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APPLICATION NUMBER:

21-618

21-681

21-682

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

OF

NDA 21- 618

NDA 21- 682

NDA 21- 681

TINIDAZOLE

SAFETY

Table of Contents

TABLE OF TABLES 3

TABLE OF FIGURES 4

INTEGRATED REVIEW OF SAFETY 5

EXECUTIVE SUMMARY 5

METHODS AND FINDINGS 6

 7.2.1 Deaths 6

 7.2.2 Other Serious Adverse Events 8

 7.2.3 Dropouts and Other Significant Adverse Events 9

 Other Significant Adverse Events 9

 7.2.4 Common Adverse Events 11

 Trichomoniasis 11

 Giardiasis 18

 Intestinal Amebiasis 22

 Amebic Liver Abscess 24

 Applicant’s Approach to Eliciting Adverse Events 27

 Incidence of Common Adverse Events 27

 Common Adverse Event Tables 27

 Additional Analyses and Explorations 28

 Sponsor BA/BE study 28

 Foreign labels 31

 7.2.5 Less Common Adverse Events 36

 7.2.6 Laboratory Findings 37

 Extent of ECG Testing in the Development Program, Including Brief Review of Pre-Clinical Results 39

 7.2.7 Human Carcinogenicity 39

 7.2.8 Human Reproduction and Pregnancy Data 41

 7.2.9 Overdose Experience 41

 7.2.10 Post-marketing Experience 42

ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 44

 7.2.11 Extent and Adequacy of Overall Clinical Experience 44

 Trichomoniasis 45

 Giardiasis 46

 Amebiasis 47

 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 50

 Primary Source Data 50

 Secondary Source Data 52

 Adequacy of Overall Clinical Experience 52

GENERAL METHODOLOGY 53

 7.2.12 Pooling Data Across Studies to Estimate and Compare Incidence 54

 Pooled Data vs. Individual Study Data 54

 7.2.13 Explorations for Predictive Factors 55

SAFETY CONCLUSIONS 55

ADDITIONAL CLINICAL ISSUES 56

 DRUG-DRUG INTERACTIONS 56

 PEDIATRICS 57

OVERALL ASSESSMENT 58

 CONCLUSIONS ON AVAILABLE DATA 58

 RECOMMENDATION ON REGULATORY ACTION 59

 LABELING REVIEW 60

Table of Tables

Table 7.1: Unaccounted Patients at Follow Up

Table 7.2: Laboratory Findings in Amebiasis Trials

Table 7.3: Common Gastrointestinal Adverse Events (Trichomoniasis)

Table 7.4: Randomized and Double Blinded Trials: GI Adverse Events (Trichomoniasis)

Table 7.5: Adverse Events Listed in Reference #28 (Trichomoniasis)

Table 7.6: Comparison of Gastrointestinal Adverse Events (Trichomoniasis)

Table 7.7: Neurologic Adverse Event (Trichomoniasis)

Table 7.8: Allergic + Other Adverse Events (Trichomoniasis)

Table 7.9: Adverse Event Rate Comparison in Trichomoniasis – Sponsor and Medical Officer

Table 7.10: Studies Reporting Total # and % of Male Patients with Adverse Effects (Trichomoniasis)

Table 7.11: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Trichomoniasis, One Time 2g Dose

Table 7.12: Comparative Giardiasis Safety Data: Reference #127, Speelman

Table 7.13: GI Adverse Event, Tinidazole in Pediatric Giardiasis

Table 7.14: Tinidazole Related Neurological Events, Giardiasis Studies

Table 7.15: Adverse Event Rate Comparison in Giardiasis – Sponsor and Medical Officer

Table 7.16: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Trichomoniasis, One Time 2g Dose

Table 7.17: Gastrointestinal Events, Intestinal Amebiasis

Table 7.18: Adverse Event Rate Comparison in Intestinal Amebiasis – Sponsor and Medical Officer

Table 7.19: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Intestinal Amebiasis

Table 7.20: Adverse Events – Amebic Liver Abscess (All Evaluable Studies)

Table 7.21: Adverse Event Rate Comparison in Intestinal Amebiasis – Sponsor and Medical Officer

Table 7.22: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Amebic Liver Abscess

Table 7.23: Common Adverse Events: 2 g Dose Studies with Available Subjects as Denominator (9.1% Adverse Event Rate 282/3085)

Table 7.24: Adverse Events in BA/BE Study (N=18)

Table 7.25: Comparison of Adverse Event Between Primary and Secondary Sources

Table 7.26: Indications from Foreign Labels

Table 7.27: Dose and Duration of Tinidazole/Indication – Foreign Labels

Table 7.28: Less Common Adverse Events: 2 g Dose Studies with Available Subjects as Denominator

Table 7.29: Major Human Metronidazole Retrospective Cancer Studies

<u>Table 7.30:</u>	Adverse Events from Australia and UK Spontaneous Post Marketing Reporting Systems
<u>Table 7.31:</u>	Submitted Literature
<u>Table 7.32:</u>	Evaluable Studies for Safety (Trichomoniasis)
<u>Table 7.33:</u>	Dose Distribution in Trichomoniasis Trials
<u>Table 7.34:</u>	Evaluable Studies for Safety (Giardiasis)
<u>Table 7.35:</u>	Dose Distribution in Giardiasis Trials
<u>Table 7.36:</u>	Evaluable Studies for Safety (Intestinal Amebiasis)
<u>Table 7.37:</u>	Dose Distribution in Intestinal Amebiasis Trials
<u>Table 7.37:</u>	Dose Distribution in Intestinal Amebiasis Trials
<u>Table 7.39:</u>	Dose Distribution in Amebic Liver Abscess Trials
<u>Table 7.40:</u>	Submitted Data Quality
<u>Table 7.41:</u>	Submitted Randomized, Blinded Trials
<u>Table 7.42:</u>	Tinidazole vs. Metronidazole common adverse effects from directly comparative studies 2g and multi-day dose comparison

Table of Figures

<u>Figure 1(a-e):</u>	Relative Frequencies of Adverse Events Noted in Foreign Labels
<u>Figure 2:</u>	Contraindications in Foreign Labels
<u>Figure 3:</u>	Interactions in Foreign Labels
<u>Figure 4a:</u>	Excel Tinidazole Pivot Table – Studies of Adult Patients
<u>Figure 4b:</u>	Excel Tinidazole Pivot Table – Adult Randomized Studies
<u>Figure 5:</u>	Interactions in Foreign Labels

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INTEGRATED REVIEW OF SAFETY

Executive Summary

Tinidazole is a nitroimidazole that has been widely used for more than two decades in non-US markets for the treatment of trichomoniasis, giardiasis and amebiasis. The sponsor, Presutti Laboratories Inc. has submitted 93 published citations as a 505(b)(2) application to the FDA in support tinidazole safety. Pressutti has supplemented these literature citations with labels from 12 foreign regulatory agencies outlining the recommended use and specific safety concerns related to tinidazole. Further supporting data has been submitted from the post marketing surveillance systems of Australia and the United Kingdom. The sponsor's bioequivalence study also captured adverse events and was submitted as well.

The literature citations submitted to the FDA regarding the safety of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis are from different decades that employed different trial designs, different types of safety reporting as well as the use of different dosages and schedules of tinidazole. These citations were therefore independently analyzed to insure consistency with the sponsor's conclusions regarding the safety of tinidazole use. For further background information see Dr. Alivasatos's and Dr. Tierney's efficacy reviews.

The safety evaluation conducted for the sought indications of trichomoniasis (NDA 21-618), giardiasis (NDA 21-681), intestinal amebiasis and amebic liver abscess (NDA 21-682) revealed no deaths or serious adverse events considered related to tinidazole use. Adverse events considered related to tinidazole use for the specific indications sought were of similar quality and frequency between the sponsor's and FDA's evaluation. The majority of events described in the submitted publications were categorized as either gastrointestinal or neurological and were present in all the indications for which citations were submitted. The most frequent gastrointestinal events reported were nausea, taste change, anorexia, and vomiting for all indications evaluated. The most frequent neurological events reported were weakness, dizziness, and headache for all indications evaluated. Other events reported were pruritis, rash, and darkened urine.

Use of tinidazole in children for the four indications sought was likewise not found to harbor risks greater than those reported in the adult populations. There was limited clinical experience related to pediatric tinidazole use for the 5 day duration recommended in the treatment of amebic liver abscess. Treatment of pediatric amebic liver abscess patients should therefore occur with the proviso that patients will be closely monitored. Tinidazole use during pregnancy after the first trimester was submitted in the form of 3 literature reports that show no elevated risk. However, significant narrative data was insufficient to make specific conclusions.

Labels from 12 countries that have already approved the use of tinidazole were also submitted as supportive data. The indications of trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess were present in the majority of these labels. Amebic

liver abscess was not indicated in 5 of the labels (Australia, France, Germany, Japan and Sweden). Giardiasis and intestinal amebiasis were not present in the Japanese label. The labels that contained all indications for which Presutti is seeking approval (Belgium, India, Netherlands, South Africa, Spain, Switzerland, and the UK) also contained the same dose and duration that is included in the sponsor's proposed labeling.

Since tinidazole has had a long history of use in overseas markets the sponsor has also submitted the post marketing surveillance data from Australia and the UK for events captured from market introduction (1975 and 1982 for Australia and the UK, respectively) through August, 2000. This would provide 25 years of marketing history in Australia and 18 years of marketing history in the UK. There were 350 events reported in the Australian system and 48 events reported in the UK. The events were similar in nature to those evident in the literature submission with other rarer events that have been incorporated into the proposed label.

Overall, the literature submitted to the FDA regarding the safety of tinidazole for the treatment of trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess are sufficient for the sought indications

Compliance may also be improved with a tinidazole regimen since it is shorter in duration. Furthermore, the following key issues support the safety of tinidazole use for the proposed indications:

1. A minimal spectrum of risk based on the adverse event evaluation conducted
2. Congruency of adverse event evaluation between the sponsor and FDA
3. Lack of events with significant severity, frequency or unexpected character
4. Utilization history in non-US markets for more than two decades without significant adverse event reporting

Tinidazole is therefore considered safe for the proposed dosages and durations sought for the treatment of trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess, respectively.

Methods and Findings

7.2.1 Deaths

Per the sponsor's description (see below) in 11.4 Integrated Summary of Safety, 3 deaths were reported in patients receiving tinidazole in the published literature for the indication of amebic liver abscess.

Published Literature:

1. The report by Kundu, 1976⁽²⁹⁷⁾ compared metronidazole and tinidazole in a randomized comparative trial in amebic liver abscess in India. Both drugs were dosed at 2g single daily dose for 3 days. Twenty two patients were originally enrolled in the study. One patient died in each group. The male tinidazole patient had an abscess in the left lobe of the liver and open drainage had to be done but eventually the patient went into a hepatic coma and died.

MO Comment: There is insufficient data present in the publication to determine any type of drug attribution.

2. Scragg, 1977⁽³⁰¹⁾ reported an open-label administration of tinidazole at 50-57mg/kg/day for 3-5 days in 25 malnourished children with amebic liver abscess in South Africa. One 11 month old female died. The infant, with bronchopneumonia, remained ill and febrile after a 5 day course of tinidazole. Needle aspiration of the liver was inadequate and the liver continued to enlarge. Laparotomy was carried out. A huge abscess containing 300mL pus occupying almost the entire right lobe of the liver was found. The left lobe of the liver was adherent to the diaphragm and pericardium but no actual abscess was shown. Postoperatively she received emetine and appeared to be doing well. However, 2 weeks later the signs of pneumonia increased and x-ray confirmed extension of the consolidation. There were no signs of pericardial involvement. She failed to respond to antibiotic therapy and died on the 23rd day.

MO Comment: Per the narrative in the publication it appears that the patient responded to drainage and antimicrobial therapy of the hepatic abscess. Two weeks later the patient developed a nosocomial pneumonia which is presumably the cause of death.

3. Mathur, 1977⁽¹⁹⁸⁾ studied the administration of tinidazole (2g/day x 2-3 days) to 15 adult male amebic liver abscess patients in India. One patient, age 40, had a sudden onset of breathlessness, pulmonary edema and peripheral circulatory failure on the 6th day and died within a few hours. Screening of the chest did not show any evidence of rupture of the abscess into the lungs. Post-mortem could not be performed and the most probable cause of death was myocardial infarction or pulmonary embolism. The author indicated that the cause of death was unrelated to treatment with tinidazole.

MO Comment: Given the fact that there are alternate plausible explanations for the death of this patient who had been hospitalized for six days (pulmonary embolism and acute myocardial infarction) it is unlikely that tinidazole contributed to the death of this patient. Without further information, however, diagnostic certainty is not possible.

Three other deaths were noted from postmarketing use in the United Kingdom (UK) and Australia as stated below (11.4.7, page 59).

1. UK – (Cerebrovascular accident/Hemiparesis (right)/Atrial Fibrillation) An 80 year old man was treated with omeprazole 40mg/d, tinidazole 1g/d and clarithromycin 500mg/d for duodenal ulcer for 11 days until death from cerebrovascular accident and gastric ulcer hemorrhage on ——— He was also taking aspirin 75mg/d, enalapril 5mg/d and frusemide 40mg/d for 1-2 months for myocardial infarction but had stopped them in the weeks before death.
2. Australia – (Miscarriage) Female took 1g single dose in 1995. Pregnancy was confirmed about 1 week later. Reported miscarriage 2 weeks later.

3. Australia – (Anencephalic fetus/death) A 27 year old Australian woman delivered an anencephalic fetus in 1984. 2g Fasigyn was given during the 3rd week of pregnancy. Mogadon (nitrazepam) was given intermittently throughout pregnancy. Prostaglandin F2 alpha use is mentioned for induction. The fetus died. The Australian ADR report lists “causality possible”.

MO Comment: Case (1) is likely not related to tinidazole given alternate plausible explanations. The specifics of the case are not fully provided but an 80 year old that was on therapy for a duodenal ulcer that then developed a gastrointestinal bleed likely had a subsequent ischemic stroke secondary to hypovolemia/anemia. Cases (2) and (3) may be related to tinidazole use.

7.2.2 Other Serious Adverse Events

Two reports of congenital malformations were submitted from the spontaneous reporting of the UK and Australia (11.4.7, page 60).

1. UK – (Congenital abnormality/dental disorder NOS) TNZ administered at 20 weeks gestation on 6/09/93 for giardiasis. Child had mild dental abnormalities (listed as Dental Disorder NOS) at age 7. Suspected due to possible intrauterine effect of drugs given in pregnancy. Dose was “4 STAT” which likely means four 500mg tablets at one time.
2. Australia – (Cardiac birth defect) Two year old diagnosed with heart malformation. Mother received Fasigyn for 2 weeks at 4-6 weeks gestation in 1991. Severe Ebstein malformation of tricuspid valve. Small right ventricle, abnormal pulmonary valve. The child “recovered with sequelae”. The ADR lists “causality possible”.

MO Comment: Cases (1) and (2) may be related to tinidazole use.

Other serious adverse events provided by the sponsor:

1. **Cranial nerve lesion** (Palsy) (Australia) - 2g tinidazole administered to 35 year old male in 1998. Patient was also taking Nelfinavir, Stavudine, Didanosine for approximately 2-3 months prior to event. 7 nerve (Bells) palsy onset 4/24 post ingestion (sponsor suspects 4/24 means 4 hours, 24 minutes or 4 x 24 hours). Patient had not recovered at time of report (5 days post event). Past exposure to metronidazole had caused sensory peripheral neuropathy. The ADR lists “causality possible.”

MO: Although alternate associations of Bell’s palsy are present (HIV, HAART therapy, viral infection not stated) given the temporal proximity of the tinidazole dose the event may be causally linked albeit other probable causes exist.

2. Convulsion (Australia) - 1 instance of a Gran Mal seizure was reported to the Australian government. Several instances of neuropathy were reported in UK and Australia's ADR's. ((Sponsor ISS, 11.4.9.5, page 80).

7.2.3 Dropouts and Other Significant Adverse Events

Specific dropout data was not available for evaluation due to submission under a 505(b)(2) literature application. During review of the articles submitted for each indication, however, the number of patients noted to be available at the time of reported safety evaluation was noted and tallied. Below (*Table 7.1*) are the denoted unaccounted patients ascribed to each of indications with the percent of total patients evaluated that were unaccounted in the contiguous column.

Table 7.1: Unaccounted Patients at Follow Up

Indication	Total Patients	Unavailable at Follow-Up (N)	Unavailable at Follow-Up (%)
Trichomoniasis	1874	274	14.6
Giardiasis	697	83	12
Intestinal Amebiasis	685	72	10.5
Amebic Liver Abscess	213	1	0.5

MO Comment: *Given the unstructured data submission as well as the variability of safety evaluation in the literature provided, 10-15% of patients that were unavailable is not considered impactful on the safety evaluation for these indications.*

Other Significant Adverse Events

Blood Chemistry Evaluations (Sponsor's ISS 11.4.9.1, page 67)

Leukopenia/Liver Function Tests

From sponsor's integrated summary of safety:

“With regards to leukopenia and neutropenia, 12 trichomoniasis trials (performing white blood cell counts and differentials) of 749 trichomoniasis patients treated with a single 2g dose of tinidazole revealed no cases of leukopenia. One patient had an increase in lymphocytes and a decrease in neutrophils following therapy (Schwarz, 1974⁽⁸²⁾). No other abnormal values were seen in the remaining 749 patients. (Schmor, 1974⁽⁸⁵⁾; Wallin, 1974⁽⁸¹⁾; Quartararo, 1974⁽⁸⁸⁾; Dellenbach, 1974⁽⁸⁹⁾; Weidenbach, 1974⁽⁹⁹⁾; Milek, 1974⁽²⁶⁾ Anjanelyalu, 1977⁽⁹⁶⁾, Akinla, 1975⁽²⁷⁸⁾, Ward, 1976⁽⁸⁷⁾, Rao, 1978⁽⁹⁷⁾, Psaroudakis, 1977⁽⁹⁰⁾, Swarz, 1974⁽⁸²⁾).

Liver function tests were performed in 9 trichomoniasis studies of 402 patients treated with a single 2g dose of tinidazole. One paper (Ward⁽⁸⁷⁾) revealed 1 patient with

increased SGPT. One paper (Ali ⁽¹⁸³⁾) revealed 4 patients with increased bilirubin, and 2 patients with increased alkaline phosphatase. These patients were cases with infectious hepatitis and raised levels were found pretreatment.

Liver function tests (i.e.: SGOT, SGPT, alkaline phosphatase, serum bilirubin) were performed pre and post therapy in 171 giardia patients from five trials (Gadzer, 1977⁽¹²⁸⁾; Sabchareon, 1980⁽¹³⁰⁾; Krishnamurthy, 1978⁽¹⁹⁰⁾; Bassily, 1987⁽¹¹⁴⁾; Nigam, 1991⁽¹⁹¹⁾) treated with a single 2g dose of tinidazole. No abnormalities were noted.

Liver function tests were performed in 202 patients with amebiasis from six trials (Misra, 1974⁽¹⁹³⁾; Misra, 1977⁽¹⁹⁴⁾; Mabadeje, 1977⁽¹⁹⁵⁾; Singh, 1977⁽¹⁹⁶⁾; Swami, 1977⁽¹⁹⁷⁾; Mathur, 1977⁽¹⁹⁸⁾) given a 2g dose of tinidazole for 2-3 consecutive days. Follow up laboratory evaluations were performed 30 days post therapy in the amebiasis trials. Zuberi, 1973 ⁽²⁹¹⁾ reported a raised serum transaminase level noted on the 30th day after treatment initiation. It was not indicated if the patient had intestinal or hepatic amebiasis. The specific dose of tinidazole for this patient was not stated but dosing for the study ranged from 450mg/d x 5 days to 1200mg/d x 5 days.

Other laboratory findings include this summary from 13 amebiasis trials reporting on laboratory findings. *The number of studies reporting specific measured laboratory endpoints with tinidazole use are provided in Table 7.2 below.*

Table 7.2: Laboratory Findings in Amebiasis Trials

Number studies reporting	Findings
1	No abnormalities in laboratory investigations recorded
1	No drug-related toxicity observed
4	No biochemical changes detected
6	No hematological changes detected
6	No untoward changes in hepatic function
5	No untoward changes in renal function
3	No cardiac abnormalities
3	No abnormal changes in urine analysis
1	No toxic effect on bone-marrow
5	No abnormal changes in blood chemistry

MO Comment: *Multiple studies that evaluated short term laboratory evaluations provided no evidence of toxicity.*

Complete laboratory data was also obtained for the 18 subjects involved in Sponsor's BA/BE study. Measurements were made prior to the first 2g dose and 72 hours after the third and final 2g dose (doses were 1 week apart). No clinically significant changes were found and no significant trends were noted.

Complete laboratory data (also included in the trichomoniasis clinical efficacy section of this NDA) for the 5 compassionate use patients follow. Five patients on high dose tinidazole supplied by sponsor (1 patient on 1g oral tid + 500mg vaginally tid x 14

days and 4 patients on 1g oral bid + 500mg vaginally bid x 14 days) were monitored for multiple laboratory parameters at day 4 of dosing and 1 day after completion of dosing. No clinically significant abnormalities were noted.”

MO Comment: *In reviewing the citations separately there is agreement with the sponsor’s evaluation. Specifically, only one case of LFT elevation was found and no evidence of leucopenia or other blood chemistry changes were noted.*

7.2.4 Common Adverse Events

Trichomoniasis

The following tables represent adverse events categorized by organ system. The first column includes all doses used in the studies provided whereas the third column reflects only the 2g dose for which the sponsor is seeking the indication. Table 7.3 describes pooled gastrointestinal events. As denoted, there was little variation between all doses versus the 2g dose. Taste change was the most frequent followed by nausea and diarrhea, with some minor hierarchical variations of these events compared to the 2g dose. When evaluating these events relative to comparator studies (including both metronidazole and ornidazole), the event rates were lower in all categories.

Table 7.3: Common Gastrointestinal Adverse Events

GI Adverse Events	Dose			
	All Doses	%	2.0 g	%
Tinidazole				
# Studies	30		27	
# Available Subjects	1600		1450	
Taste Change	56	3.5	56	3.9
Nausea	61	3.8	61	4.2
Diarrhea	11	.7	9	.62
Abdominal Pain	19	1.2	17	1.2
Anorexia	30	1.9	30	2.1
Vomiting	20	1.2	20	1.4
Distension	6	.4	6	.4
Nonspecific GI	38	2.4	32	2.2
Constipation	11	.7	11	.8
Dry Mouth	8	.5	8	.5
Comparator	All Doses	%	2.0 g	%
# Available Subjects	569		535	
Taste Change	46	8.1	46	8.6
Nausea	96	16.9	96	17.9
Diarrhea	10	1.8	10	1.9
Abdominal Pain	21	3.7	21	3.9
Anorexia	45	7.9	45	8.4
Vomiting	33	5.8	33	6.2
Distention	5	.9	5	.9
Nonspecific GI	9	1.6	5	.9
Constipation	12	2.1	12	2.2
Dry Mouth	2	.3	2	.4

MO Comment: *Although event rates are lower for tinidazole use when pooled relative to comparator regimens, it should be noted that the studies compiled were of different design and utilized variations in safety evaluation. Specific comparative conclusions regarding the incidence of adverse events should not be drawn from these pooled data due to their inherent instability.*

Since the 2g dose is the dose for which the sponsor is seeking FDA approval, data was evaluated separately based on dosage. 3 studies used alternative dosage regimens (1g, 1.6g, and 1.8g) with 2 studies (Wallin, reference #81 and Sucharit, reference #276) having an open label noncomparative design with spontaneous reporting. The third study (Kawamura, reference #95) was an open label comparative study of 1g single dose tinidazole with no safety data provided. Given the variations in reporting with resultant bias in adverse event rates a filter was applied to the submitted studies based on randomization, blinding and studies that used a specific query to evaluate adverse events. (Table 7.4).

**Table 7.4: Randomized and Double Blinded Trials (Active Controlled):
GI Adverse Events (References 28, 86, 185, 299)**

Tinidazole	All Queries	Percent Subjects	Specific Query	Percent Subjects
# Studies	4		2	
# Available Subjects	121		62	
Taste Change	28	23.1	25	40.3
Nausea	18	14.9	16	26
Diarrhea	0	0	0	0
Abdominal Pain	4	3.3	2	3.2
Anorexia	11	9.1	11	17.7
Vomiting	4	3.3	2	3.2
Distension	0	0	0	0
Nonspecific GI	2	1.7	2	3.2
Constipation	0	0	0	0
Dry Mouth	1	.8	1	1.6
Total AE	68		59	
Comparator				
Available Subjects	143		83	
Taste Change	25	17.5	24	28.9
Nausea	30	21.0	30	36.1
Diarrhea	2	1.4	2	2.4
Abdominal Pain	1	.7	1	1.2
Anorexia	11	7.7	11	13.2
Vomiting	8	5.6	8	9.6
Distension	0	0	0	0
Nonspecific GI	0	0	0	0
Constipation	0	0	0	0
Dry Mouth	2	1.4	2	2.4
Total AE	79		78	

MO Comment: *It was assumed that a safety evaluation that specifically queried patients would result in a higher incidence rate. As seen, there was an overall increase in event rate that may be more reflective of the true incidence rate of adverse events. This disparity underscores the potential marked variability in adverse event rate estimation. Although the four studies were considered randomized controlled trials (RCT) with 2 trials conducting specific adverse event queries, they were nonetheless incomplete datasets and on closer inspection somewhat difficult to interpret. The two studies that included a specific query for safety evaluation were (1) reference 28 (Oprassersawat) and (2) reference 185 (Chaudhuri).*

Chaudhuri conducted a randomized active-control trial in 77 women with trichomoniasis and their male partners comparing tinidazole (2g one time dose) with carnidazole (2g one time dose). The author states that side effects were recorded in 25/78 cases that received carnidazole (it is assumed that the 78 cases included the patients and their partners) and in 12/76 cases that received tinidazole (it is assumed that the 76 cases included the patients and their partners). No data is provided as to why 68% of the carnidazole cases did not provide follow-up information or why 84% of the tinidazole cases did not provide follow-up information. Therefore, although there were reportedly fewer events in patients treated with tinidazole (total AE for tinidazole vs. carnidazole is 14 vs. 31), the conclusion of improved safety is not valid given the lack of data on the subjects that did not follow-up.

Oprassersawat conducted a randomized active-control trial in 132 women with trichomoniasis comparing split dose metronidazole (800 mg bid) with single dose tinidazole (2g once daily). Included in the safety table (Table 7.5) are adverse event data from all enrolled patients without a statistically significant difference between groups. 4 gastrointestinal and 2 central nervous system adverse events are listed with the following distribution:

Table 7.5: Adverse Events Listed in Reference #28

Adverse Event	Metronidazole (N=67) No. (%)	Tinidazole (N=65) No. (%)	P value
Bitterness	16 (23.9)	24 (36.9)	.15
Anorexia	13 (19.4)	11 (16.9)	.86
Nausea	12 (17.9)	13 (20.0)	.93
Vomiting	4 (6.0)	2 (3.1)	.68
Ataxia	5 (7.5)	2 (3.1)	.44
Vertigo	3 (4.5)	3 (4.6)	1.00

Comparing the four gastrointestinal adverse events of tinidazole in Table 7.5 with those listed in Table 7.4 (all five randomized, controlled trials independent of reporting selection) as well as Table 7.3 (all studies) the following comparison can be made:

Table 7.6: Comparison of Gastrointestinal Adverse Events

Adverse Event	1 Study ^a	4 studies ^b	30 studies ^c
	No. (%)	No. (%)	No. (%)
Taste Change	24 (36.9)	28 (23.1)	56 (3.9)
Nausea	13 (20.0)	18 (14.9)	61 (4.2)
Anorexia	11 (16.9)	11 (9.1)	30 (2.1)
Vomiting	2 (3.1)	4 (3.3)	20 (1.4)

^a RCT, specific query, all patients accounted

^b RCT

^c 2g dose studied

The event rate denoted in Table 7.6, specifically for the RCT that utilized a specific query and in which all patients were accounted, reports events that are similar to those described in the sponsors submitted BA/BE study (*section 7.1.1.4*). Specifically, in the BA/BE study, of the 18 healthy subjects given tinidazole (2g, fasting state), 2/18 (11%) experienced nausea and 1/6 (6%) experienced vomiting (sponsor’s integrated summary of safety, 11.4.5, page 54).

In expanding the safety analysis from randomized controlled trials that utilized a specific query to all randomized controlled trials and subsequently to all trichomoniasis trials that included any safety data one sees an incremental decrease in the proportion of patients that experienced the specified adverse event. The central reason for this variation is that in combining data from disparate sources, some that used specific queries and others that typically used spontaneous reporting, event rates decline due to the increasing denominator and decreasing numerator (fewer reports in spontaneous reporting studies or in studies where the methodology is not noted). This combination dilutes the event rate in a well quantified dataset with the event rate in a dataset that would only be reported if it were severe enough for a patient to consider it concerning. For rarer events that are underreported this might bias the result toward a lower incidence rate.

MO Comment: *Of importance to note, however, is that (1) the relatively high event rate reported by Oprassersawat in reference #28 is no worse than the comparator drug, metronidazole and that (2) the relative importance of the denoted adverse events remain constant. Specifically, the hierarchical frequencies remain similar with taste change > nausea > anorexia > vomiting.*

Table 7.7 describes pooled neurological events in the trichomoniasis studies. As denoted, there was little variation between tinidazole and comparator events.

Table 7.7: Neurologic Adverse Event (Trichomoniasis)

2g Dose 27 Studies	Tinidazole		Comparator	
	N	%	N	%
# Available Subjects	1450		535	
Headache	12	0.8	9	1.7
Weakness/Fatigue	23	1.6	11	2.1
Dizziness	15	1.0	12	2.2
Ataxia	2	0.1	2	0.4
Dysesthesias	1	0.1	0	0.0
Giddiness	8	0.6	16	3.0

As described with the gastrointestinal adverse events in the trichomoniasis studies, there was only one study that utilized a double-blinded randomized design with specific queries for adverse events. Included in reference #28 (Oprassersawat) are two neurologic adverse events. In comparing these event rates with those outlined in Table 7.7 there is again an elevated event rate in reference #28 with maintenance of the same relative proportions (dizziness/vertigo > ataxia). Other events described in the literature provided do not have the benefit of comparison with Oprassersawat's study which was randomized, controlled and used a specific query.

The data presented in Table 7.8 regarding allergic and other adverse events is compiled from studies that used separate reporting methods as well as variations in denominator data. Specifically, many patients were unaccounted at study analysis, some reports did not clarify the number of patients reporting an adverse event relative to the number of adverse events and some studies had disparate data. Where data was inconsistent the data presented in tabular form was used.

Table 7.8: Allergic + Other Adverse Events (Trichomoniasis)

2g Dose 27 Studies	Tinidazole		Comparator	
	N	%	N	%
# Available Subjects	1450		535	
Rash	2	0.1	4	0.7
Pruritis	9	0.62	6	1.1
Sweating	1	0.07	1	0.1
Dark Urine	15	1	27	5
Bruising	1	0.07	0	0
Palpitations	1	0.07	0	0
LFT Abnormalities	5/248	2	0/80	0
WBC Abnormalities	1/413	0.2	0/95	0

MO Comment: 7 patients were reported to have elevated liver function tests (6 patients in reference 183 (Ali) and 1 in reference 87 (Ward)). Two of the patients in reference

183 were noted to have infectious hepatitis with elevated pretreatment LFTs. The other 4 patient may have also had infectious hepatitis but the attribution is not well described in the publication. In reference 87 one woman was noted to have a change in her ALT from 8 u/L to 31 u/L with no other abnormality. The patient in reference 87 did not have a clinically significant rise in her ALT. Four other patients may have had a serum bilirubin elevation but based on the context in which they were described, they may have also had an infectious hepatitis and certainty in attribution is not possible.

Although randomized and blinded data is not available for the events described above, there is no significant difference between events reported for tinidazole and those reported for the comparator (including metronidazole).

The methods employed to evaluate the submitted literature did not yield significantly differing results from the sponsor’s adverse event summary. Below (Table 7.9) is a rate comparison of frequent adverse events between the sponsor and FDA review.

Table 7.9: Adverse Event Rate Comparison in Trichomoniasis – Sponsor and Medical Officer

Total Trich 2g publications (31)	# pts. with AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/Fatigue # pts./N (%)
Sponsor	272/2,492 (10.9%)	55/1,536 (3.6%)	61/1,536 (4.0%)	19/1,536 (1.3%)	25/1,536 (1.6%)	30/1,536 (2.0%)	17/1,536 (1.1%)
MO Review	137/1,600 (8.6%)	56/1,600 (3.5%)	61/1,600 (3.8%)	20/1,600 (1.2%)	19/1,600 (1.2%)	30/1,600 (1.9%)	11/1,600 (.7%)

MO Comment: *The adverse event rates pooled from the submitted data are not markedly different in any of the listed adverse events. Note: the denominator for adverse events is different than the denominator for overall patient incidence because the former denominator is the sum of all patients and the latter is the total number of adverse events per the sponsor’s ISS, page 18.*

The sponsor also compared adverse event rates in studies where data was available for men and women specifically (Table 7.10, Sponsor’s ISS, page 19).

“Studies involving male trichomoniasis treatment with a single 2g dose of tinidazole reporting adverse effect information were analyzed for adverse effects in males, and the results are shown below:

Table 7.10: Studies Reporting Total # and % of Male Patients with Adverse Effects

Study	N	# pts. with adverse effects	% pts. with adverse effects
Lyng ⁽⁹¹⁾	68	5	7%
Chaisilwattna ⁽¹⁰⁴⁾	52	3	6%
Dellenbach ⁽⁸⁹⁾	29	0	0%
Bedoya ⁽⁹³⁾	12	0	0%
Kawamuru ⁽⁹⁵⁾	39	6	15%
5 Total Studies	200	14	7%

There does not appear to be a significant difference in the incidence of adverse effects reported in these 5 studies in males (7%) vs. reports which were primarily in females (10.9% from 31 studies). Likewise, the types of adverse effects reported in males did not differ from those seen in females.”

MO Comment: Adverse event rates in the treated partners of treated trichomoniasis patients were comparable to the comparator treated partners (reference 91) and found to be less than their female partners (reference 104). In reference 89, male partners were not queried, female patients were asked on their behalf. In reference 93 male partners had “no complaints” (type of query is not reported). Reference 95 specifically evaluated men with trichomoniasis. 4 cases in the metronidazole arm complained of gastrointestinal disturbances and 6 cases in the tinidazole arm complained of similar events. Overall, there is no indication that event rates differ in men or women.

The sponsor also submitted analyses comparing tinidazole adverse events to metronidazole from those trials that had metronidazole as a direct comparator. For the indication of trichomoniasis seven trials using a 2g dose of tinidazole compared with a single 2g dose of metronidazole were evaluated for relative safety. As stated in the sponsors integrated summary of safety “not all papers utilized the same reporting formats so the N’s for total % of patients with adverse effects (n=269 for TNZ, n=239 for MTZ) and each individual adverse effect (n=236 for TNZ, n=214 for MTZ) are different (page 10, sponsor ISS).” The summary table for these event rates (*Table 7.11*) shows a decreased adverse event rate in subjects given tinidazole vs. metronidazole except for the weakness/fatigue column where there were two events noted in the tinidazole group and none in the metronidazole group.

Table 7.11: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Trichomoniasis, One Time 2g Dose

TNZ vs. MTZ publications (7)	# pts. w/ AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/Fatigue # pts./N (%)	Constipation # pts./N (%)	Vertigo # pts./N (%)
TNZ	58/269 (21.6%)	30/236 (12.7%)	39/236 (16.5%)	10/236 (4.2%)	7/236 (3.0%)	24/236 (10.2%)	2/236 (0.8%)	4/236 (1.7%)	3/226 (1.3%)
MTZ	94/239 (39.3%)	36/214 (16.8%)	75/214 (35.0%)	26/214 (12.1%)	20/214 (9.3%)	44/214 (20.6%)	0/214 (0%)	6/214 (2.8%)	4/214 (1.9%)

MO Comment: Given the disparate trial designs and adverse event reporting methods direct comparisons of these trials may not adequately represent true adverse event rates. In comparing cross indication adverse events the disparity between event rates becomes more evident. For example, tinidazole has a higher rate of vomiting in giardiasis trials (6% vs. 3.1%) yet a lower rate in the trichomoniasis trials detailed above (4.2% vs. 12.1%). The lack of severe, unexpected or frequent adverse events in subjects that received tinidazole does however support the drug’s safety relative to metronidazole.

Giardiasis

18 studies were evaluable for the indication of giardiasis (see Table 34). Unlike trichomoniasis, however, there were no randomized double-blinded trials submitted for evaluation. One study (reference #127, Speelman) did use a specific query for adverse event evaluation. The study was an open label comparative study of tinidazole and metronidazole in the treatment of giardiasis. The population was mixed (adult and pediatric) with 13/15 tinidazole treated patients returning the adverse event questionnaire and 14/15 of the metronidazole treated patients returning the questionnaire (data presented in Table 7.12).

Table 7.12: Comparative Giardiasis Safety Data: Reference #127, Speelman

Adverse Event	Tinidazole N=13		Metronidazole N=14	
	No.	%	No.	%
Metallic Taste	0	0	4	28.6
Nausea	1	7.7	3	21.4
Vomiting	1	7.7	1	7.1
Headache	1	7.7	2	14.3
Dizziness	1	7.7	3	21.4
Anorexia	2	15.4	1	7.1

MO Comment: 8 of the tinidazole patients received a syrup rather than a tablet formulation, potentially confounding adverse event evaluation, given the potential attribution to the formulation rather than the drug. In either case, most of the events

were noted in the Oprassersawat's trichomoniasis trial with relatively similar event rates.

Overall evaluation of adverse events are reflective of the sponsor's proposed labeling: for adults with giardiasis a 2g, one time dose and for children over the age of three a single dose of 50 mg/kg up to 2g one time dose. Studies that used these doses or greater were included in the adverse events described below. Specifically, for adults, there were 4 studies that were describes as solely adult patients that received the 2g dose of tinidazole (references 122 (Pettersson), 126 (Jokipii), 131 (Kryonseppa), and 188 (Jokipii)). For children, there were 6 studies that were described as solely including pediatric patients (reference 118 (Bakshi), 120 (Danzig), 128 (Gadzer), 130 (Sabchareon), 190 (Krishnamurthy) and 264 (Suntornpoch)). 3 separate doses of tinidazole were used in these trials, including 50 mg/kg (4 studies), 1-1.5g (1 study), and 2g (1 study) each for one time dosing.

Of the 4 adult, 2g studies, 2 were comparative but did not adequately provide data to enable a safety comparison between the study arms. Kyronseppa denotes that 5 patients experienced adverse events with the classification noted by the author as "...such as nausea, fatigue and drowsiness. The side-effects were mild, although 1 patient on tinidazole had symptoms for 3 weeks." No specific line items for the two drugs are provided as a means of comparison. Given the previously noted adverse events in adult women that received tinidazole for the indication of trichomoniasis, the events described in these four studies (taste change and nausea) are not severe, novel, or markedly frequent and support the safety profile previously denoted.

Of the 6 pediatric studies, comparative data is similarly not presented for adequate analysis. The tinidazole adverse events, are, however, similar to the previously described events above. Specifically, the compiled events in the pediatric patients, all doses utilized, are described in Table 7.13 below.

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Table 7.13: GI Adverse Event, Tinidazole in Pediatric Giardiasis

	Tinidazole	
	N	%
4 Doses		
4 Studies		
# Available Subjects	281	
Taste Change	6	2.1
Nausea	10	3.6
Diarrhea	79	28.1
Abdominal Pain	46	16.4
Anorexia	17	6
Vomiting	20	7.1
Distension	36	12.8

MO Comment: *Most of the events described are potentially confounded by the disease process itself and drug attribution is difficult to ascertain. Taste change which is less likely to be related to giardiasis occurs at a similar frequency previously described as do nausea and anorexia. These events combined from the 6 referenced studies have already been described in the trichomoniasis evaluation and given the caveats of study design (including reporting) imply that similar effects are evident in pediatric giardiasis patients but the degree is difficult to determine.*

Neurologic events described in the giardiasis literature submitted are similar to those previously noted for trichomoniasis such as headache, weakness, and dizziness (Table 7.14).

Table 7.14: Tinidazole Related Neurological Events, Giardiasis Studies

	Adult (4 studies) 2g dose		Pediatric (6 studies) All doses	
	N	%	N	%
Available Patients	106		281	
Headache	0	0	0	0
Weakness/Fatigue	10	9.4	0	0
Dizziness	1	0.94	0	0
Available Comparators	0		70	
Headache			0	0
Weakness/Fatigue			1	1.4
Dizziness			3	4.3

MO Comment: *Although 11 events were noted in the adult studies and none in the pediatric, true demographic attribution of incidences are not possible to evaluate since the type of adverse event reporting was variable. Qualitatively, however, there were no adverse events evident from the pooled pediatric studies from those patients that*

received tinidazole whereas there were adverse events in the pediatric studies in those patients that received the comparator, underscoring the relative safety of tinidazole.

As stated previously, without randomized controlled data and specific queries to evaluate safety and drug attribution, pooled data (with variable reporting and study designs) are difficult to interpret. The events described in Table 7.14 (although the true event rate is not possible to determine) are not more frequent or severe than those already describe in the trichomoniasis trials. Another event noted in the adult studies that used a 2g dose (4 publications noted above) was rash (1 subject of 106 available that received tinidazole). Other events noted in the pediatric studies submitted (6 publications, all doses utilized) were (1) liver function test (LFT) abnormality in 1/99 (1%) sampled patients (281 available) and (2) white blood cell (WBC) abnormalities noted in 0/78 sampled patients (281 available) that received tinidazole. For subjects that received a comparator drug, 4/112 (3.6%) patients reported abnormal LFTs, 2 patients reported dark urine and 0/70 reported WBC abnormalities. Of note, 3/4 abnormal LFTs reported by comparators (reference 130, Sabchareon) were related to ornidazole use and 1 was related to metronidazole use. In limiting the comparison to metronidazole and tinidazole, there is no difference in the reporting of LFT abnormalities.

The methods employed to evaluate the submitted literature did not yield significantly differing results from the sponsor’s adverse event summary. Below (Table 7.15) is a rate comparison of frequent adverse events.

Table 7.15: Adverse Event Rate Comparison in Giardiasis – Sponsor and Medical Officer

19 Giardia Studies	# pts. w/ AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/Fatigue # pts./N (%)	Headache # pts./N (%)	Dizziness # pts./N (%)
Sponsor	131/932 (11.1%)	36/932 (3.8%)	19/932 (2.0%)	17/932 (1.8%)	20/932 (2.1%)	6/932 (0.6%)	34/932 (3.6%)	23/932 (2.5%)	19/932 (2.0%)
Medical Officer	71/614 (11.6)	33/614 (5.4%)	27/614 (4.4%)	26/614 (4.2%)	49/614 (8.0%)	19/614 (3.1%)	23/614 (3.7%)	12/614 (1.9%)	12/614 (1.9%)

MO Comment: *Events that differed between the two analyses were nausea, vomiting, abdominal pain, and anorexia. Given the data presented above (Speelman, reference 127) there is clearly a broad possible range of adverse event rates that is dependent upon the trial design and safety data evaluation. Two salient reasons for the difference in rates are (1) a larger denominator used in the sponsor’s evaluation due to more studies included and (2) use of only those patients available for follow-up rather than all patients enrolled in the FDA’s evaluation.*

The sponsor also submitted analyses comparing tinidazole adverse events to metronidazole from those trials that had metronidazole as a direct comparator. For the

indication of giardiasis eleven trials had comparative data with metronidazole for safety evaluation. Five trials had a single dose comparison and six had varying metronidazole doses. Furthermore pooled data included both pediatric and adult patients with variations in randomization and blinding (page 25, sponsor’s ISS). The summary table for these event rates (*Table 7.16*) shows a decreased adverse event rate in subjects given tinidazole vs. metronidazole except for the vomiting and anorexia where there were more events noted in the tinidazole group.

Table 7.16: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Giardiasis, One Time 2g Dose

11 Studies	# pts. w/ AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/ Fatigue # pts./N (%)	Headache # pts./N (%)	Dizziness # pts./N (%)
TNZ	53/375 (14.1%)	0/151* (0.0%)	1/151* (0.7%)	9/151 (6.0%)	0/151 (0.0%)	2/151 (1.3%)	0/151 (0.0%)	1/151 (0.7%)	1/151 (0.7%)
MTZ	71/380 (18.7%)	4/97* (4.1%)	3/97** (3.1%)	3/97 (3.1%)	0/97 (0.0%)	1/97* (1.0%)	0/97 (0.0%)	2/97 (2.1%)	3/97 (3.1%)

*5 studies reported that there were taste disturbances and nausea but did not give specific data and were not used to calculate these specific adverse effects

**4 studies reported nausea without giving specific data and were not used to calculate these specific adverse effects

MO Comment: *Given the disparate trial designs and adverse event reporting methods direct comparisons of these trials may not adequately represent true adverse event rates. The lack of severe, unexpected or frequent adverse events in subjects that received tinidazole does support the drug’s safety relative to metronidazole. Again, it should be noted that tinidazole does have a higher pooled rate of vomiting and anorexia in the giardiasis trials that was not present in the trichomoniasis trials, underscoring the possible confounding of both trial designs and the population under study. Again, it should be noted that the denominator for incidences is total adverse events whereas the denominator for total % adverse events is the total number of patients.*

Intestinal Amebiasis

A total of 5 studies which included 206 patients received tinidazole at the 2.0g dose for which the sponsor is seeking the indication of intestinal amebiasis in adults, all of whom received therapy for 3 days and of which 249 patients were available for follow-up in the citations (references 117, 118, 194, 196, and 197).

A total of 2 studies that included 65 patients received tinidazole at the 50 mg/kg dose for which the sponsor is seeking the indication of intestinal amebiasis in pediatric patients, all of whom received the drug for 3 days (references 284 and 290). A group of pediatric patients received a dose of 60 mg/kg for 3 days (25 patients, reference 290). There were no adverse events reported in the cited pediatric studies. Adverse events

denoted below (*Table 7.17*) are drawn from the 5 adult studies. For the data presented, reporting was spontaneous in 4/5 studies and not provided in 1/5.

Table 7.17: Gastrointestinal Events, Intestinal Amebiasis

	Adult (5 studies, 2 g dose x 3 Days)			
	Tinidazole		Comparator	
	N	%	N	%
Available Patients	249		86	
Taste Change	36	14.5	13	15.1
Nausea	18	7.2	60	70
Diarrhea	0	0	2	2.3
Abdominal Pain	9	3.6	18	20.9
Anorexia	13	5.2	37	43
Vomiting	7	2.8	17	19.8

MO Comment: *Adverse event rates for the pooled comparator arm is higher than elsewhere. Nonetheless, tinidazole adverse events are within the range previously described and are lower than the comparator in the 2g, 3 day dosing regimen, supporting safety for the longer duration of therapy.*

The data presented in table 7.17 above are reflective of studies with spontaneous reporting as well as composite data from previous studies (Bakshi, reference 118). Similar gastrointestinal events noted in studies described before regarding trichomoniasis and giardiasis are present in Table 7.17 with the most marked difference being an increase in adverse events attributed to the comparator drug (s) that include metronidazole (e.g., 7.2% nausea for tinidazole and 70% nausea for comparator).

There were no neurological events described in the two pediatric studies included in the evaluation of intestinal amebiasis. Of the 5 adult studies evaluated at the 2g x 3 day dosing regimen there were 1/249 patients reporting dizziness whereas in the comparator arm 2/86 patients reported dizziness as well as 1/86 reporting headache and 1/86 reporting weakness or fatigue.

Regarding allergic and other adverse events for the pediatric studies evaluated no adverse events for patients receiving tinidazole were described and 2 patients in the comparator arm reported dark urine, which has previously been described above. The studies that included safety data in adults described 4/249 (1.6%) patients with dark urine that received tinidazole and 3/86 (3.5%) comparator patients that likewise described dark urine.

The methods employed to evaluate the submitted literature did not yield significantly differing results from the sponsor’s adverse event summary. Below (*Table 7.18*) is a rate comparison of frequent adverse events.

Table 7.18: Adverse Event Rate Comparison in Intestinal Amebiasis – Sponsor and Medical Officer

19 Amebiasis Studies	# pts.with AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/Fatigue # pts./N (%)	Constipation # pts./N (%)
Sponsor	219/1416 (15.5%)	60/842 (7.1%)	43/842 (5.1%)	10/842 (1.2%)	11/842 (1.3%)	21/842 (2.5%)	11/842 (1.3%)	8/842 (1.0%)
Medical Officer	67/613 (10.9%)	52/613 (8.5%)	33/613 (5.4%)	10/613 (1.6%)	9/613 (1.5%)	20/613 (3.3%)	11/613 (1.8%)	8/613 (1.3%)

MO Comment: *There were no marked differences in the adverse event rates denoted above between the sponsor and FDA’s evaluation of the submitted citation that were subsequently pooled for rate estimation.*

The sponsor also submitted analyses comparing tinidazole adverse events to metronidazole from those trials that had metronidazole as a direct comparator. For the indication of intestinal amebiasis nine trials had comparative data with metronidazole for safety evaluation. Specific adverse events data is available for 361 tinidazole patients and 313 metronidazole patients (page 38, sponsor’s ISS). The summary table for these event rates (Table 7.19) shows a decreased adverse event rate in subjects given tinidazole vs. metronidazole except for metallic taste where more events were noted in the tinidazole group (13.3% in the tinidazole group and 7.3% in the metronidazole group).

Table 7.19: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Intestinal Amebiasis

TNZ vs. MTZ publications (9)	# pts. with AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/Fatigue # pts./N (%)
TNZ	111/443 (25.1%)	48/361 (13.3%)	28/361 (7.7%)	9/361 (2.5%)	9/361 (2.5%)	16/361 (4.4%)	1/361 (0.3%)
MTZ	151/397 (38.0%)	23/313 (7.3%)	90/313 (28.7%)	21/313 (6.7%)	20/313 (6.4%)	50/313 (16.0%)	1/313 (0.3%)

MO Comment: *Given the disparate trial designs and adverse event reporting methods direct comparisons of these trials may not adequately represent true adverse event rates. The lack of severe, unexpected or frequent adverse events in subjects that received tinidazole does support the drug’s safety.*

Amebic Liver Abscess

15 studies were submitted for the indication of amebic liver abscess, of which 5 were considered inadequate for evaluation. 294, 295, 298, 301, 302 References 294 (Esesarte), 295 (Hatchuel), 298 (Lassere), 301 (Scragg), and 302 (Simjee) provided no specific safety data. In spite of the lack of reported data, it was noted that reference 301

(Scragg), in which 25 children with amebic liver abscess (ages 3 months to 6 years) were treated with a 5 day course of tinidazole. A general statement of safety was made, specifically that *“tolerance was excellent with no toxic effects shown by the blood counts, liver function tests, blood ureas, and urines.”*

Overall 10 studies (9 references) were considered evaluable for safety and included 213 patients (Table 7.38). When more than one dose or duration was used in the same reference, they were considered separate studies for the purposes of review. For the indication of amebic liver abscess all studies used a dose of 2g but the duration of therapy varied from 2-3 days. There was no evaluable amebic liver abscess study that included only pediatric patient but reference 296 (Islam) included both adult and pediatric patients, albeit in small numbers (N=16). Adverse events denoted below are reflective of pooled data from these 9 references without specific regard to pediatric or adult populations.

Table 7.20: Adverse Events – Amebic Liver Abscess (All Evaluable Studies)

	<u>Tinidazole</u>		<u>Comparator</u>	
	N	%	N	%
Available Patients	212		53	
Taste Change	15	7.1	2	3.8
Nausea	8	3.8	9	17
Diarrhea	2	0.9	1	1.9
Abdominal Pain	6	2.8	1	1.9
Anorexia	8	3.8	8	15.1
Vomiting	1	0.5	4	7.5
Constipation	9	0.4	0	0
Headache	6	2.8	9	17
Weakness/Fatigue	2	0.9	4	7.5
Dizziness	4	1.9	2	3.8
Giddiness	0	0	1	1.9
Rash	0	0	0	0
Pruritis	2	0.9	0	0
Dark Urine	0	0	8	15.1

MO Comment: *Events described in Table 7.20 are similar to events described for the previously discussed indications. 6 of the studies did not describe the type of reporting employed for safety evaluation whereas 2 used a specific query and 2 used spontaneous reporting. Combining such disparate data has the same difficulties as previously discussed (variations in trial design with inherent bias) yet there were no severe, novel, or markedly frequent events in the tinidazole arms that were disparate from previous data submitted.*

The methods employed to evaluate the submitted literature did not yield significantly differing results from the sponsor’s adverse event summary. Below (Table 7.21) is a rate comparison of frequent adverse events.

Table 7.21: Adverse Event Rate Comparison in Intestinal Amebiasis – Sponsor and Medical Officer

TNZ for amebic liver abscess (14 studies)	# pts. w/ AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/ Fatigue # pts./N (%)	Headache # pts./N (%)	Dizziness # pts./N (%)	Constipation # pts./N (%)
Sponsor	25/349 (7.1%)	15/334 (4.5%)	10/334 (3.0%)	1/334 (0.3%)	6/334 (1.8%)	8/334 (2.4%)	2/334 (0.6%)	6/334 (1.8%)	4/334 (1.2%)	9/334 (2.7%)
Medical Officer	Not captured	15/212 (7.1%)	8/212 (3.8%)	1/212 (.3%)	6/212 (2.8%)	8/212 (3.8%)	2/212 (.9%)	6/212 (2.8%)	4/212 (1.9%)	9/212 (4.2%)

All numerator data is essentially equivalent between the two analyses. The variations in rates are therefore attributable to denominator data that as before are most likely related to (1) a larger denominator used in the sponsor’s evaluation due to more studies included and (2) use of only those patients available for follow-up rather than all patients enrolled in the division’s evaluation.

The sponsor also submitted analyses comparing tinidazole adverse events to metronidazole from those trials that had metronidazole as a direct comparator. For the indication of amebic liver abscess seven trials had comparative data with metronidazole for safety evaluation. Five of these trials were not blinded and all were randomized (page 46, sponsor’s ISS). The summary table for these event rates (*Table 7.22*) shows a decreased adverse event rate in subjects given tinidazole vs. metronidazole except for dizziness where more events were noted in the tinidazole group.

Table 7.22: Comparative Adverse Events, Tinidazole and Metronidazole in the treatment of Amebic Liver Abscess

7 trials	# pts. w/ AE/N (%)	Metallic Taste # pts./N (%)	Nausea # pts./N (%)	Vomiting # pts./N (%)	Abdominal Pain # pts./N (%)	Anorexia # pts./N (%)	Weakness/ Fatigue # pts./N (%)	Headache # pts./N (%)	Dizziness # pts./N (%)
TNZ	6/115 (5.2%)	3/147 (2.0%)	5/147 (3.4%)	1/147 (0.6%)	0/147 (0.0%)	5/147 (3.4%)	1/147 (0.6%)	6/147 (4.1%)	4/147 (2.7%)
MTZ	29/105 (27.6%)	12/138 (8.7%)	28/138 (20.3%)	16/138 (11.6%)	1/138 (0.7%)	23/138 (16.7%)	4/138 (2.9%)	9/138 (6.5%)	2/138 (1.4%)

MO Comment: *Given the disparate trial designs and adverse event reporting methods direct comparisons of these trials may not adequately represent true adverse event rates. The lack of severe, unexpected or frequent adverse events in subjects that received tinidazole does support the drug’s safety.*

Applicant's Approach to Eliciting Adverse Events

Adverse events evaluation was based on compiled data from (1) the published literature, (2) spontaneous reporting from Australia and the UK, (3) sponsor's BA/BE study as well as foreign labels.

Incidence of Common Adverse Events

Given the marked heterogeneity of submitted literature in support of the 505(b)(2) application a specific incidence of adverse events related to the use of tinidazole is difficult to characterize. Qualifying adverse events by those that were evaluated in comparative trials with metronidazole is however reasonable and useful since metronidazole has a long utilization history within the United States. Since the background symptoms of intestinal amebiasis are markedly different from trichomoniasis, adverse event rates from uncontrolled and unblinded studies will be biased by these background symptoms and cause a marked variation in event rates. For example, nausea attributed to tinidazole in intestinal amebiasis is estimated to be 7.7% whereas in trichomoniasis studies the event rate is estimated to be 16.5%. Specific rates must therefore be considered within the context of each indication as described above.

Common Adverse Event Tables

Overall adverse event rates occurring at a rate >1% compiled by internal review, independent of indication, are presented in Table 7.23. Due to variations in reporting from the individual publication, however, reported rates were reflective of all events reported in some studies and a percent of all patients enrolled in others. Therefore the rates reported are gross estimates and serve only to provide a sense of organ systems affected with some indication of frequency.

Table 7.23: Common Adverse Events: 2 g Dose Studies with Available Subjects as Denominator (9.1% Adverse Event Rate 282/3085)

Adverse Event	Percent of Available Subjects (2g Dose)
Taste Alteration	5.5
Nausea	4.6
Anorexia	2.7
Fatigue/Malaise	2.1
Abdominal Pain	1.5
Vomiting	1.3
Constipation	1.3
Dizziness	1.0
Headache NOS	.9
Abnormal Urine	.9

MO Comment: *The overall adverse event rate of 9.1% was similar to the sponsor’s evaluations that had a range between 7-15%. As stated earlier and denoted above, the categorization of events fell mainly into gastrointestinal and neurological.*

Additional Analyses and Explorations

Sponsor BA/BE study

The sponsor BA/BE study (N=18). Events previously described from alternate data (literature submissions) were similar in nature to those described in the BA/BE study (Table 7.24). Since the size of the study was small (N=18) rates should not even be considered reasonable estimates but from a qualitative perspective it is evident that similar events to those already described were evident in this small study.

Table 7.24: Adverse Events in BA/BE Study (N=18)

Adverse Event	(fasted)	Fasigyn (fasted)	(after high fat meal)	(crushed in cherry syrup, fasted)
# of subjects dosed	18 (100%)	18 (100%)	9 (100%)	9 (100%)
# of subjects with adverse events	10 (56%)	12 (67%)	5 (56%)	7 (78%)
# of subjects without adverse events	8 (44%)	6 (33%)	4 (44%)	2 (22%)
Gastrointestinal disorders				
Dry mouth	0 (0%)	1 (6%)	1 (11%)	1 (11%)
Nausea	2 (11%)	2 (11%)	1 (11%)	2 (22%)
Vomiting NOS	1 (6%)	1 (6%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders				
Back pain	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Myalgia	1 (6%)	0 (0%)	0 (0%)	1 (11%)
Pain in limb	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders				
Dizziness	0 (0%)	1 (6%)	0 (0%)	1 (11%)
Dysgeusia	8 (44%)	9 (50%)	4 (44%)	6 (67%)
Headache NOS	3 (17%)	4 (22%)	1 (11%)	1 (11%)
Reproductive system and breast disorders				
Dysmenorrhoea	1 (6%)*	0 (0%)	0 (0%)	0 (0%)

Specifically, gastrointestinal and nervous system effects were most prominent and are echoed in the Flagyl® label as well as the cited sources already noted. To confirm congruency between these data, adverse events were compiled between primary and secondary sources to insure congruency of effect (not to ascertain incidence rate). Shaded cells in Table 7.25 below imply that there was either no data or there was a lack of corroborative data from the alternate data sources. When two or more sources had evidence of the same event the cell was left without shading and the event was bolded (e.g., **Confusion**).

Table 7.25: Comparison of Adverse Event Between Primary and Secondary Sources

Adverse Event	Foreign Labels: Presence/Absence (% Submitted Labels)	Literature (%Available Subjects-2.0g)	UK/Australia (% Available Reported AE)	BA/BE Study (Healthy Volunteers)	Sponsor Safety Summary
Headache NOS	8.3	0.9	3.3	17.0	1.3
Dizziness	75.0	1.0	2.3	0.0	1.1
Paraesthesia	0.0	0.0	2.3	0.0	0.0
Incoordination	50.0	0.0	0.0	0.0	0.0
Confusion	16.7	0.0	0.8	0.0	0.0
Syncope	0.0	0.0	0.5	0.0	0.0
Vertigo	75.0	0.0	0.5	0.0	0.0
Dizziness	75.0	1.0	2.3	0.0	1.1
Tremor	0.0	0.0	0.5	0.0	0.0
Neuropathy	58.3	0.0	0.5	0.0	0.0
Neuritis	0.0	0.0	0.5	0.0	0.0
Hemiparesis	0.0	0.0	0.5	0.0	0.0
Vision abnormal	0.0	0.0	0.5	0.0	0.0
Dystonia	0.0	0.0	0.5	0.0	0.0
Ataxia	91.7	0.1	0.5	0.0	0.0
Psychosis	0.0	0.0	0.5	0.0	0.0
Hallucination	0.0	0.0	0.5	0.0	0.0
Photosensitivity reaction	0.0	0.0	0.5	0.0	0.0
Somnolence	0.0	0.0	0.3	0.0	0.0
Convulsions - Gran Mal	58.3	0.0	0.3	0.0	0.0
Coma	0.0	0.0	0.3	0.0	0.0
Insomnia	0.0	0.0	0.3	0.0	0.0
Cranial nerve lesion	0.0	0.0	0.3	0.0	0.0
Paralysis	0.0	0.0	0.3	0.0	0.0
Diplopia	0.0	0.0	0.3	0.0	0.0
Sensory disturbance	0.0	0.0	0.3	0.0	0.0
Hypoaesthesia	0.0	0.0	0.3	0.0	0.0
Dysesthesias	0.0	0.1	0.0	0.0	0.0
Extrapyramidal disorder	0.0	0.0	0.3	0.0	0.0
Hypertonia	0.0	0.0	0.3	0.0	0.0
Hypotonia	0.0	0.0	0.3	0.0	0.0
Paranoia	0.0	0.0	0.3	0.0	0.0
Depression NOS	0.0	0.0	0.3	0.0	0.0
Anxiety	0.0	0.0	0.3	0.0	0.0
Euphoria	0.0	0.0	0.3	0.0	0.0
Nausea	100.0	4.6	4.8	11.0	3.2
Taste Altered	83.3	5.5	4.5	0.0	3.7
Diarrhea NOS	91.7	0.5	3.5	0.0	0.0
Vomiting	100.0	1.3	3.5	6.0	1.5
Abdominal pain	75.0	1.5	2.3	0.0	1.8
Anorexia	91.7	2.7	1.3	0.0	1.5
Hepatic function abnormal NOS	16.6	0.0	1.0	0.0	0.0
Taste Loss	0.0	0.0	1.0	0.0	0.0
Hepatitis	0.0	0.0	0.8	0.0	0.0
Weight decrease	0.0	0.0	0.5	0.0	0.0
Constipation	8.3	1.3	0.3	0.0	0.4
Dysphagia	0.0	0.0	0.3	0.0	0.0
Steatorrhea	0.0	0.0	0.3	0.0	0.0
Rectal Hemorrhage	0.0	0.0	0.3	0.0	0.0

Table 7.25: Comparison of Adverse Event Between Primary and Secondary Sources

	Foreign Labels: Presence/Absence (% Submitted Labels)	Literature (%Available Subjects- 2.0g)	UK/Australia (% Available Reported AE)	BA/BE Study (Healthy Volunteers)	Sponsor Safety Summary
Bruising	0.0	0.1			
Anemia	8.3		0.0	0.0	
Thrombophlebitis	8.3	0.0	0.0	0.0	
Alcohol interaction	91.7	0.0	0.5	0.0	
Myalgia	0.0	0.0	0.5	6.0	0.0
Limb Pain	0.0	0.0	0.0	6.0	0.0
Thrombocytopenia	0.0	0.0	0.3	0.0	0.0
Hypokalemia	0.0	0.0	0.3	0.0	0.0
Epistaxis	0.0	0.0	0.3	0.0	0.0
Congenital abnormality NOS	0.0	0.0	0.3	0.0	0.0
Anencephalic foetus	0.0	0.0	0.3	0.0	0.0
Heart malformation	0.0	0.0	0.3	0.0	0.0
Death - fetal	0.0	0.0	0.3	0.0	0.0
Hypothyroidism	0.0	0.0	0.3	0.0	0.0
Rectal Hemorrhage	0.0	0.0	0.3	0.0	0.0
Dental disorder NOS	0.0	0.0	0.3	0.0	0.0
Pallor	0.0	0.0	0.3	0.0	0.0
Pain	0.0	0.0	0.3	0.0	0.0
Unexpected therapeutic effect	0.0	0.0	0.3	0.0	0.0
Prothrombin activity increased	58.3	0.0	0.3	0.0	0.0
Rhabdomyolysis	0.0	0.0	0.3	0.0	0.0
Arthritis	16.7	0.0	0.3	0.0	0.0
Arthrosis	0.0	0.0	0.0	0.0	0.0
Euphoria/giddiness	0.0	0.4	0.3	0.0	0.0
Breast engorgement	0.0	0.0	0.0	0.0	0.0
Frequent erection	0.0	0.0	0.3	0.0	0.0
Lactation puerperal decreased	0.0	0.0	0.3	0.0	0.0
Abortion	0.0	0.0	0.3	0.0	0.0
Renal Pain	0.0	0.0	0.3	0.0	0.0
Albuminuria	0.0	0.0	0.3	0.0	0.0
Anuria	0.0	0.0	0.3	0.0	0.0
Hematuria	0.0	0.0	0.3	0.0	0.0
Urinary Retention	0.0	0.0	0.3	0.0	0.0
Lymphadenopathy	0.0	0.0	0.3	0.0	0.0
Purpura	0.0	0.0	0.3	0.0	0.0
Death - fetal	0.0	0.0	0.3	0.0	0.0

MO Comment: Rates describe above are comparative as they reflect separate sets of data. The comparative goal is qualitative and not quantitative. A concentration of positive rates under gastrointestinal and neurological events above further underscore the gastrointestinal and neurological concerns related to tinidazole use. Specifically, that these events are probably drug related due to the frequency that disparate sources of safety data distinguish these events as being related to tinidazole.

Foreign labels

Tinidazole was originally patented in 1968 and has been widely used in non-US markets. The sponsor has submitted foreign labels as non-primary data supportive of proposed labeling. Included in table 7.26 below is a summary of the countries where distribution of tinidazole is ongoing with the indications approved for the respective country. These label submission are intended as supportive material for the indication sought by the sponsor. Specifically, the indications of (1) trichomoniasis, (2) giardiasis, and (3) amebiasis are present in 11 of 12 submitted labels (*Table 7.26*), reflecting the regulatory approval for these indications by many foreign agencies.

The indications currently sought are present in almost all labels save the following exceptions. Japan's label only has trichomoniasis approved for tinidazole use and lacks indications for giardiasis, amebiasis and amebic liver abscess. Australia, France, Germany and Sweden all have indications for trichomoniasis, giardiasis, and amebiasis but do not have a specific indication for amebic liver abscess (see *Table 7.26*). Nonetheless, there are 7 foreign labels that have all 4 indications denoted in their respective labels.

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Table 7.26: Indications from Foreign Labels

Country	Trade Name	Last Labeling	Indication (s)				
			(1)	(2)	(3)	(4)	(5)
Australia	Fasigyn	1999	Trichomoniasis	Giardiasis	Amebiasis	Surgical Prophylaxis	
Belgium	Fasigyn	1994	Trichomoniasis	Giardiasis	Amebiasis (+) Liver Abscess	Anaerobic Infections	Vaginitis (Gardnerella)
France	Fasigyne	1999	Trichomoniasis	Giardiasis	Amebiasis	Surgical Prophylaxis	Vaginitis (Nonspecific)
Germany	Simplotan	1999	Trichomoniasis	Giardiasis	Amebiasis	Surgical Prophylaxis	Vaginitis (Nonspecific)
India	Fasigyn	Not Provided	Trichomoniasis	Giardiasis	Amebiasis (+) Liver Abscess	Surgical Prophylaxis	Vaginitis (Nonspecific)
(6) Acute ulcerative gingivitis							
(7) Anaerobic infections							
Japan	Haisigyn	Not Provided	Trichomoniasis				
Netherlands	Fasigyn	Not Provided	Trichomoniasis	Giardiasis	Amebiasis (+) Liver Abscess		
South Africa	Fasigyn	2000	Trichomoniasis	Giardiasis	Amebiasis (+) Liver Abscess	Surgical Prophylaxis	Anaerobic Infections
(6) Acute ulcerative gingivitis							
Spain	Tricolam	Not Provided	Trichomoniasis	Giardiasis	Amebiasis (+) Liver Abscess	Surgical Prophylaxis	Vaginitis (Nonspecific)
(6) Acute ulcerative gingivitis							
Sweden	Fasigyn	Not Provided	Trichomoniasis	Giardiasis	Amebiasis	Surgical Prophylaxis	Vaginitis (Nonspecific)
(6) Anaerobic infections							
Switzerland	Fasigyne	2003	Trichomoniasis	Giardiasis	Amebiasis (+) Liver abscess	Surgical Prophylaxis	Vaginitis (Nonspecific)
(6) Anaerobic infections							
(7) Endometritis, salpingo-ovarian abscess							
(8) bacterial septicemia							
(9) skin and soft tissue infections							
(10) upper and lower respiratory tract infections (pneumonia, empyema, pulmonary abscess)							
(11) Acute ulcerative gingivitis							
UK	Fasigyn	1998	Trichomoniasis	Giardiasis	Amebiasis (+) Liver abscess	Surgical Prophylaxis	Vaginitis (Nonspecific)
(6) Anaerobic infections							
(7) Endometritis, salpingo-ovarian abscess							
(8) bacterial septicemia							
(9) skin and soft tissue infections							
(10) Upper and lower respiratory tract infections (pneumonia, empyema, pulmonary abscess)							
(11) Acute ulcerative gingivitis							
(12) Eradication of H. pylori associated with duodenal ulcers (with antibiotic and acid suppressant therapy)							

As further supportive documentation for the dose and duration sought, included in Table 7.27 below is the dose and duration specified for the respective foreign label indications. The 2g one time dose for trichomoniasis is common to all foreign labels (12/12). The giardiasis indication has a recommended dose and duration of 2g for one day in 11/12 of foreign labels (giardiasis is not indicated in the Japanese label).

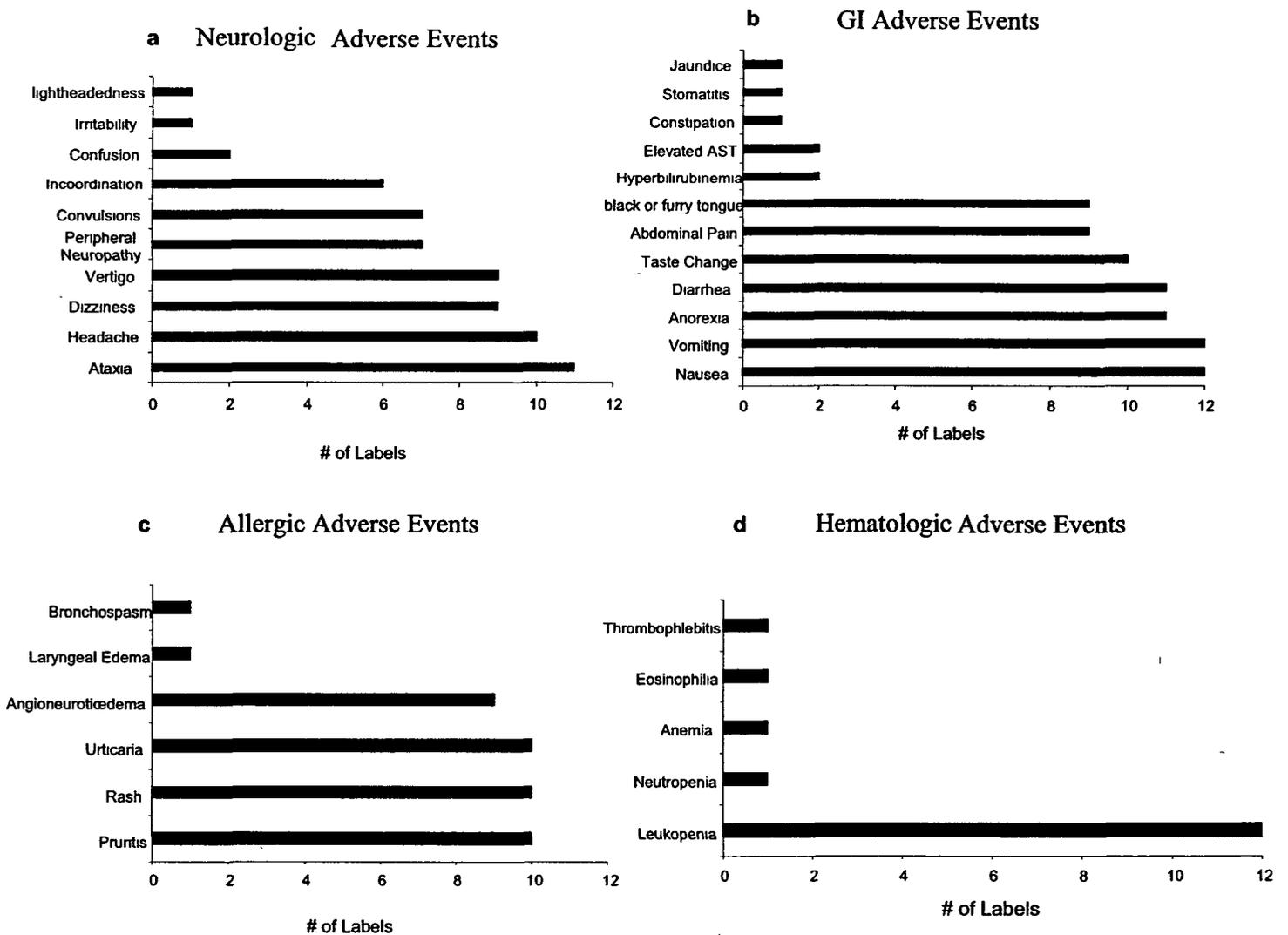
Table 7.27: Dose and Duration of Tinidazole/Indication – Foreign Labels

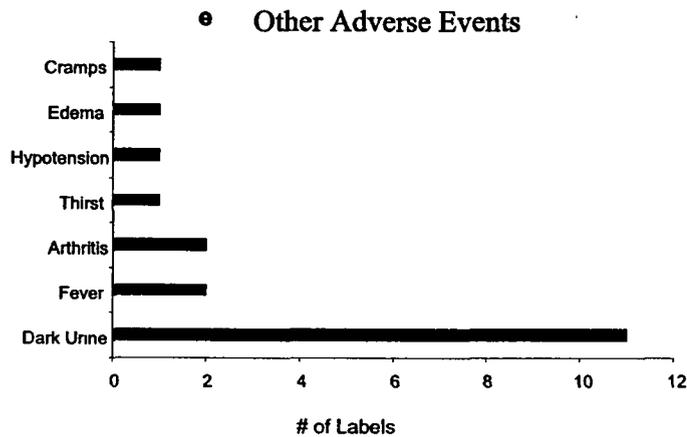
Country	Indication	Recommended Dose	Recommended Frequency	Recommended Duration
Australia				
1	Trichomoniasis	2 g	1x/day	1 day
2	Giardiasis	2g (50mg/kg, max 2g)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	2g (50mg/kg, max 2g)	1x/day (1x/day)	2-10 days (1 day)
4	Amebic Liver Abscess	2g (50mg/kg, max 2g)	1x/day(1x/day)	3-5 days (5 days)
Belgium				
1	Trichomoniasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day(1 day)
2	Giardiasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day(1 day)
3	Amebiasis	2g (50-60 mg/kg)	1x/day (1x/day)	2-3 days (3 days)
4	Amebic Liver Abscess	1.5-2g(50-60 mg/kg)	1x/day (1x/day)	5-6 days (5 days)
France				
1	Trichomoniasis	2g	1x/day	1 day
2	Giardiasis	2g (50-70mg/kg)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	1.5g	1x/day	4-5 day
4	Amebic Liver Abscess	-	-	-
Germany				
1	Trichomoniasis	2g (2g if >12, 1g if >6)	1x/day (1x/day)	1 day (1 day)
2	Giardiasis	2g (2g if >12, 1g if >6)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	2g (2g if >12, 1g if >6)	1x/day (1x/day)	2-3 days (3 days)
4	Amebic Liver Abscess	2g (2g if >12, 1g if >6)	1x/day (1x/day)	3-5 days (5 days)
India				
1	Trichomoniasis	2g (50-75 mg/kg, max 2g)	1x/day (1x/day)	1 day (1 day)
2	Giardiasis	2g (50-75 mg/kg, max 2g)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	2g (50-60 mg/kg, max 2g)	1x/day (1x/day)	3 days (3 days)
4	Amebic Liver Abscess	2g(50-60 mg/kg, max 2g)	1x/day(1x/day)	2-3 days (5 days)
Japan				
1	Trichomoniasis	200 mg or 2 g	2x/day or 1x/day	7 days or 1 day
2	Giardiasis	-	-	-
3	Amebiasis	-	-	-
4	Amebic Liver Abscess	-	-	-
Netherlands				
1	Trichomoniasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day(1 day)
2	Giardiasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	2g (50-60 mg/kg)	1x/day (1x/day)	2-3 days (3 days)
4	Amebic Liver Abscess	1.5-2g(50-60 mg/kg)	1x/day (1x/day)	3-6 days (5 days)
South Africa				
1	Trichomoniasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day(1 day)
2	Giardiasis	2g (50-75 mg/kg)	1x/day (1x/day)	1 day (1 day)
3	Amebiasis	2g (60 mg/kg)	1x/day (1x/day)	3 days (3 days)
4	Amebic Liver Abscess	2g(60 mg/kg)	1x/day (1x/day)	3-5 days (5 days)
Spain				
1	Trichomoniasis	2g	1x/day	1 day
2	Giardiasis	2g	1x/day	1 day
3	Amebiasis	2g (50-60 mg/kg)	1x/day (1x/day)	2-3 days (3 days)
4	Amebic Liver Abscess	1.5-2g(50-60 mg/kg)	1x/day (1x/day)	3-6 days (5 days)

The intestinal amebiasis indication has a recommended dose and duration of 2g for 2-3 days and amebic liver abscess has a recommended dose and duration of 2g for 3-5 days (50 mg/kg in children).

Most of the adverse events described in foreign labels were present in the submitted literature. There were a few, however, that were not described. In particular urticaria, angioneurotic edema and leukopenia, present in most labels, were absent in the submitted literature. Figure 1a-e below details the relative frequencies of listed adverse events in the 12 submitted labels.

Figure 1(a-e): Relative Frequencies of Adverse Events Noted in Foreign Labels



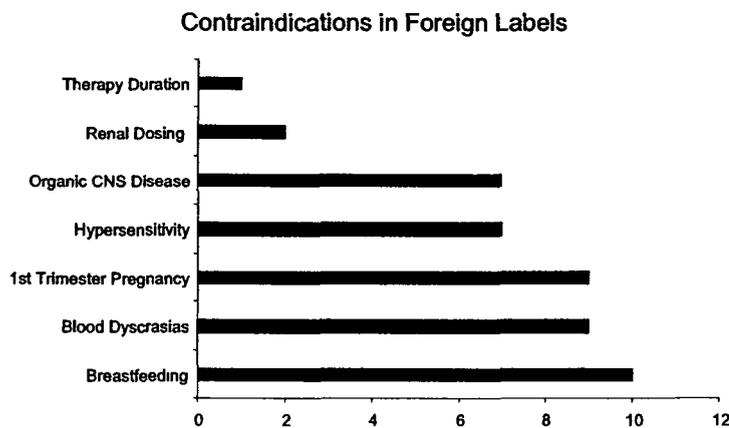


Australian label recommends evaluating WBC should a second course of tinidazole be required

French label: hematological monitoring must be performed during the treatment of amebiasis

There are 7 contraindications listed in foreign labels. Contraindicated use during the 1st trimester of pregnancy or breastfeeding is common to the nitroimidazoles. Concerns regarding use of tinidazole in patients with blood dyscrasias does not reflect the safety reports present in the submitted literature but seem reasonable given the possible attribution in a few reports of leukopenia and anemia. The relative frequency of these contraindications in foreign labels is provided in Figure 2 below.

Figure 2: Contraindications in Foreign Labels



German label: Therapy duration not to exceed 10 days given increased rate of certain tumors in animal experiments

Indian label: no need for renal adjustment

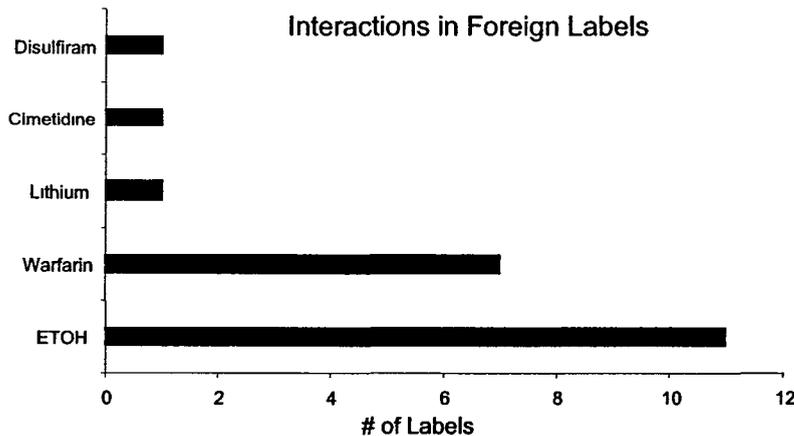
Netherlands label: no need for renal adjustment

UK label: no need for renal adjustment

MO Comment: *The need for renal dosing, present in 2 foreign labels, is only supported by a remark from reference 156 (Robson). In the article the author states that “no adjustment for renal failure unless the patient is expected to receive multiple doses over time...dosage may need to be adjusted for patients with decreased renal function receiving multiple doses.” The need for renal dosing is specific to multiple dose regimens (not single dose) and is speculated by the author, not based on pharmacokinetic data.*

There are 5 interacting medications listed in foreign labels, their relative frequencies noted in figure 3. Medications of concern are disulfiram, cimetidine, lithium and warfarin. Similar to other imidazoles, alcohol ingestion can cause an antabuse (disulfiram-like) reaction and should commonly be avoided as noted in these labels.

Figure 3: Interactions in Foreign Labels



7.2.5 Less Common Adverse Events

Infrequent adverse events related to the 2g dose (events < 1% of available patients) are detailed in Table 7.28 below. As stated above, the rates reported are gross estimates and serve only to provide a sense of organ systems affected with some indication of frequency. Given the disparity in trial designs and safety evaluations in the submitted citations, the events detailed in Table 7.28 should be considered qualitatively and not quantitatively other than they occur rarely. Similar events were noted in the sponsor’s ISS and spontaneous reporting events captures in the UK and Australian post marketing surveillance data.

Table 7.28: Less Common Adverse Events: 2 g Dose Studies with Available Subjects as Denominator

Adverse Event	Percent of Available Subjects
Diarrhea	.5
Euphoria/Giddiness	.4
Dry Mouth	.4
Abdominal distension	.3
Pruritis	.3
Ataxia	.1
Dysesthesias	.1
Rash	.1
Palpitations	.1
Sweating	.1

7.2.6 Laboratory Findings

As stated in 7.1.5 above, comparison of tinidazole drug-related laboratory events with comparator drugs did not show any organ specific toxicity. Events noted in the pediatric studies submitted (6 publications, all doses utilized) were liver function test (LFT) abnormalities noted in 1/99 (1%) sampled patients (281 available) and white blood cell (WBC) abnormalities noted in 0/78 sampled patients (281 available) that received tinidazole. For subjects that received a comparator drug, 4/112 (3.6%) patients reported abnormal LFTs, 2 patients reported dark urine and 0/70 reported WBC abnormalities. Of note, 3/4 abnormal LFTs reported by comparators (reference 130, Sabchareon) were related to ornidazole use and 1 was related to metronidazole use. In limiting the comparison to metronidazole and tinidazole, there is no difference in the reporting of LFT abnormalities.

From the sponsor's ISS the following evaluation was cited (sponsor's ISS, page 67).

“With regards to leukopenia and neutropenia, 12 trichomoniasis trials (performing white blood cell counts and differentials) of 749 trichomoniasis patients treated with a single 2g dose of tinidazole revealed no cases of leukopenia. One patient had an increase in lymphocytes and a decrease in neutrophils following therapy (Schwarz, 1974⁽⁸²⁾). No other abnormal values were seen in the remaining 749 patients. (Schmor, 1974⁽⁸⁵⁾; Wallin, 1974⁽⁸¹⁾; Quartararo, 1974⁽⁸⁸⁾; Dellenbach, 1974⁽⁸⁹⁾; Weidenbach, 1974⁽⁹⁹⁾; Milek, 1974⁽²⁶⁾ Anjanelyalu, 1977⁽⁹⁶⁾, Akinla, 1975⁽²⁷⁸⁾, Ward, 1976⁽⁸⁷⁾, Rao, 1978⁽⁹⁷⁾, Psaroudakis, 1977⁽⁹⁰⁾, Swarz, 1974⁽⁸²⁾).

Liver function tests were performed in 9 trichomoniasis studies of 402 patients treated with a single 2g dose of tinidazole. One paper (Ward⁽⁸⁷⁾) revealed 1 patient with increased SGPT. One paper (Ali⁽¹⁸³⁾) revealed 4 patients with increased bilirubin, and 2 patients with increased alkaline phosphatase. These patients were cases with infectious hepatitis and raised levels were found pretreatment.

Liver function tests (i.e.: SGOT, SGPT, alkaline phosphatase, serum bilirubin) were performed pre and post therapy in 171 giardia patients from five trials (Gadzer, 1977⁽¹²⁸⁾; Sabchareon, 1980⁽¹³⁰⁾; Krishnamurthy, 1978⁽¹⁹⁰⁾; Bassily, 1987⁽¹¹⁴⁾; Nigam, 1991⁽¹⁹¹⁾) treated with a single 2g dose of tinidazole. No abnormalities were noted.

Liver function tests were performed in 202 patients with amebiasis from six trials (Misra, 1974⁽¹⁹³⁾; Misra, 1977⁽¹⁹⁴⁾; Mabadeje, 1977⁽¹⁹⁵⁾; Singh, 1977⁽¹⁹⁶⁾; Swami, 1977⁽¹⁹⁷⁾; Mathur, 1977⁽¹⁹⁸⁾) given a 2g dose of tinidazole for 2-3 consecutive days. Follow up laboratory evaluations were performed 30 days post therapy in the amebiasis trials. Zuberi, 1973⁽²⁹¹⁾ reported a raised serum transaminase level noted on the 30th day after treatment initiation. It was not indicated if the patient had intestinal or hepatic amebiasis. The specific dose of tinidazole for this patient was not stated but dosing for the study ranged from 450mg/d x 5 days to 1200mg/d x 5 days.

Other laboratory findings include this summary from 13 amebiasis trials reporting on laboratory findings. The following was noted:

Table 7.2: Laboratory Findings in Amebiasis Trials

Number studies reporting	Findings
1	No abnormalities in laboratory investigations recorded
1	No drug-related toxicity observed
4	No biochemical changes detected
6	No hematological changes detected
6	No untoward changes in hepatic function
5	No untoward changes in renal function
3	No cardiac abnormalities
3	No abnormal changes in urine analysis
1	No toxic effect on bone-marrow
5	No abnormal changes in blood chemistry

Complete laboratory data was also obtained for the 18 subjects involved in Sponsor's BA/BE study. Measurements were made prior to the first 2g dose and 72 hours after the third and final 2g dose (doses were 1 week apart). No clinically significant changes were found and no significant trends were noted. Those data can be found in section 9 of the NDA (Human PK/BA).

Complete laboratory data (also included in the trichomoniasis clinical efficacy section of this NDA) for the 5 compassionate use patients follow. Five patients on high dose tinidazole supplied by sponsor (1 patient on 1g oral tid + 500mg vaginally tid x 14 days and 4 patients on 1g oral bid + 500mg vaginally bid x 14 days) were monitored for multiple laboratory parameters at day 4 of dosing and 1 day after completion of dosing. No clinically significant abnormalities were noted."

MO Comment: *In reviewing the citations separately there is agreement with the sponsor's evaluation. Specifically, only one case of LFT elevation was found and no evidence of leukopenia or other blood chemistry changes were noted. However, the*

attribution of elevated bilirubin in reference 183 (Ali) to infectious hepatitis is somewhat uncertain given the inadequate description in the submitted citation.

The sponsor also submitted data from 5 patients that received tinidazole (1g oral bid or tid and .5g vaginal tid) under a compassionate use protocols that underwent laboratory evaluation with a 15 day follow up. Laboratory evaluation occurred at baseline, day 4 and day 15 post therapy initiation. Complete blood count, basic metabolic panel, and hepatic function panel was conducted.

MO Comment: There were no abnormal laboratory values that were of clinical concern.

Extent of ECG Testing in the Development Program, Including Brief Review of Pre-Clinical Results

Specific ECG evaluation or preclinical QT studies (e.g. HERG) were not performed.

MO Comment: Given the long history of use in at least 12 foreign markets since the mid-1970s with no safety signal related to arrhythmias or cardiac disease noted, a reasonable safety profile has already been demonstrated.

7.2.7 Human Carcinogenicity

The sponsor summarized nitroimidazole carcinogenicity studies specifically related to metronidazole and ornidazole. Below are the relevant finding from the sponsor's ISS.

“In a 2 year, 250mg/kg/day po study, tinidazole was not shown to be carcinogenic in rats (reported in Simplotan (tinidazole) German labeling⁽²³⁰⁾). In addition, Rosignol 1984⁽⁶⁰⁾, in a review of nitroimidazoles mentions that results were negative in a 2 year tinidazole rat carcinogenicity study and that ornidazole at 400mg/kg/day for 2 years was also negative.

Metronidazole has been reported to be carcinogenic in rats but the validity of the results with metronidazole have been questioned.^(19, 66, 68) Metronidazole, however, has been clearly shown to cause an increase in the incidence of lung tumors in mice, a species in which lung tumors are commonly seen spontaneously.^(15, 16) Because of the finding with metronidazole in mice and the mutagenicity of this class of compounds in bacterial assays *in-vitro*, a number of epidemiological reviews have been done to examine a possible relationship of the exposure to metronidazole and incidence of cancer. Since metronidazole was the first (and only) nitroimidazole introduced in the U.S., there is much more human experience with it than the other nitroimidazoles.

The retrospective data attempting to link U.S. human use of metronidazole to long term cancer development have concluded that there is no association. Attached is a table, titled “Major Human Metronidazole Retrospective Cancer Studies”. This table displays the overall findings of the large retrospective cancer studies for metronidazole.

Table 7.29: Major Human Metronidazole Retrospective Cancer Studies

Study	Population	Finding
Beard 1979 (167) (Mayo clinic)	771 F trich pts w/MTZ 237 F trich pts w/o MTZ	Overall: RR vs. population: 1.1 (0.7-1.6), RR= 1.3 (0. 7-1.9) excluding cervical cancer Lung: 4 cases vs. 0.6 expected All 4=smokers
Beard 1988 (168) (Mayo clinic)	Same group of 771 MTZ pts (571) (15-25 yr follow-up) (vs. age specific incidence rates)	Overall: RR 1.4 (0.9-2.2) Bronchial RR 2.5 (1.7-4.4) (9 of 11 pts were smokers) Breast RR 1.3 (0.8-2.1)
Friedman 1989 (171) (Kaiser)	2460 persons w MTZ (11-15 year follow-up) (FDA & NCI funded)	Overall: RR 1.0 (.8-1.7) Lung: RR 1.3 (0.6-2.4) Breast: RR 0.8 (0.4-1.3) Cervical: RR= 2.1 (1.5 - 2.9)
Falagas 1998 (215) (Puget Sound)	5222 age & sex matched pairs of short term MTZ use (12.6 year median follow-up, minimum of 7 yrs)	Overall: RR 0.98 (0.8-1.2) Lung: RR 0.99 (0.5-2.1) Breast: RR 1.0 (0.7-1.6)
Thapa 1998 (216) (Tennessee Medicaid)	Explored cancer development in 328,000 children < 5 years old born in TN with/without in-utero exposure to MTZ	Overall: RR .81 (0.51-1.59)

Early small studies (771 patients, Beard, 1979⁽¹⁶⁷⁾ & 1988⁽¹⁶⁸⁾) reported slightly elevated but statistically insignificant risk ratios for cancer. These were confounded by the high number of smokers in the metronidazole sample, leading to an elevated risk of bronchial cancer.

More recent and larger studies by Friedman; 1989⁽¹⁷¹⁾, Falagas; 1998⁽²¹⁵⁾ and Thapa; 1998⁽²¹⁶⁾ covering 2460 metronidazole patients with 11-15 year follow-up, 5222 age and sex matched pairs, with mean of 12.6 yr follow-up and 328,000 children in Tennessee with and without in-utero exposure to metronidazole, respectively, demonstrated an overall cancer risk ratio of 1.0 or less. The Friedman work was funded by the FDA and the NCI.

From these studies, it can be concluded that there is no evidence to indicate that short term use of metronidazole is carcinogenic in humans.

MO Comment: *The cited literature in Table 7.25 does not indicate a significant carcinogenicity risk with short term exposure to metronidazole. Multiple confounders where small trends were evident as well as long term follow-up in larger studies support this observation. This does not insure that tinidazole carries the same safety profile but given the historic use in overseas markets for thirty years as well as the similarities between these two compounds there is reasonable cause to suspect that a similar safety profile would be applicable. See Dr. Hundley's*

Pharmacology/Toxicology review.

7.2.8 Human Reproduction and Pregnancy Data

Three publications included information on the use of tinidazole during pregnancy page 74, Sponsor's ISS):

1. Aimakhu, Reference #184, 1975
4 pregnant women treated with 2g TNZ. 3 of 4 were cured, all 4 babies were normal.

MO Comment: Long term follow up was not provided

2. Patil, Reference # 279, 1983
5 pregnant patients treated with 2g TNZ. 2 pregnant women (> 24 weeks when treated) underwent full term deliveries – normal. 3 other women terminated their pregnancies uneventfully.

MO Comment: The reason for the three pregnancy terminations is not provided in reference 279. Without further information the lack of narrative cannot be interpreted.

3. Akinla, reference #278, 1975
15 pregnant women (all in 2nd or 3rd trimester of pregnancy) treated with 2g TNZ
no comments made about deliveries.

MO Comment: Exposure data is provided without any relevant safety data regarding short term or long term follow up. See Dr. Hundley's pharmacology/toxicology review.

7.2.9 Overdose Experience

In the sponsor's ISS one case is reported concerning a serious adverse event related to metronidazole administration in excess of that recommended from foreign labels or the currently submitted application (page 80, ISS).

“There is a report of a patient who developed neurologic disturbances with metronidazole but did not have these disturbances with successful tinidazole therapy. In a case from Australia Lawford, 1993 ⁽²⁸³⁾ reported on a 30 year old male who was treated with 21 grams of metronidazole over 14 days for amebic liver abscess. One day after completion of therapy, he complained of tinnitus, vertigo and a staggering gait. Symptoms resolved after one month. Several months later he was again diagnosed with amebic liver abscess. Within 48 hours of starting metronidazole he complained of vertigo, left sided deafness, and ataxic gait, which resolved when therapy was changed to tinidazole (2g/day). He completed a 10 day course of tinidazole. Relapse diagnosed as amebic spleen abscess