 1.6, 3.1, 6.2, 12     |
|               | CYP2C9     | 2.2                         | 0, 0.55, 1.1, 2.2, 4.4, 8.8    |
|               | CYP2C19    | 0.48                        | 0, 0.12, 0.24, 0.48, 0.96, 1.9 |
| CGA274204     | CYP2C8     | 0.71                        | 0, 0.18, 0.36, 0.71, 1.4, 2.8  |
|               | CYP2C9     | 0.65                        | 0, 0.16, 0.33, 0.65, 1.3, 2.6  |

**RESULTS**

All the positive controls successfully inhibited CYP enzymes. TCBZ and its metabolites showed a combination of competitive, mixed, and noncompetitive inhibition of CYP enzymes as shown in Table -15.16.

**Table -15.16. Ki Values Corrected for Microsomal Protein Binding. Adapted from Table 6-14.**

| CYP Enzyme (probe reaction)                      | Protein (mg/mL)   | Test compound | Type of Inhibition | Total Ki ( $\mu\text{M}$ ) | $f_{u_{\text{mlo}}}$ | Unbound Ki ( $\mu\text{M}$ ) |
|--------------------------------------------------|-------------------|---------------|--------------------|----------------------------|----------------------|------------------------------|
| CYP1A2 (phenacetin O-deethylation)               | 0.2               | CGP023030     | Competitive        | 1.77 $\pm$ 0.08            | 0.00913              | 0.0162 $\pm$ 0.0007          |
| CYP2A6 (coumarin 7-hydroxylation)                | 0.05              | CGP023030     | Mixed              | 7.73 $\pm$ 1.8             | 0.0562               | 0.434 $\pm$ 0.1              |
| CYP2B6 (bupropion hydroxylation)                 | 0.1               | CGP023030     | Competitive        | 0.829 $\pm$ 0.12           | 0.0221               | 0.0183 $\pm$ 0.003           |
| CYP2C8 (amodiaquine N-deethylation)              | 0.02 <sup>a</sup> | CGP023030     | Mixed              | 0.937 $\pm$ 0.22           | 0.0562               | 0.0527 $\pm$ 0.01            |
|                                                  |                   | CGP023031     | Noncompetitive     | 4.25 $\pm$ 0.36            | 0.425                | 1.81 $\pm$ 0.2               |
|                                                  |                   | CGA274204     | Mixed              | 0.498 $\pm$ 0.06           | 0.738                | 0.368 $\pm$ 0.04             |
| CYP2C9 (diclofenac 4'-hydroxylation)             | 0.05              | CGP023030     | Mixed              | 1.09 $\pm$ 0.29            | 0.0562               | 0.0613 $\pm$ 0.02            |
|                                                  |                   | CGP023031     | Competitive        | 1.33 $\pm$ 0.063           | 0.425                | 0.565 $\pm$ 0.03             |
|                                                  |                   | CGA274204     | Competitive        | 0.341 $\pm$ 0.011          | 0.658                | 0.224 $\pm$ 0.007            |
| CYP2C19 (S-mephenytoin 4'-hydroxylation)         | 0.3               | CGP023030     | Competitive        | 1.40 $\pm$ 0.079           | 0.00639              | 0.00895 $\pm$ 0.0005         |
|                                                  |                   | CGP023031     | Competitive        | 0.449 $\pm$ 0.020          | 0.111                | 0.0498 $\pm$ 0.002           |
| CYP3A4/5 (testosterone 6 $\beta$ -hydroxylation) | 0.05              | CGP023030     | Competitive        | 2.65 $\pm$ 0.19            | 0.0562               | 0.149 $\pm$ 0.01             |

**Reviewer Assessment:** This study was appropriately designed to assess kinetics of CYP inhibition of TCBZ and its metabolites. The probe substrates agreed with those recommended by the Agency. A suitable range of concentrations was used as it correlated with the range of expected CYP inhibition based on the IC50 value determined in a previous study.

**DMPK R1700971-01: In Vitro Assessment of Fluvoxamine and Rofecoxib as Inhibitors of Triclabendazole S-oxidation Metabolism**

Date(s): April 2017

Sponsor: Novartis

Testing Site: DDI and Induction/In Vitro ADME/PKS, Novartis, East Hanover, New Jersey, USA

**METHODS**

This study was designed to assess the ability of fluvoxamine and rofecoxib (CYP1A2 inhibitors) on triclabendazole (TCBZ, CYP1A2 substrate) metabolism in pooled human liver Microsomes (HLM).

**RESULTS**

Both fluvoxamine and rofecoxib were shown to inhibit the metabolism of TCBZ as shown in Table -15.17.

**Table -15.17. In Vitro Effect of CYP1A2 Inhibitors on TCBZ. Adapted from Table 7-1.**

| Inhibitor   | Probe reaction     | IC <sub>50</sub> (μM) <sup>a</sup> |         |
|-------------|--------------------|------------------------------------|---------|
|             |                    | Total                              | Unbound |
| Fluvoxamine | EGA230 S-oxidation | 0.29                               | 0.0058  |
| Rofecoxib   |                    | 3.0                                | 0.06    |

<sup>a</sup> Inhibitor concentration estimated to inhibit probe substrate reaction by 50%. Total = (bound + unbound); unbound = corrected for microsomal protein binding, where unbound fraction in liver microsomes (f<sub>mic</sub>) was 0.02 for 0.1 mg/mL protein

**Reviewer Assessment:** CYP1A2 inhibitors appear to decrease the in vitro metabolism of TCBZ. This agrees with the metabolism study showing that TCBZ is 64% metabolized by CYP1A2.

**EGA2302-B2101: Comparison of Triclabendazole Bioavailability from 250 mg Veterinary and New Pharmaceutical Tablets after Single Oral Postprandial Administration of 750 mg (3 Tablets) to Twelve Healthy Volunteers**

Date(s): March-April 1992

Sponsor: CIBA-GEIGY Ltd., Basel, Switzerland

Clinical Site: Human Pharmacology Unit, CIBA-GEIGY Ltd., Basel, Switzerland

**METHODS**

**Study Design:** Study B2101 was a randomized, two-period, crossover study designed to compare the bioavailability of 750 mg TCBZ from a veterinary formulation (Fasinex) and from an interim human formulation. 750 mg TCBZ was given 30 min after a standardized breakfast to 12 healthy male volunteers. Subjects had a minimum two-week washout period between doses of each formulation.

750 mg TCBZ was supplied as three 250 mg tablets for both formulations. The standardized breakfast consisted of 400 mL decaffeinated coffee, one roll with cheese, and one roll with butter and jam. 11 samples of TCBZ and its metabolites were drawn over 72 h after the dose of TCBZ in each formulation.

**Reviewer Comment:** The veterinary formulation (Fasinex) was used in the food-effect study and several clinical studies to support the efficacy of TCBZ. The interim human formulation is not the to-be-market formulation and was not used to support the establishment of efficacy for TCBZ. Therefore, for the purpose of this review, only data regarding the veterinary formulation will be presented.

**Analytical Method:** Bioanalytical assay R21/1991 was used to measure the concentrations of TCBZ and its metabolites in plasma. The performance was satisfactory (refer to Section 15.4.1).

**RESULTS**

**Pharmacokinetics:**

The PK parameters identified in this study are displayed in Table -15.18.

**Table -15.18. PK Parameters of TCBZ and Its Metabolites after Administering 750 mg TCBZ as Fasinex to Healthy Volunteers (Mean  $\pm$  SD, n=12). Adapted from Page 8 of the Study Report.**

| Parameter                                               | Compound        | Veter. Tab      |
|---------------------------------------------------------|-----------------|-----------------|
| AUC(0-72h)<br>( $\mu\text{mol}\cdot\text{h}/\text{l}$ ) | Triclabendazole | 8.08 $\pm$ 2.51 |
|                                                         | Sulphoxide met. | 778 $\pm$ 184   |
|                                                         | Sulphone met.   | 73.4 $\pm$ 30.7 |
| Cmax<br>( $\mu\text{mol}/\text{l}$ )                    | Triclabendazole | 1.68 $\pm$ 0.77 |
|                                                         | Sulphoxide met. | 61.0 $\pm$ 7.9  |
|                                                         | Sulphone met.   | 4.03 $\pm$ 0.98 |
| Tmax<br>(h, median)                                     | Triclabendazole | 2               |
|                                                         | Sulphoxide met. | 4               |
|                                                         | Sulphone met.   | 6               |
| T1/2*<br>(h, median)                                    | Triclabendazole | 7.4             |
|                                                         | Sulphoxide met. | 13.7            |
|                                                         | Sulphone met.   | 10.8            |

**Reviewer Assessment:** The sampling scheme appears to be sufficient to capture the full PK profile of TCBZ and its metabolites. TCBZ appeared to be well tolerated in each subject. The sulfoxide metabolite appears to have the highest AUC and Cmax in plasma relative to TCBZ and TCBZ sulfone. Please note that a fixed dose of 750 mg was tested in this study, while the proposed dose (10 mg/kg) is bodyweight-based.

**EGA230-B2212: Combined Clinico-pharmacokinetic Trial with Triclabendazole (CGP 23030) in Peruvian Patients Infected with *Fasciola hepatica* (liver fluke): Influence of food on the pharmacokinetics of triclabendazole and its metabolites after oral administration of a 10 mg/kg dose to patients from Peru**

Date(s): April-November 1991

Sponsor: CIBA-GEIGY Ltd., Basel, Switzerland

Clinical Site: Regional Medical Center, Pharma International Latin America, Lima, Peru

**METHODS**

Study Design: Study B2212 was a single-center, open-label, non-randomized, cross-over study designed to compare the bioavailability of TCBZ and its major metabolites in adult patients infected with *Fasciola hepatica* in fasting and fed conditions. Twenty-two patients (11 male and 11 female) were enrolled in the study and received 10 mg/kg TCBZ fasting and 10 mg/kg TCBZ immediately after a standardized meal with a 2-day washout period in either order.

10 mg/kg TCBZ was supplied as 250 mg tablets. The standardized meal for patients receiving TCBZ under fed conditions consisted of 2 cups of sweetened white coffee, one roll with cheese, and one roll with butter and jam, comprising approximately 560 kcal. Eight plasma samples of TCBZ and its metabolites were drawn over 48 h after each dose of TCBZ.

**Analytical Method:** Bioanalytical assay R21/1991 was used to measure the concentrations of TCBZ and its metabolites TCBZ sulfoxide (TCBZ-SO) and TCBZ sulfone (TCBZ-SO<sub>2</sub>) and in plasma. The performance was satisfactory (refer to Section 15.4.1).

**RESULTS**

Results are available for 22 patients treated in this trial. The actual dose administered ranged from 250-625 mg with mean dose administered 437 mg.

**Safety:**

82% of patients experienced abdominal pain within 4 days of drug administration, and it did not appear to be affected by administration with or without food.

**Efficacy:**

20/21 patients had negative *F. hepatica* egg cultures in feces at the end of the study.

**Pharmacokinetics:**

Table -15.19. below shows the relative differences in PK parameters of TCBZ and its metabolites under the fed versus fasting state stratified by sex for AUC.

**Table -15.19. PK Parameters of TCBZ and Its Metabolites after Administering 10 mg/kg TCBZ Under Fasting and Fed Conditions to Patients Stratified by Sex (n=20, 10 male and 10 female patients), Mean (SD). Reviewer's Table.**

| Pharmacokinetic Parameter      | Analyte              | Sex    | Fasting        | Fed         | Percent Increase |
|--------------------------------|----------------------|--------|----------------|-------------|------------------|
| AUC <sub>0-48</sub> (μmol·h/L) | TCBZ                 | All    | 1.55<br>(1.38) | 5.72 (3.8)  | 269%             |
|                                |                      | Male   | 1.49<br>(1.56) | 4.8 (4.22)  | 222%             |
|                                |                      | Female | 1.61<br>(1.25) | 6.64 (3.29) | 312%             |
|                                | TCBZ-SO              | All    | 177 (73)       | 386 (159)   | 118%             |
|                                |                      | Male   | 166 (83)       | 316 (123)   | 90%              |
|                                |                      | Female | 188 (64)       | 455 (166)   | 142%             |
|                                | TCBZ-SO <sub>2</sub> | All    | 13.9 (6.4)     | 30.5 (16.3) | 119%             |
|                                |                      | Male   | 13.2 (6.5)     | 24.2 (10.7) | 83%              |
|                                |                      | Female | 14.5 (6.6)     | 36.9 (18.9) | 154%             |
| C <sub>max</sub> (μmol/L)      | TCBZ                 | All    | 0.34<br>(0.27) | 1.16 (0.75) | 241%             |
|                                | TCBZ-SO              | All    | 15.8 (6.8)     | 38.6 (13.8) | 144%             |
|                                | TCBZ-SO <sub>2</sub> | All    | 1.04<br>(0.43) | 2.29 (0.91) | 120%             |
| T <sub>max</sub> (hr)          | TCBZ                 | All    | 2              | 3           | 50%              |
|                                | TCBZ-SO              | All    | 2              | 4           | 100%             |
|                                | TCBZ-SO <sub>2</sub> | All    | 4              | 4           | 0%               |

SD: Standard Deviation, SD for T<sub>max</sub> not provided.

Following a single dose of TCBZ 10 mg/kg, the AUC was statistically significantly higher in women relative to men in the fed state but not in the fasted state: 8%, 13%, and 10% higher AUC in woman in the fasted state and 38%, 44%, and 52% higher AUC in women in the fed state for TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub>, respectively. However, the difference in gender was not significant when compared between adult patients.

In addition, 7 of the 20 patients were under 15 years of age and had lower AUC values of TCBZ sulfoxide (30% lower in the fasted state, 20% lower in the fed state) relative to the 13 patients above 15 years of age. However, this difference was not considered statistically significant.

**Reviewer Assessment:** Administration of TCBZ with food appears to result in 2-3 fold higher AUC and C<sub>max</sub> values for TCBZ and its metabolites. The effect of food appears to have a larger effect in increasing AUC in women. The values of AUC and C<sub>max</sub> appear to be higher in Study B2101 relative to Study B2212. However, this could be due to the use of weight-based dosing (as proposed in the label) in Study B2212 vs a fixed dose of 750 mg in Study B2101 or the difference in population (healthy volunteers in B2101 and patients with fascioliasis in Study B2212).

One significant caveat is that the composition of the meal. The Food-Effect Guidance recommends a meal of 800 to 1000 calories where at least half of the calories are provided by fat. However, this meal was only 560 calories. No calorie breakdown was provided, but it appears that the most calories were the carbohydrates from the 2 rolls. Because the meal used in this study was not “high-fat” as defined by FDA guidance, a true high-fat meal may increase the exposure of TCBZ and its metabolites higher than what was seen in this study. It should be noted that this study was completed 11 years before the Food-Effect Guidance was published.

Another significant caveat is that the washout period (2 days) appears to have been too short. Eighteen and 8 out of 22 patients administered the second dose had non-zero pre-dose concentrations of TCBZ-SO and TCBZ-SO<sub>2</sub>, respectively. At the time 0 h PK sample taken at the second dose administration, the average predose TCBZ-SO and TCBZ-SO<sub>2</sub> concentrations were 3% and 4% of the respective C<sub>max</sub>; 80% and 75% of the pre-dose concentrations of TCBZ-SO and TCBZ-SO<sub>2</sub> were ≤ 5% of the respective C<sub>max</sub>. Thus, the pre-dose concentrations are unlikely to have a significant confounding effect in interpreting the food effect on the change in AUC and C<sub>max</sub> of TCBZ and its metabolites.

Overall, because of these two caveats, the study may underestimate the true food effect of TCBZ. Food increases the AUC and C<sub>max</sub> of TCBZ and metabolites, but the extent of the increase was not well determined.

### 15.3.3. Physiologically based Pharmacokinetics Review

#### Executive Summary

The Applicant, Novartis, proposed to use physiologically based pharmacokinetic (PBPK) modeling and simulation to assess the drug-drug interaction (DDI) liability of TCBZ (proposed trade name ‘Egaten’). Specifically, PBPK was used to assess the effect of cytochrome P450 (CYP) inhibitors on the pharmacokinetics (PK) of TCBZ and its sulfoxide (TCBZ-SO), and sulfone (TCBZ-SO<sub>2</sub>) metabolites, both of which were active. In addition, the Applicant used a static model and PBPK models to estimate the impact of TCBZ on the PK of multiple CYP substrates.

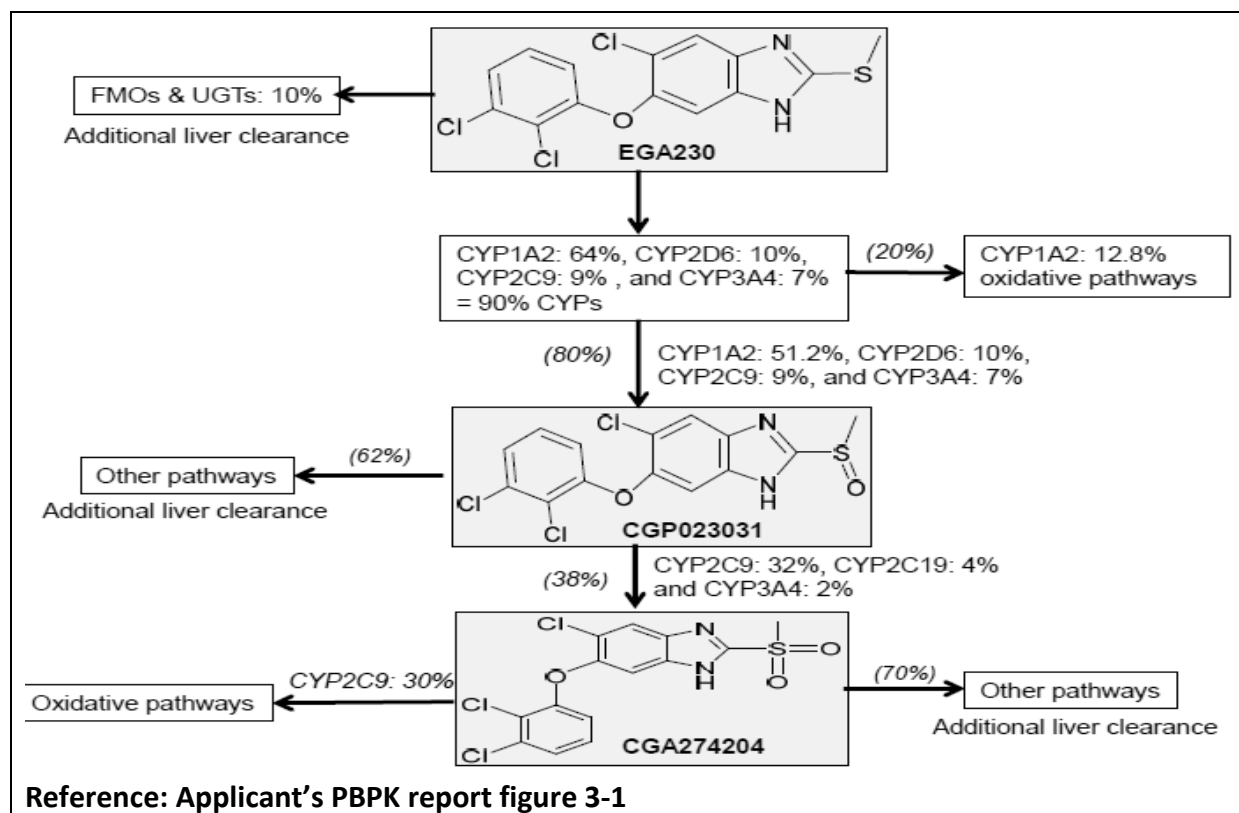
The Division of Pharmacometrics reviewed the PBPK analyses report (Study 1701024) entitled “Cytochrome P450 clinical drug interaction risk assessment of EGA230 and its metabolites, CGP023031 and CGA274204”, and concluded that the applicant’s PBPK model is inadequate to predict the DDI effects of CYP modulators on the PK of TCBZ and its active metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>) when Egaten is used concomitantly with CYP modulators due to the lack of verification of key input parameters, *f<sub>m</sub>cyp* (contribution of major CYP enzymes to metabolism) for TCBZ and its metabolites.

The submitted Egaten PBPK model is adequate to assess the risk of an effect of Egaten on the PK of some sensitive CYP substrates. When Egaten is co-administered with CYP substrates, the PBPK simulation suggested TCBZ could lead to a moderate increase in the exposure of a

CYP2C19 substrate (such as omeprazole); as well as mild to moderate increase (less than 2.5-fold) in the exposure of substrates of CYP1A2, 2C8, 2C9, 2D6 and 3A. The DDI assessment of Egaten's effect on the PK of a CYP2B6 substrate is inconclusive due to a concern about the CYP2B6 substrate (bupropion) model. As the proposed dosing regimen for Egaten (b) (4) or 20 mg/kg/day as two doses given 12 hours apart (FDA's proposal), the final dose recommendation for CYP substrate drugs co-administered with Egaten should be considered in the context of the short dosing duration of Egaten as well as the safety and efficacy margins of the co-administered CYP substrate drugs.

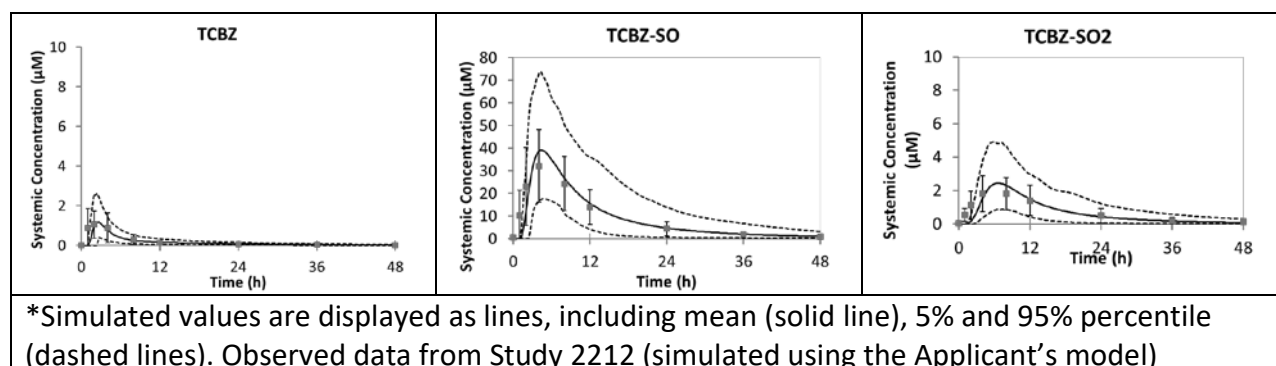
### **Evaluation of the PBPK model for DDI potential assessment of Egaten as a victim of CYP modulators**

In vitro study indicated that hepatic oxidative metabolism of TCBZ was mediated mainly by CYP1A2 to form its major metabolite TCBZ-SO (CGP023031) (DMPK R1600737). The relative contribution of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A to total clearance was estimated to be 64%, 8.9%, 0%, 10%, and 7.1%, respectively based on in-vitro inhibition results. TCBZ-SO was further metabolized by multiple CYP enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A) where the  $f_{mCYP2C9}$  value was estimated to be 84%. The Applicant proposed that TCBZ-SO<sub>2</sub> (CGA274204) was metabolized by CYP2C9 from TCBZ-SO based on ADMET™ predictor developed by GastroPlus. However, there was only a trace amount of TCBZ-SO<sub>2</sub> identified in oxidative metabolites of TCBZ-SO in in vitro study (DMPK 1700972). Figure 15-3 illustrates the elimination pathway of TCBZ proposed by the Applicant in the PBPK model.

**Figure 15-3. Proposed Metabolism Profiles of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> in the PBPK Model**

In vivo TCBZ is oxidized to TCBZ-SO, and further oxidized to the TCBZ-SO<sub>2</sub>. The TCBZ-SO (sulfoxide form) is predominant in plasma and AUCs of TCBZ and TCBZ-SO<sub>2</sub> are approximately 1% and 10% of that of the sulfoxide, respectively. The Applicant used Simcyp V15 to develop a full PBPK model with first order oral absorption to describe the PK of TCBZ. Fa (fraction absorbed) for TCBZ was estimated to be 0.65 based on reported absorption about 19.3 – 50% of the dose in cattle, sheep, rat and dog. Clearance for TCBZ was set to be 53 L/h based on observed human PK data. The steady-state volume of distribution (V<sub>ss</sub>) for TCBZ was predicted to be 7.6 L/kg using method 2 with a K<sub>p</sub> scalar value of 2.3 in Simcyp. The Applicant noted that the V<sub>ss</sub> value for TCBZ was similar to that observed in sheep following TCBZ treatment. The minimal PBPK model was selected for TCBZ-SO and TCBZ-SO<sub>2</sub>. No excretion studies were conducted in human. The Applicant assumed no renal clearance based on animal data. The submitted PBPK model was able to simultaneously describe the plasma-time profiles of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> after a single dose of 10 mg/kg TCBZ under fed condition (Figure 15-4Error! Reference source not found.).

**Figure 15-4. Observed and simulated mean concentration-time profile of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> after a single dose of 10 mg/kg under fed conditions.**



\*Simulated values are displayed as lines, including mean (solid line), 5% and 95% percentile (dashed lines). Observed data from Study 2212 (simulated using the Applicant's model)

**Table -15.20. Summary of observed and simulated PK of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> after a single dose of 10 mg/kg under fed conditions**

|                      | AUC(µM·hr)           |                      | P/O <sup>a</sup> | Cmax (µM)            |                      | P/O <sup>a</sup> | Tmax (hr)    |                    |
|----------------------|----------------------|----------------------|------------------|----------------------|----------------------|------------------|--------------|--------------------|
|                      | Observed             | simulated            |                  | Observed             | simulated            |                  | Observed     | simulated          |
| TCBZ                 | 6.41<br>(5.27, 9.27) | 6.56<br>(5.96, 7.21) | 1.02             | 1.24<br>(1.03, 1.84) | 1.23<br>(1.12, 1.34) | 0.99             | 4<br>(1, 8)  | 2.3<br>(1.3, 4.4)  |
| TCBZ-SO              | 390<br>(329, 505)    | 390<br>(358, 426)    | 1.00             | 35.9<br>(31.2, 44.3) | 37.5<br>(35.0, 40.2) | 1.04             | 4<br>(2, 8)  | 4.5<br>(2.8, 7.3)  |
| TCBZ-SO <sub>2</sub> | 28<br>(22.8, 42.9)   | 28<br>(25.4, 30.9)   | 1.00             | 2.03<br>(1.75, 2.73) | 2.31<br>(2.10, 2.54) | 1.14             | 4<br>(2, 12) | 6.9<br>(3.6, 14.1) |

<sup>a</sup>P/O Simulated/Observed ratio; Reference: Application's PBPK report Table 7-5

The Applicant then used TCBZ PBPK model to predict the effects of ciprofloxacin (a moderate CYP1A2 inhibitor) and fluvoxamine (a dual CYP1A2 and CYP2C9 inhibitor) on the PK of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> in virtual healthy subjects. The Applicant predicted approximately 1.4 and 2-fold increase in TCBZ exposure when it was co-administered with ciprofloxacin (50 mg QD for 20 days) and fluvoxamine (500 mg QD for 20 days) respectively (Table -15.21.).

**Table -15.21. Simulated geometric mean and ratios of AUC and Cmax for TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> after two doses of 10 mg/kg TCBZ in the absence or presence of ciprofloxacin and fluvoxamine**

|                     | TCBZ (parent)                          |                           | TCBZ-SO                                |                           | TCBZ-SO <sub>2</sub>                   |                           | Total active moiety <sup>c</sup>       |
|---------------------|----------------------------------------|---------------------------|----------------------------------------|---------------------------|----------------------------------------|---------------------------|----------------------------------------|
|                     | AUC<br>( $\mu\text{M}\cdot\text{hr}$ ) | Cmax<br>( $\mu\text{M}$ ) | AUC<br>( $\mu\text{M}\cdot\text{hr}$ ) | Cmax<br>( $\mu\text{M}$ ) | AUC<br>( $\mu\text{M}\cdot\text{hr}$ ) | Cmax<br>( $\mu\text{M}$ ) | AUC<br>( $\mu\text{M}\cdot\text{hr}$ ) |
| control             | 15.3                                   | 2.2                       | 817                                    | 65.2                      | 62                                     | 3.9                       | 894.3                                  |
| +Cipro <sup>a</sup> | 21.5                                   | 2.78                      | 825                                    | 2.78                      | 60.7                                   | 3.38                      | 907.2                                  |
| Ratio               | 1.41                                   | 1.29                      | 1.01                                   | 0.92                      | 0.98                                   | 0.87                      | 1.01                                   |
| +Fluv <sup>b</sup>  | 32.4                                   | 3.2                       | 865                                    | 51.9                      | 49.5                                   | 2.4                       | 946.9                                  |
| Ratio               | 2.12                                   | 1.48                      | 1.06                                   | 0.8                       | 0.8                                    | 0.63                      | 1.05                                   |

<sup>a</sup>Simcyp file SV-Ciprofloxacin\_Male was used. <sup>b</sup>Simcyp file SV- fluvoxamine was used.

<sup>c</sup>Reviewer derived AUC ratio of total active moieties (sum of molar normalized AUC of TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub>)

Reference: Applicant's PBPK report Table 7-8.

**Reviewer's Comments:** Applicant did not conduct in vitro studies to evaluate the transporter-mediated DDIs. In the PBPK model, a large portion of TCBZ-SO and TCBZ-SO<sub>2</sub> (62% and 70% respectively) (see Figure 15-3) metabolism was allocated to non-CYP-mediated 'other' pathways in vivo. This assumption is inconsistent with in-vitro results. As there are multiple oxidative metabolites of TCBZ-SO identified in-vitro, CYP enzymes might be involved in these 'other' pathways. Nevertheless, there was no in vivo study to confirm the assumption. Finally, as both TCBZ-SO and TCBZ-SO<sub>2</sub> are active metabolites, it is important to understand the relative potency of each moiety including TCBZ, and its metabolites TCBZ-SO and TCBZ-SO<sub>2</sub> against flukes for the treatment of Fascioliasis. Multiple information requests (IRs) were issued to communicate these concerns with the Applicant.

*On September 11, 2018*, FDA issued an IR requesting information and/or a plan to verify the fmcyp values of TCBZ and its metabolites in vivo. FDA also suggested the Applicant to conduct in vitro studies to assess potential for transporter-mediated DDIs. In the response, the Applicant stated the submitted in vitro and modeling results had suggested the DDI risk with modulators of these enzymes was low. The Applicant also had no plan to conduct any studies to evaluate the transporter-mediated DDI liability given the short treatment duration of TCBZ. The Applicant provided clinical information from the CIBA/WHO studies where efficacy data were available for 17 patients who used modulators of these enzymes (CYP1A2 and CYP2C9) and transporters (p-gp, BCRP, OATP1A1 and OATP1A3) as concomitant medications. 16 out of 17 patients were cured by Day 60. The Applicant concluded that the loss of efficacy of Egaten with the modulators (inhibitors and inducers) of CYP1A2 and CYP2C9 enzymes is unlikely.

*On September 24, 2018*, FDA issued an IR requesting information about the relative activity of TCBZ, TCBZ-SO, and TCBZ-SO<sub>2</sub> against flukes for the treatment of Fascioliasis. The Applicant reported that the order of potency of these compounds inhibiting fluke tubulin was TCBZ-SO > TCBZ-SO<sub>2</sub> >> TCBZ. The Applicant reported that TCBZ, TCBZ-SO and TCBZ-SO<sub>2</sub> resulted in about

5%, 75% and 35% inhibition of colchicine binding to fluke homogenates, respectively, at 10 µM based on literature data.

On September 25, 2018, FDA issued an IR to the Applicant requesting detailed information on how the elimination pathways of TCBZ were proposed in vivo. FDA also recommended the Applicant to conduct “worst-case” scenario simulations and link the exposure changes to anti-fluke activity in order to propose appropriate dosing recommendation for Egaten. The Applicant conducted additional DDI simulations with CYP1A2 or 2C9 inhibitors by increasing the TCBZ fmCYP1A2 value and fmCYP2C9 value for TCBZ-SO and TCBZ-SO<sub>2</sub>. However, the Applicant stated that they could not conclude the impacts of different fmcyp values on overall activity as the absolute or relative potency of the parent drug and metabolites has not been measured in vitro and the IC<sub>50</sub> values for the compounds have not been characterized.

Data suggested that TCBZ is generally well-tolerated. The review team had concerns on the potential loss of efficacy with co-administration with a CYP inducer. The Reviewer conducted a worst-case scenario simulation when TCBZ is co-administrated with rifampin which is a strong CYP3A4 and moderate CYP2C9 inducer. By using the original PBPK model submitted by the Applicant, the reviewer assigned ‘other’ pathways as CYP2C9-mediated pathways for TCBZ-SO and TCBZ-SO<sub>2</sub>. The Reviewer also included the induction of CYP1A2 in the default rifampin model in Simcyp. The CYP enzyme activities would increase 2.5, 3.5 and 6- fold for CYP 1A2, 2C9 and 3A4, respectively, following 600 mg rifampin once daily for 14 days using the modified rifampin PBPK model.

**Table -15.22. Simulated geometric mean AUC and Cmax ratio values of TCBZ and its metabolites in the absence and presence of rifampin**

| with Rifampin*   | TCBZ (parent) | TCBZ-SO | TCBZ-SO <sub>2</sub> |
|------------------|---------------|---------|----------------------|
| Cmax Ratio       | 0.31          | 0.82    | 0.91                 |
| AUC Ratio        | 0.22          | 0.37    | 0.39                 |
| Total Moiety AUC |               |         | 0.37                 |

\*Rifampin model from Simcyp library was modified to induce CYP1A2 pathway

The worst-case scenario simulation showed a significant reduction in the exposure of TCBZ and total active moieties (Table -15.22.). This information should be considered as supportive and can not be used to support dose recommendation alone. Major deficiencies were identified in the submitted PBPK models including lack of mass-balance study and clinical DDI study to verify the fmcyp values of TCBZ and its metabolites. The Reviewer concluded that the Applicant’s PBPK model is inadequate to support quantitative dosing recommendation when Egaten is co-administered with a CYP modulator.

**Evaluation of the PBPK model for DDI potential assessment of Egaten as a perpetrator of CYP substrates**

In vitro studies have shown that TCBZ and its metabolites can inhibit multiple CYP enzymes (DMPK R1700893) as showed in Table -15.23. The Applicant used the submitted PBPK model to

evaluate the effects of Egaten on the PK of multiple CYP substrates. Substrate models (theophylline (CYP1A2), bupropion (CYP2B6), repaglinide (CYP2C8), S-warfarin (CYP2C9), omeprazole (CYP2C19), desipramine (CYP2D6), midazolam (CYP3A)) from the Simcyp V15.1 drug model library were directly used. Table -15.24. summarized the simulated effects of Egaten on various CYP substrates when they were co-administrated with two doses of Egaten 10 mg/kg given 12-hour apart.

**Table -15.23. In-vitro Ki values for TCBZ and its metabolites**

|         | TCBZ Ki ( $\mu\text{M}$ ) | TCBZ-SO Ki ( $\mu\text{M}$ ) | TCBZ-SO <sub>2</sub> Ki ( $\mu\text{M}$ ) | Maximum R1 value* |
|---------|---------------------------|------------------------------|-------------------------------------------|-------------------|
| CYP1A2  | 0.016                     | 0.75                         | 12.50                                     | 3.6               |
| CYP2B6  | 0.018                     | 1.03                         | 1.27                                      | 3.8               |
| CYP2C8  | 0.053                     | 1.81                         | 0.37                                      | 1.5               |
| CYP2C9  | 0.061                     | 0.57                         | 0.22                                      | 1.7               |
| CYP2C19 | 0.009                     | 0.05                         | 2.77                                      | 8.7               |
| CYP2D6  | 0.166                     | 4.32                         | 13.00                                     | 1.3               |
| CYP3A   | 0.149                     | 2.31                         | 10.20                                     | 1.3               |

Source: Applicant's PBPK report tables 7-2, 7-3, and 7-4. \*Calculated as  $R1 = 1 + (I_{\text{max,u}} / K_i)$ ; where  $I_{\text{max,u}}$  is the maximal unbound plasma concentration of the interacting compound (TCBZ, TCBZ-SO or TCBZ-SO<sub>2</sub>)<sup>4</sup>. R1 cut-off value is 1.02

**Table -15.24. Simulated effects of Egaten on the PK of various CYP substrates when they are co-administrated with Egaten (two doses of 10 mg/kg)**

| Target Pathway | Substrate    | Dosing regimen of the substrate | f <sub>m</sub> cyp <sup>a,b</sup> | C <sub>max</sub> ratio <sup>c</sup> | AUC ratio <sup>c</sup> |
|----------------|--------------|---------------------------------|-----------------------------------|-------------------------------------|------------------------|
| CYP1A2         | theophylline | 125 mg single dose              | 0.75                              | 1.0                                 | 1.5                    |
| CYP2B6         | bupropion    | 150 mg single dose              | 0.46                              | 1.2                                 | 1.3                    |
| CYP2C8         | repaglinide  | 0.25 mg single dose             | 0.62                              | 1.0                                 | 1.2                    |
| CYP2C9         | S-warfarin   | 10 mg single dose               | 0.99                              | 1.0                                 | 1.4                    |
| CYP2C19        | omeprazole   | 20 mg single dose               | 0.79                              | 2.2                                 | 3.6                    |
| CYP2D6         | desipramine  | 50 mg single dose               | 0.96                              | 1.1                                 | 1.1                    |
| CYP3A          | midazolam    | 5 mg single dose                | 0.84                              | 1.0                                 | 1.2                    |

Reference. Applicant's PBPK report table 3-2 and 7-1. <sup>a</sup> f<sub>m</sub>cyp value of the target pathway for the substrate; <sup>b</sup> Extracted from the reference documents available from Software developer's website; <sup>c</sup>Geometric mean

### Reviewer's Comments

The submitted PBPK models is adequate to predict the risk of an effect of Egaten on the PK of a sensitive CYP substrate as the PBPK model reasonably described the plasma concentration-time profile of TCBZ and its metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>) as showed in Table -15.23. and Table -15.24. However, since there is no information on whether TCBZ or its metabolites is a

<sup>4</sup> FDA's in vitro DDI draft guidance (<https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf>)

substrate of hepatic uptake transporters (such as OATP1B1), the possibility of higher liver concentration, subsequently, more potent inhibition of TCBZ and/or its metabolites on the CYP substrates can not be ruled out. The Reviewer conducted a sensitivity analysis on CYP1A2 Ki values to evaluate the effects of Egaten on theophylline (CYP1A2 substrate) (Table -15.25.). One twentieth of measured in vitro Ki values were used to account for uncertainty associated with the liver concentration and in vitro Ki values. The AUC ratio of theophylline increased from 1.48 to 2.18 when the Ki was reduced by 20-fold.

**Table -15.25. Simulated effects of TCBZ and its metabolites on PK of theophylline**

| CYP1A2                  | TCBZ Ki = 0.016 $\mu$ M; TCBZ-SO Ki = 0.75 $\mu$ M; TCBZ-SO <sub>2</sub> Ki = 12.5 $\mu$ M (original) | Set new Ki values as original Ki/2 | Set new Ki values as original Ki/20 |
|-------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------|-------------------------------------|
|                         | Predicted GM                                                                                          | Predicted GM                       | Predicted GM                        |
| Theophylline Cmax Ratio | 1.02                                                                                                  | 1.02                               | 1.02                                |
| Theophylline AUC Ratio  | 1.48                                                                                                  | 1.63                               | 2.18                                |

In addition to the acceptability of Egaten PBPK model as a CYP perpetrator, the Reviewer had concerns whether some of the substrate models were appropriate. For example, for the bupropion PBPK model, the software developer has noted there is a discrepancy between in vivo DDI dataset and the emerging in vitro metabolic data. Given uncertainty in fmCYP2B6 value in the bupropion PBPK model, the simulated DDI results could be inconclusive. Thus, the reviewer concluded that the DDI assessment of Egaten's effects on PK of a CYP2B6 substrate was inadequate.

PBPK simulations suggested TCBZ and its metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>) could moderately increase the PK of sensitive CYP2C19 substrates. PBPK simulations also suggested that TCBZ may have mild to moderate (less than 2.5-fold) effects on PK of substrates of CYP1A2, 2C8, 2C9, 2D6 and 3A. The needs to conduct in vivo DDI studies to assess the inhibitory effects of Egaten on these CYP enzymes-mediated pathways should be evaluated considering the safety margins of the substrate drugs and the short treatment duration of Egaten.

## 15.4. Clinical Microbiology

### 15.4.1. Summary of in vitro studies

Summary of in vitro studies supporting the activity of TCBZ and/or its metabolites against the immature (juvenile) worms (Table 15.26), adult worms (Table 15.26) and/or eggs (Table 15.27) of *F. hepatica* and/or *F. gigantica*.

**Table 15.26:** In vitro activity of TCBZ and/or its metabolites against the immature/mature worms of *F. hepatica* and *F. gigantica*.

| <i>Fasciola</i> species – not specified (Reference)                                                           | Study Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <b>Motility - Juvenile and Adult Worms</b>                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <i>F. hepatica</i> – not specified (Coles, 1986)                                                              | AWs (> 12-week-old) were incubated for 24 hrs with TCBZ at a concentration of 2.5 µg/mL. The motility of the worms was inhibited under the experimental conditions tested.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <i>F. hepatica</i> – not specified (Kohler, 1987)                                                             | TCBZ at a concentration of 10-25 µM i.e., 3.6 – 9.0 µg/mL inhibits motility of juvenile and AWs within 24-48 hr of incubation and changes the resting tegument membrane potential.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <i>F. hepatica</i> – not specified (Bennett and Kohler, 1987)                                                 | <p>Juvenile (3-week old) and mature adult (15-week old) worms were incubated at 37°C with TCBZ and/or TCBZ-SO. Within 8 hours of incubation, 10 µM of TCBZ (3.6 µg/mL) was more effective than TCBZ-SO (3.8 µg/mL), in inhibiting motility of the immature worms; however, at 24 hours, TCBZ-SO was more active than the parent drug. This may be due to a more rapid penetration of TCBZ into the parasite compared to TCBZ-SO; however, the activity increased as the metabolite accumulated within the parasite.</p> <p>Similar observations were reported in another experiment; the experimental design was similar to that summarized above except that only TCBZ was tested at 0, 3, 10 and 25 µM concentrations against juvenile and adult worms. The results show juvenile worms to be more sensitive to the drug than adults; exposure of juvenile worms for 24 hrs to 10 µM of TCBZ (3.6 µg/mL) resulted in a complete immobilization. For adult worms, however, such an effect was observed at a 2.5-fold higher concentration of TCBZ.</p> <p>Activity of TCBZ was reduced in the presence of BSA (35 mg/mL).</p> |
| <i>F. hepatica</i> – Pacific Northwest wild strain (Duthaler <i>et al.</i> , 2010)                            | The effect of TCBZ (15 µg/mL), TCBZ-SO (30 µg/mL), and TCBZ-SO <sub>2</sub> (30 µg/mL) was measured on adult and juvenile worms obtained from rats infected for >8 weeks and 3-4 weeks, respectively. Survival of the adult and juvenile stages of the parasite was measured up to 72 hrs of incubation <i>in vitro</i> with TCBZ and the metabolites. TCBZ was more active against juvenile worms than the AWs. Incubation of AWs with the TCBZ-SO and TCBZ-SO <sub>2</sub> metabolites resulted in decreased movement and the death of 50 to 67% of the AWs by 48 hrs. Both TCBZ-SO and TCBZ-SO <sub>2</sub> reduced the viability of the adult flukes; however, the juvenile worms showed reduced <i>in vitro</i> sensitivity to the TCBZ metabolites compared to AWs.                                                                                                                                                                                                                                                                                                                                                      |
| <i>F. hepatica</i> - TCBZ sensitive (Cullompton) and resistant (Oberon) strains (Meaney <i>et al.</i> , 2013) | AWs were incubated with and without TCBZ-SO (15 and 50 µg/mL) for different time periods, depending on the particular experiment, but no experiment was allowed to go beyond 24 hrs. The AWs were observed for motility at an hourly interval under a light microscope. When all worms ceased to move, that time was taken as the time to inactivity. The results show TCBZ-SO at a concentration of 15 µg/mL had no effect on worm motility of either of the strains. However, at the higher concentration of 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| <b>Fasciola species – not specified (Reference)</b>                                                                                      | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|                                                                                                                                          | µg/mL, the Cullompton strain was more sensitive than the Oberon strain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Morphology/Ultrastructure - Juvenile and Adult Worms</b>                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>F. hepatica – not specified</b><br><br>(Stitt and Fairweather, 1993)                                                                  | Incubation of juvenile worms and AWs with TCBZ-SO (20 or 50 µg/mL) for up to 18 hrs and 24 hrs, respectively, was associated with ultrastructural changes as measured by SEM; the ultrastructural changes progressed over time and include swelling of the tegument, spine loss at the oral cone, exposure of the basal lamina, and deep furrows especially on the ventral surface.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>F. hepatica – not specified</b><br><br>(Stitt and Fairweather, 1994)                                                                  | Juvenile worms were incubated with TCBZ-SO (20 µg/mL) for up to 18 hrs whereas AWs were incubated with 15 or 50 µg/mL of TCBZ-SO 24 hrs. Ultrastructural changes were measured by TEM; the results show that the ultrastructural changes progressed over time. and include progressive convolution at the apex, severe vacuolation at the basal regions, accumulation of T1 or T2 secretory bodies in the tegumental cells, abnormal tegument with accumulation of secretory bodies towards the base of the syncytium; the tegument was completely sloughed away and the tegumental cells became synthetically inactive after longer incubation times.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>F. hepatica – Drug sensitive (obtained from (b) (4); name not specified) and resistant (Sligo)</b><br>(Robinson <i>et al.</i> , 2002) | Worms of TCBZ-sensitive and -resistant strains were incubated with TCBZ-SO (50 µg/ml) for 24 hrs at 37°C and processed for SEM, TEM and immuno-cytochemistry. Extensive damage was reported for TCBZ-sensitive strain whereas resistant strain showed only localized and relatively minor disruption of the tegument covering the spines. Also, disruption of the tubulin organization in the tegument of TCBZ-sensitive worms was reported but not in the TCBZ-resistant strain of <i>F. hepatica</i> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>F. gigantica – obtained from buffaloes in India</b><br>(Meaney <i>et al.</i> , 2002)                                                  | AWs, recovered from the bile duct of buffalo in the Peramber slaughterhouse in Chennai, India, were incubated with TCBZ-SO (10 µg/mL) at 37°C for up to 24 hours. Worms were processed for SEM. The results show that morphological changes observed at 6 hrs increased in severity over time by 24 hours; the ventral surface was more severely disrupted than the dorsal and the tail region of the worms more disrupted than the anterior.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>F. hepatica - Cullompton</b><br>(Halferty <i>et al.</i> , 2009)                                                                       | <p>The AWs were incubated with 15 µg/mL of either TCBZ or its metabolites for 24 hrs, fixed and processed for SEM and TEM; the worms were active prior to fixation. The TCBZ exposed AW were most active but had little gut contents; the TCBZ-SO<sub>2</sub> exposed worms had little or no gut contents, were paler, and showed a low level of activity; the TCBZ-SO treated AWs had no gut contents, were very pale and only very minor movement was observed. TCBZ-SO appears to be most active and TCBZ least active against AWs i.e., the activity would be TCBZ-SO&gt;TCBZ-SO<sub>2</sub>&gt;TCBZ.</p> <p>The morphological changes include alteration in the surface (swelling and blebbing) of the worms; TCBZ-SO<sub>2</sub> was more disruptive anteriorly and TCBZ-SO posteriorly.</p> <p>The ultrastructural changes reported by SEM and TEM include swelling of the basal infolds and mitochondria in the tegumental syncytium as well as a reduction in the number of secretory bodies, disruption of the Golgi complexes and swelling of the mitochondria in the tegumental cell bodies. Also, the internal tissues were flooded with TCBZ-SO<sub>2</sub> and, to a lesser extent, with TCBZ-SO and TCBZ. Overall, the study suggests that TCBZ as well as its metabolites (TCBZ-SO and TCBZ-SO<sub>2</sub>) are active against the AWs. There were some regional differences in changes against the anterior vs posterior region of the two metabolites. The type and severity of changes induced by TCBZ and its metabolites varied depending on the parameter measured. For example, for</p> <ul style="list-style-type: none"> <li>• motility – TCBZ-SO&gt;TCBZ-SO<sub>2</sub>&gt;TCBZ.</li> <li>• morphology (swelling and blebbing): TCBZ-SO<sub>2</sub> was more disruptive anteriorly</li> </ul> |

| <b><i>Fasciola</i> species – not specified (Reference)</b>                                                                  | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                             | and TCBZ-SO posteriorly. <ul style="list-style-type: none"> <li>• overall ultra-structural changes: TCBZ-SO<sub>2</sub> &gt; TCBZ-SO &gt; TCBZ.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b><i>F. hepatica</i> – Cullompton (drug sensitive) and Oberon (drug resistant) strain</b><br>(Devine <i>et al.</i> , 2010) | AWs were incubated with 13.3 µg/mL of TCBZ and TCBZ-SO for 24 hrs at 37°C and processed for SEM after fixation. The surface changes observed for the Cullompton strain were similar to those reported by Halferty <i>et al.</i> , 2009 (summarized above). For the AWs of Oberon strain, incubated with TCBZ and TCBZ-SO, there was no change in morphology in the apical cone region, but some swelling and/or disruption were observed in the interspinal tegument and/or tail region. Overall, there was greater disruption of the worms of TCBZ-sensitive strain than the TCBZ-resistant strain in the presence of TCBZ or TCBZ.SO.<br><br>Pre-exposure of AWs to ketoconazole for 2 hrs followed by co-incubation with ketoconazole + TCBZ or TCBZ-SO lead to more severe changes of the resistant strain. However, there was limited potentiation of the action of TCBZ-SO in combination with KTZ, for the sensitive strain.                                                                                       |
| <b><i>F. hepatica</i> - TCBZ sensitive (Cullompton) and resistant (Oberon) strains</b><br>(Meaney <i>et al.</i> , 2013)     | The effect on morphology was evaluated by SEM after incubation of AWs in the presence and absence of TCBZ (15 or 50 µg/mL) and/or PgP inhibitor, R(+) verapamil (VPL; 10 <sup>-4</sup> M), known to inhibit PgP mediated drug efflux. Worms were incubated with VPL for 24 hrs.<br><br>AWs were incubated for different time periods up to 24 hrs, depending on the particular experiment. AWs were incubated with and without TCBZ-SO and observed for motility at an hourly interval under a light microscope. When all flukes had ceased to move, that time was taken as the time to inactivity, and the experiment was stopped at that point. The flukes were recovered and processed for SEM. The results show that TCBZ-SO at a concentration of 15 µg/mL or VPL alone did not alter the motility of the worms of either the Cullompton or the Oberon strains up to 24 hrs; however, at a higher concentration of 50 µg/mL, the worms of Cullompton and Oberon strains were inactive at 9 and 15 hrs, respectively. |
| <b><i>F. gigantica</i> – not specified</b><br>(Shalaby <i>et al.</i> , 2009)                                                | The AWs were incubated with 10 or 20 µg/mL TCBZ-SO for 24 hrs at 37°C and processed for SEM. The results show alteration in the surface architecture of the tegument that include eruption, swelling or sloughing; the effect was more pronounced at a concentration of 20 µg/mL compared to 10 µg/mL of TCBZ-SO.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| SEM=scanning electron microscopy; TEM=transmission electron microscopy; hrs=hours; AWs=adult worms                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

**Table 15.27: In vitro effect of TCBZ and/or its metabolites on egg hatching of *F. hepatica*.**

| <b><i>Fasciola</i> strain<br/>(Reference)</b>                                                                                                                                                                                             | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Not specified</b><br>Fetterer (1986)                                                                                                                                                                                                   | TCBZ was not effective at concentration of $\leq 10$ $\mu\text{M}$ i.e., 3.6 $\mu\text{g}/\text{mL}$ in preventing embryonation of fluke eggs. Higher concentrations were not tested.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>• <b>TCBZ sensitive:</b><br/><b>Cullompton</b></li> <li>• <b>TCBZ resistant:</b><br/><b>Sligo</b></li> </ul><br>(Alvarez <i>et al.</i> , 2009)                                                     | Eggs were washed and incubated with and without different concentrations (5, 10 or 20 nM/mL of TCBZ (1.8, 3.6, or 7.2 $\mu\text{g}/\text{mL}$ ) or TCBZ-SO (1.9, 3.8 or 7.5 $\mu\text{g}/\text{mL}$ ) for 12 hrs or 15 days at 25°C. The eggs were washed and exposed to daylight for an hour and fixed in formalin to stop egg-hatching. The proportion of hatched and unhatched eggs was evaluated using an optical microscope. The mean egg hatch percentage in control cultures (based on testing in different experiments) ranged between 45.2 and 79.8% (TCBZ sensitive strain) and from 39.4 to 50.2% (TCBZ resistant strain). There was no significant reduction in the presence of either of the concentrations of TCBZ or TCBZ-SO for 12 hr. Albendazole, however, was effective in decreasing egg hatching. Incubation of the eggs with 5 nM/mL of drugs for 15 days was also not effective in decreasing egg hatching of both the drug sensitive and resistant isolates.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <ul style="list-style-type: none"> <li>• <b>TCBZ sensitive:</b><br/><b>Cullompton, Fairhurst,<br/>Leon, and Patagonia.</b></li> <li>• <b>Drug resistant:</b><br/><b>Dutch and Oberon</b></li> </ul><br>(Fairweather <i>et al.</i> , 2012) | <p>Eggs of the different drug sensitive and resistant strains were incubated with TCBZ-SO for 14 days at 25°C and exposed to light for 1–2 hrs to stimulate hatching. The number of eggs at each stage of development were recorded using a tally chart. The multidishes were placed back into the incubator, then exposed again to light over the succeeding 2 days to allow hatching of any eggs with the potential to do so. The overall count for the different stages was used for the final tally of results. The development and hatching of fluke eggs was divided into 6 distinct stages, namely, dead, empty, unembryonated, cell division, eye spot and hatched.</p> <p>Different concentrations of TCBZ-SO (1-100 <math>\mu\text{g}/\text{mL}</math>) were tested using Cullompton strain; repeat testing showed that concentrations of 56, 58, and 60 <math>\mu\text{g}/\text{mL}</math> were shown to yield hatch rates of 3%, 2%, and 1%, respectively; &gt;70% of the egg were dead; 60 <math>\mu\text{g}/\text{mL}</math> concentration was used for testing all strains. The results show that the hatch rate of the eggs of TCBZ sensitive strains (Fairhurst, Leon, and Patagonia strains) was similar to that of Cullompton strain whereas the hatch rate was lower for the TCBZ resistant strains [Oberon (11%) and Dutch (18%)]. There were some differences in the developmental stage affected. The hatch rate in the control cultures of different strains varied between 48-90%.</p> |
| SEM=scanning electron microscopy; TEM=transmission electron microscopy; hrs=hours                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

### 15.4.2. Summary of in vivo studies (animal models)

Summary of studies supporting the activity of TCBZ and/or its metabolites in animals experimentally (Table 15.28) and naturally (Table 15.29) infected with *F. hepatica* or *F. gigantica*.

**Table 15.28: In vivo activity of TCBZ in animals experimentally infected *F. hepatica* or *F. gigantica*.**

| <i>Fasciola</i> species<br>(Reference)                 | Study Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Rats</b>                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <i>F. hepatica</i><br>(Coles, 1986)                    | TCBZ was administered by gavage and the activity determined against mature worms by comparing number of worms in treated and control animals. TCBZ, at a single dose of 40 mg/kg or 100 ppm in diet for 7 days, was effective in killing AWs. Complete details of the experimental design such as the number of metacercariae used for infection, route of infection, time of initiation of treatment PI, and the time post-treatment when the worm burden was measured were not included.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Guinea pigs</b>                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <i>F. gigantica</i><br>(El-Boshy <i>et al.</i> , 2015) | Guinea pigs infected orally, by a stomach tube, with 20 metacercariae of <i>F. gigantica</i> were treated with 36 mg/kg TCBZ at Week 8 PI. Fecal samples were collected at the end of the 8th week PI and examined for the presence of eggs, in fecal specimens by the sedimentation method, as well as liver function. The results of the effect of treatment on egg count were not shown. The liver function was restored within 2 weeks of treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Sheep</b>                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <i>F. hepatica</i><br>(Boray <i>et al.</i> , 1983)     | <p>Animals were infected intra-luminally with 200 metacercariae and treated intra-luminally with different doses (2.5 – 15 mg/kg) of TCBZ at different time interval (Day 1; Weeks 1, 2, 4, 6, 8, or 12) PI. Animals were followed for body weights, laboratory parameters and parasite burden; for parasite burden, animals were euthanized at Week 14 PI and the worms in the liver, bile ducts and gall bladder counted. The results show that TCBZ decreased the recovery of worms; such an effect was dose-dependent. Overall, the study suggests that TCBZ is effective against both juvenile and AWs; at a dose of 12.5 and 15 mg/kg, TCBZ is effective as early as 24 hrs PI.</p> <p>In another experiment, the effect of treatment with 7.5 mg/kg TCBZ, at Week 4 PI by different routes (intra-abomasal, intra-ruminal or oral routes) was evaluated; otherwise, the experimental design was same as summarized above. The results show TCBZ was effective in reducing worm burden irrespective of the route of administration.</p> <p>In another experiment, animals were infected with a higher number of metacercariae (500 or 600-900) and treated with 10 mg/kg TCBZ at Week 1, 2, or 8 PI. The results show similar activity against immature and mature worms.</p> |
| <i>F. hepatica</i><br>(Eckert <i>et al.</i> , 1984)    | <p>Sheep were infected, orally, with 150 metacercariae and treated with TCBZ at Week 4 or 13 PI. The results show clearance of eggs in fecal specimens at Week 15 PI. At the time of slaughter, liver and/or gall bladder was collected and processed for parasite examination. A single dose of 10 mg/kg TCBZ was effective against 4- and 13-week old worms; no eggs were detected in fecal specimens.</p> <p>In another experiment, low doses (0.5, 1.0 or 2.0 mg/kg) of TCBZ administered over 5 or 10 days to sheep at the end of pre-patent period were effective in inhibiting egg excretion.</p> <p>The worms recovered from liver of treated animals were shorter in length compared to untreated animals. The control animals in both experiments contained large quantities of <i>Fasciola</i> eggs in</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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| <b><i>Fasciola</i> species<br/>(Reference)</b>            | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                           | the gall-bladder; in vitro most of the eggs were stated to be capable of development. A large number of eggs (3400) were isolated from only one of the treated groups (0.5 mg/kg for 5 days). These and a few eggs from the other animals were not capable of development ex vivo.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <i>F. hepatica</i><br>(Büscher <i>et al.</i> , 1999)      | <p>Sheep were infected with 100-200 metacercariae and treated with 10 mg/kg of TCBZ, at different time intervals post-infection (Days 3, 7, 14, 21, 28, 35, or 42). Worms were counted in bile duct and liver at Weeks 8-17. A group of animals were treated with either TCBZ-SO or TCBZ-SO<sub>2</sub> at Week 28 post-exposure and the number of worms counted as summarized above.</p> <p>The results show TCBZ was effective in reducing the worm burden by &gt;90% irrespective of the time of administration. The activity of TCBZ-SO was similar to TCBZ when administered on Day 28; TCBZ-SO<sub>2</sub> was, however, less effective (41% worm reduction).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <i>F. hepatica</i><br>(Halferty <i>et al.</i> , 2008)     | <p>Sheep were infected orally with 200 metacercariae of TCBZ sensitive strain (Cullompton) and treated orally with TCBZ 10 mg/kg at Week 4 PI. Animals were euthanized at Days 2, 3, or 4 post-treatment and immature worms were collected from liver and processed for SEM. The results show that worms collected from untreated animals as well as those treated at 48 hrs post-treatment were active and had full gut content. Also, there was some blebbing and sloughing of the tegument around the oral sucker. However, worms from animals euthanized at Day 3 post-treatment were dead; one worm was stated to be less active with sparse gut content. Worms recovered on Day 4 post-treatment were all dead; they were elongated with no gut content; by SEM more severe disruptive changes were reported that include absence of tegument with deep lesions and internal tissues exposed. Overall, there was a progressive increase in the level of disruption over the 72-hr time period. The ventral surface was more severely affected than the dorsal surface and the disruption was greater in the posterior region of the worm and along the lateral margins.</p> |
| <b>Cattle/Bufferaloes</b>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <i>F. gigantica</i><br>(Hyman <i>et al.</i> , 1984)       | <p>Cattles were infected orally with 250 metacercariae of <i>F. gigantica</i> and treated with 12 mg/kg of TCBZ at Weeks 2, 4, and 8 PI. Another group of animals were treated with 6 mg/kg at Week 8 or 14 PI. At Week 16 PI, the animals were slaughtered and tissues (gall bladder, liver/bile duct) processed for determining worm count. TCBZ was more effective in reducing worm burden when administered at Weeks 8 or 14 weeks PI compared to Week 2 or 4 PI.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <i>F. gigantica</i><br>(Estuningsih <i>et al.</i> , 1990) | <p>Bufferaloes were infected orally with 950 metacercariae and treated with TCBZ at Weeks 2, 6, and 10 PI; the animals were slaughtered at Week 13. The results show a reduction in worm burden in treated animals compared to untreated controls; however, the difference was not statistically significant. A majority of the worms recovered were immature and eggs were detected in fecal specimens prior to the normal prepatent period of 13 to 16 weeks. The animals were not shedding eggs at the time of initiation of the study; however, a possibility of prior infection that was in the pre-patent phase cannot be ruled out.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <i>F. gigantica</i><br>(Sanyal and Gupta, 1996)           | <p>Bufferaloes, in Gujarat, India, were screened for the presence of eggs daily for 10 days to ensure absence of <i>Fasciola</i> infection. The animals were infected with 400 metacercariae and treated at Week 2 or 10 PI with TCBZ at doses of 12 mg/kg, 24 mg/kg, or 36 mg/kg by the intra-luminal route. Eggs in fecal samples were quantitated two times a week until Week 14. Animals were euthanized and liver, bile ducts, and gall bladder processed for enumeration of AWs. No worms were detected in the animals treated with 24 or 36 mg/kg. The lower dose of 12 mg/kg was ineffective.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <i>F. hepatica</i><br>(Brockwell <i>et al.</i> , 2013)    | <p>Cattle (yearling Angus X Wagyu steers) were pre-screened for egg excretion in fecal specimens, as well as coproantigen and serum antibodies by ELISAs; 12 animals were found to be negative and treated for other parasitic infections. On Day 0, animals were infected by oral route with either 100 (n=4), 200 (n=4) or 500 (n=4) metacercariae of a TCBZ-sensitive strain (Sunny Corner); on Day 84 PI, two animals per group were treated orally with TCBZ (2.5 mL/25 g of 120 g/L formulation) and two were left untreated. Blood and fecal samples were collected at weekly interval between Days 28 and 112 PI for parasitological observations that include presence of eggs in fecal samples</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| <b><i>Fasciola</i> species<br/>(Reference)</b>                                         | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                        | <p>by the sedimentation method, serum antibodies (IgG) by ELISA, and coproantigens in supernatants of fecal specimens by ELISA, collected at each of the time point. Animals were slaughtered on Day 126 and worms counted in the gall bladder, bile duct and liver. Also, a fecal specimen was collected on Day 125 as well.</p> <p>Eggs were detected in one animal (infected with 500 metacercariae on Day 49. Eggs were detected in all animals at the time of treatment. There was variability in egg shedding (2 to 4-fold) in fecal samples and was higher in animals infected with 500 metacercariae compared to other groups. No eggs were detected in any of the treated animals within a week of TCBZ treatment.</p> <p>Coproantigen was detected on Day 42 PI in 3 animals (1 infected with 200 metacercariae and 2 infected with 500 metacercariae). All 12 animals were coproantigen positive on Day 56 PI and remained positive until the day of treatment i.e., Day 84. There was variability in antigen levels (2- to 6-fold). All animals became antigen negative within a week and remained negative. Untreated animals remained antigen positive. In animals with higher burdens coproantigen positives preceded fecal egg excretion.</p> <p>Majority of the animals (11 of 12) were antibody positive on Day 28 i.e., prior to becoming coproantigen positive.</p> <p>No eggs, coproantigens (OD &lt;0.014) and worms were detected at the time of slaughter, in all treated animals; all untreated animals remained egg, antigen, and worm positive. However, all animals, treated or untreated, remained serum antibody positive. There was a correlation between egg excretion and coproantigen levels as well as coproantigen and worm burden.</p> |
| <p>PI=post-infection; hrs=hours; AW=adult worms; SEM=scanning electron microscopy.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

**Table 15.29: In vivo activity of TCBZ against *F. hepatica* and/or *F. gigantica* in naturally infected livestock animals.**

| <b><i>Fasciola</i> species<br/>(Reference)</b>          | <b>Study Summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>F. hepatica</i><br>(Eckert <i>et al.</i> , 1984)     | <p>The naturally infected <b>sheep, goat, cows, and fallow deers</b> were treated with TCBZ (5, 6, 10, or 12 mg/kg) and egg excretion measured at Weeks 4, 6, and 8/9 post-treatment. The results show a reduction in egg excretion (99-100%) as well as the number of sheep excreting eggs (83-100%).</p> <p>Frequent treatment of sheep with 5 mg/kg TCBZ, every 5-8 weeks was effective in reducing egg excretion; 1-2 immature and mature worms were reported in 4 of the 6 sheep that were slaughtered at Week 10 of the last dose; this could be due to re-infection. During the control program there was no report of deaths due to fascioliasis that were observed in previous years. Both older animals and lambs developed normally.</p>                                                                                                                                                       |
| <i>F. hepatica</i><br>(Boray <i>et al.</i> , 1985)      | <p>Animals living on a farm, in New Zealand, that include Coopworths <b>sheep</b> (lambs, ewes, and rams), <b>cows</b> and <b>horses</b>, known to be infected, with <i>F. hepatica</i> were treated with 10 mg/kg TCBZ. The lambs had been treated with mebendazole 8 weeks and with levamisole 4 weeks prior to TCBZ administration. The adult sheep had been treated with a broad-spectrum anthelmintic against nematodes and with rafoxanide, 12 and 8 months, respectively, prior to the TCBZ treatment. The results show fecal egg clearance at Month 14 post-treatment that was associated with a reduction in pasture contamination to a negligible level. A reduction in pasture contamination was based on survey of snails present on the farm, for the presence of larvae to determine infectivity and comparing with snails on neighboring property where no treatment was administered.</p> |
| <i>F. hepatica</i><br>(Stansfield <i>et al.</i> , 1987) | <p><b>Sheep</b> and <b>cattle</b> living on severely affected farms (30-40 animals per farm; 2 sheep farms and 2 cattle farms) were treated with 10 mg/kg or 12 mg/kg TCBZ, respectively. <i>F. hepatica</i> eggs were examined by a flotation method based on saturated zinc sulfate solution prior to treatment. The infection level at both sheep farms was high and worms of all age groups were observed at post-mortem. The results show a rapid reduction in egg count at Weeks 2, 3, 4, 6, and 8 post-treatment of animals on all the farms. Recurrence of eggs in fecal specimens was reported in sheep but not in cattle at Week 10. Overall, the study suggests TCBZ is effective against early immature, immature and mature worms in sheep and cattle.</p>                                                                                                                                   |
| <i>F. gigantica</i><br>(Suhardono <i>et al.</i> , 1991) | <p>Indonesian <b>cattle</b> infected with <i>F. gigantica</i> were treated with 12 mg/kg TCBZ every 8 weeks for 1 year. The authors state that a decrease in egg count, almost to zero, was observed at all time points including after the first treatment. However, the time fecal specimens were examined for the presence of eggs was not specified.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <i>F. gigantica</i><br>(Waruira <i>et al.</i> , 1994)   | <p>Naturally infected <b>cattle</b> living in 2 farms in Kenya were treated with a single dose of 12 mg/kg TCBZ. Fecal samples were collected prior to treatment and every 2 weeks post-treatment for up to Day 56 for egg count by the zinc sulfate flotation concentration technique. The results show TCBZ was effective in reducing egg count of animals, in both farms, by &gt; 90% at Days 14 and 28. However the egg count increased on Days 42 and 56. It is unclear if this is due to resistance or re-infection.</p>                                                                                                                                                                                                                                                                                                                                                                            |
| <p>PI=post-infection; hrs=hours; AW=adult worms</p>     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

### 15.4.3. Parasitological assessments in clinical trials

The parasitological methods used in the clinical studies for patient enrollment and post-treatment follow-up are summarized in Table 15.30.

**Table 15.30: Summary of parasitological assessments used in the clinical studies for patient enrollment and post-treatment follow-up.**

| Study ID<br>(Endemic area –<br><i>Fasciola</i> species)                                                                                                                                                                                                              | Parameter                                                                                                             | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Acute fascioliasis</b>                                                                                                                                                                                                                                            |                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Hien <i>et al.</i> , 2008:<br>ISRCTN<br>75869075<br><br>(Vietnam – <i>F.</i><br><i>gigantica</i> or<br>hybrid)*                                                                                                                                                      | <b>Fecal smears</b>                                                                                                   | Not done as the eggs are not shed during the acute phase.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                      | <b>Serology:</b><br>Anti- <i>Fasciola</i><br>specific antibodies<br>by ELISA using<br>purified protein as<br>antigen. | Prior to patient enrollment and at the time of discharge from the hospital on Day 10.<br><br>No change in serum antibody titers at Day 10.<br><br>Testing performed at the [REDACTED] (b) (4)<br><br>Details of the method and performance of the serological assay not available for review.                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                      | <b>Other parameters</b>                                                                                               | Symptomatic subjects with parenchymal liver lesions consistent with acute fascioliasis by ultrasound, abdominal pain, and eosinophil counts were enrolled.<br><br><i>Primary endpoint</i> - abdominal pain.<br><br><i>Secondary endpoints</i> - based on complete response that include resolution of all symptoms, normalization of eosinophil count, and improvement in ultrasound appearances.                                                                                                                                                                                                                                                                                                                     |
| <b>Chronic fascioliasis</b>                                                                                                                                                                                                                                          |                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Maco <i>et al.</i> ,<br>2015: EGA230B<br><br>(Peru – <i>F.</i><br><i>hepatica</i> : Study<br>conducted in 5<br>rural parts:<br>Asillo, Lachaqui,<br>Anta, Sicuani<br>and Jauja)*<br>Fasinex<br>treatment at one<br>of the site in<br>Asillo. Egaten<br>used at other | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• RST</li> </ul>                     | <i>Primary endpoint:</i> Presence (parasitological failure) or absence (parasitological cure) of eggs by the RST or KK methods at Day 60. Testing performed on 2 specimens, collected on 2 consecutive days, at baseline and at different time points post-treatment Days 1, 3, 5, 10, 30 and 60 in Asillo and Days 30, 60, 90, 120, 150, and 180 at 4 other sites.<br><br>Quantitative egg count, to determine egg reduction rate, was performed on specimens from Asillo site only.<br><br>Slides examined by an experienced technician using RST for qualitative diagnosis in a central laboratory - [REDACTED] (b) (4)<br><br>[REDACTED]<br><br>Details of the method and QC parameters implemented not included. |

| Study ID<br>(Endemic area –<br><i>Fasciola</i> species)                                          | Parameter                                                                                                                                                                                        | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| sites.                                                                                           | <b>Serology:</b><br>Antibodies against 25KDa excretory/secretory antigen, Fas2, by ELISA.                                                                                                        | Conducted on subjects prior to enrollment. An OD value of >0.2 units measured at 450 nm was considered positive.<br><br>Testing performed in a central laboratory - (b) (4)<br>[Redacted]<br><br>The performance characteristics of the assay and QC parameters implemented not included.                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Keiser <i>et al.</i> , 2011<br><br>(Egypt – <i>F. gigantica</i> , <i>F. hepatica</i> or hybrid)* | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• MIF concentration test at baseline at the (b) (4)<br/>[Redacted]<br/>No data by this method shown.</li> </ul> | Subjects that remained positive for <i>Fasciola</i> eggs in stool, after treatment with artemether, were enrolled.<br><br>KK method used for 3 consecutive days at study site laboratories in different villages. From each stool sample, 3–6 thick smears were prepared on microscope slides. Each slide was examined independently in a blind manner by two microscopists. For quality control, several slides were re-examined by a senior staff.<br><br><i>Primary endpoint:</i> Day 30 cure rates by the KK method.<br>Qualitative and quantitative assessment of egg in fecal specimens to determine cure rates and egg reduction rates, respectively.<br><br>Details of the methods not included; QC parameters implemented not specified. |
| <b>Other parameters</b>                                                                          |                                                                                                                                                                                                  | Full clinical examination performed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Chronic fascioliasis (CIBA/WHO studies)</b>                                                   |                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| EGA230B2201 – AH/FH2<br><br>(Iran - <i>F. gigantica</i> , <i>F. hepatica</i> or hybrid)*         | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• Telemann concentration method</li> </ul> <b>Duodenal fluid aspiration</b> by Enterotest                       | <i>Primary endpoint:</i> absence of eggs.<br><br>Details of the method included. However, unclear as to how many aliquots were processed. QC parameters implemented not specified.<br><br>Duodenal fluid aspiration by Enterotest performed on Day 60 to confirm final status; if positive, the outcome assigned as failure.                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Other parameters</b>                                                                          |                                                                                                                                                                                                  | Not specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| EGA230B2208 – AH/FH2<br><br>(Bolivia - <i>F. hepatica</i> )*                                     | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• RST</li> </ul>                                                                                                | Qualitative assessments of eggs in fecal specimens performed to determine cure rates. Details of the method included. However, unclear as to how many aliquots were processed. QC parameters implemented not specified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Other parameters</b>                                                                          |                                                                                                                                                                                                  | Ultrasound and clinical assessments performed. Hepatobiliary ultrasonography demonstrated a reversal of parasite-induced changes within 60 days post-treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| EGA230B2207 - AH/FH2<br><br>(Bolivia - <i>F. hepatica</i> )*                                     | <b>Fecal smears:</b><br>KK method                                                                                                                                                                | Qualitative assessment of fecal smears to determine cure rates. Details of the method included. However, unclear as to how many aliquots were processed. QC parameters implemented not specified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Other parameters</b>                                                                          |                                                                                                                                                                                                  | Ultrasound and clinical assessments performed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| EGA230B2203<br>AH/F2                                                                             | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> </ul>                                                                                                               | Details of the method included. However, unclear as to how many aliquots were processed. QC parameters implemented not specified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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| Study ID<br>(Endemic area –<br><i>Fasciola</i> species)                                                                     | Parameter                                                                                                                                                                  | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (Cuba - <i>F. hepatica</i> )*                                                                                               | <b>Duodenal fluid aspiration</b> by Enterotest                                                                                                                             | Cure rates at Day 60 by different methods <ul style="list-style-type: none"> <li>• KK method: 12/14 (86%)</li> <li>• Enterotest: 13/14 (93%)*</li> </ul> *Enterotest performed on Day 60 to confirm final status; if positive, the outcome assigned as failure.                                                                                                                                                                                                                                                                                                     |
|                                                                                                                             | <b>Other parameters</b>                                                                                                                                                    | Ultrasound and clinical assessments performed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| EGA230B2202 - AH/FH2<br><br>(Chile - <i>F. hepatica</i> )*                                                                  | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• Telemann concentration method</li> </ul> <b>Duodenal fluid aspiration</b> by Enterotest | Details of the method included. Three samples from a single specimen tested. However, QC parameters implemented not specified.<br><br>Different cure rates were obtained depending on the method used. <ul style="list-style-type: none"> <li>• Sedimentation test: 19/24 cured (79%).</li> <li>• KK method: 3/7 cured (43%).</li> </ul> *Enterotest performed on Day 60 to confirm final status; if positive, the outcome assigned as failure. Enterotest was found to be positive in all 17 patients according to the information given in the Case Record Forms. |
|                                                                                                                             | <b>Serology:</b><br>Antibodies against a soluble extract of somatic antigen of mature worms of <i>F. hepatica</i> .                                                        | Details of the method and data supporting performance of the serological assay not available.<br><br>Of the 24 subjects that were <i>Fasciola</i> egg positive by the sedimentation method, 19 were parasitologically cured at Month 2 after treatment with a single dose of TCBZ. Of the 24 subjects, 20 (83.3%) were serum antibody positive prior to treatment. By Months 2 and 12, 40% and 91.3%, respectively, of the 15 subjects were serum antibody negative. All the 5 subjects that were parasitological failure remained antibody positive until Month 6. |
|                                                                                                                             | <b>Other parameters</b>                                                                                                                                                    | Not specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| EGA230B2212 - AH/FH1<br><br>(Peru - <i>F. hepatica</i> )*                                                                   | <b>Fecal smears:</b> <ul style="list-style-type: none"> <li>• KK method</li> <li>• Enterotest</li> </ul>                                                                   | Details of the method included. Eggs detected on 3 samples from a single specimen. However, QC parameters implemented not specified.                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                             | <b>Other parameters</b>                                                                                                                                                    | Ultrasound                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Chronic fascioliasis (Egyptian government studies)</b>                                                                   |                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| EGA230B2209<br><br>(Egypt – <i>F. gigantica</i> , <i>F. hepatica</i> or hybrid – <i>Fasciola</i> species based on egg size) | <b>Fecal smears:</b><br>KK method                                                                                                                                          | Details of the method and QC parameters implemented not included.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                             | <b>Other parameters</b>                                                                                                                                                    | Hepatobiliary ultrasonography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| EGA230B2210<br><br>(Egypt – <i>F. gigantica</i> , <i>F. hepatica</i> or hybrid)*                                            | <b>Fecal smears:</b><br>KK method                                                                                                                                          | Details of the method and QC parameters implemented not included.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                             | <b>Other parameters</b>                                                                                                                                                    | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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| Study ID<br>(Endemic area –<br><i>Fasciola</i> species)                                                                                                                                                                                                                                    | Parameter                         | Comments                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| EGA230B2211<br><br>(Egypt – <i>F. gigantica</i> , <i>F. hepatica</i> or hybrid)*                                                                                                                                                                                                           | <b>Fecal smears:</b><br>KK method | Details of the method and QC parameters implemented not included.<br>Testing performed at a site laboratory:<br>[REDACTED] (b) (4) |
|                                                                                                                                                                                                                                                                                            | <b>Other parameters</b>           | None                                                                                                                               |
| KK=Kato-Katz method; RST=rapid sedimentation test; MIF=merthiolateiodine formaldehyde concentration technique; QC=quality control; ELISA=enzyme linked immunosorbent assay<br>* <i>Fasciola</i> species based on epidemiological findings in all clinical studies except Study EGA230B2209 |                                   |                                                                                                                                    |

## 15.5. CIBA/WHO Paragonimiasis Data

Table 15.31 TEAE Occurrence After Treatment of Paragonimiasis with TCBZ 10 mg/kg and 20 mg/kg

| SOC                                                  | PT             | Triclabendazole 10mg/kg<br>N=105 (%) | Triclabendazole 20mg/kg<br>(10 mg/kg q12h x 2)<br>N=104 (%) |
|------------------------------------------------------|----------------|--------------------------------------|-------------------------------------------------------------|
| Gastrointestinal disorders                           | Abdominal pain | 5 (4.8%)                             | 4 (3.8%)                                                    |
|                                                      | Diarrhoea      | 1 (0.9%)                             | 4 (3.8%)                                                    |
|                                                      | Vomiting       | 1 (0.9%)                             | 0                                                           |
| General disorders and administration site conditions | Chills         | 0                                    | 1 (0.9%)                                                    |
|                                                      | Pyrexia        | 5 (4.8%)                             | 1 (0.9%)                                                    |
| Hepatobiliary disorders                              | Jaundice       | 1 (0.9%)                             | 0                                                           |
| Musculoskeletal and connective tissue disorders      | Arthralgia     | 0                                    | 1 (0.9%)                                                    |
| Nervous system disorders                             | Dizziness      | 5 (4.8%)                             | 4 (3.8%)                                                    |
|                                                      | Headache       | 2 (1.9%)                             | 3 (2.9%)                                                    |

Source: Clinical reviewer's analysis in JMP from .xpt AE dataset provided by the Applicant on 2/6/19

## **16 Division Director (Clinical)**

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Concur with the review.

## **17 Office Director (OAP)**

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Concur with the review.

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/s/  
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JACQUELYN C ROSENBERGER  
02/13/2019 02:35:06 PM

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