NDA20-666

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Draft LBLg

D.v.Dir. memo

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Exclusivity Summ.

Patent Info

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Clin.Pharm/Bio

Pharm/Tox

Clin.micro

Chem

EA + Fonsi

Co.Corres

AP Ltr
Draft LBLJ

**NDA 20-266**

Ms. Deborah Hackett
Manager
U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
Philadelphia PA 19101

Dear Ms. Hackett:

Please refer to your December 8, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ALBENZA™ (albendazole) 200 mg tablets.

We acknowledge receipt of your amendments dated February 22, March 12 & 27, April 5 & 16, and May 8, 1996.

This new drug application provides for the treatment neurocysticercosis and hydatid disease.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommende . _ the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draftt labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-666. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated June 7, 1996. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

The phase 4 commitments to which you agreed includ the following:

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Pauline Fogarty
Consumer Safety Officer
(301) 827-2125

Sincerely yours,

David Feigal, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-666
HFD-520/Div. files
HFD-520/PM/P.Fogarty
HFD-520/BLeissa BL 6/7/96
HFD-2/M.Lumpkin
HFD-104/D.Feigal
HFD-101/L.Carter (with labeling)
HFD-520/MFanning
HFD-830/E.Sheinin
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)
HFD-021/J.Treacy (with labeling)

drafted: /June 7, 1996/
r/d Initials:pf

final

APPROVAL [with Phase 4 Commitments]

**DRAFT LABELING: June 6, 1996**

# ALBENZA™

## (albendazole) Tablets

**DESCRIPTION**

ALBENZA (albendazole) is an orally administered broad-spectrum anthelmintic. Chemically it is Methyl-5-(propylthio)-2-benzimidazolecarbamate. Its molecular formula is $C_{12}H_{15}N_3O_2S$. Its molecular weight is 265.34. It has the following chemical structure:

[ STRUCTURE ]

Albendazole is a white to off-white powder. It is soluble in dimethylsulfoxide, strong acids and strong bases. It is slightly soluble in methanol, chloroform, ethyl acetate, and acetonitrile. Albendazole is practically insoluble in water. Each white to off-white, film-coated tablet contains 200 mg of albendazole.

Inactive ingredients consist of carnauba wax, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium saccharin, sodium starch glycolate, starch, and coloring agent (opadry clear YS-2-19071A).

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**Absorption and Metabolism** Albendazole is poorly absorbed from the gastrointestinal tract due to it low aqueous solubility. Albendazole concentrations are negligible or undetectable in plasma as it is rapidly converted to the sulfoxide metabolite prior to reaching the systemic circulation. The systemic anthelmintic activity has been attributed to the primary metabolite, albendazole sulfoxide. Oral bioavailability appears to be enhanced when albendazole is coadministered with a fatty meal (estimated fat content 40 g) as evidenced by higher (up to 8-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state.

Maximal plasma concentrations of albendazole sulfoxide are typically achieved 2 to 5 hours after dosing and are on average 1.31 mcg/mL (range 0.46 to 1.58 mcg/mL) following oral doses of albendazole (400 mg) in hydatid disease patients, when administered with a fatty meal. Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range following ingestion of a fatty meal (fat content 43.1 g). The mean apparent terminal elimination half-life of albendazole sulfoxide typically ranges from 8 to 12 hours in normal subjects, as well as in hydatid and neurocysticercosis patients.

Following 4 weeks of treatment with albendazole (200 mg three times daily), patients' plasma concentrations of albendazole sulfoxide were approximately 20% lower than those observed during the first half of the treatment period, suggesting that albendazole may induce its own metabolism.

**Distribution**
Albendazole sulfoxide is 70% bound to plasma protein and is widely distributed throughout the body; it has been detected in urine, bile, liver, cyst wall, cyst fluid, and cerebrospinal fluid (CSF). Concentrations in plasma were 3- to 10-fold and 2- to 4-fold higher than those simultaneously determined in cyst fluid and CSF, respectively. Limited *in vitro* and clinical data suggest that albendazole sulfoxide may be eliminated from cysts at a slower rate than observed in plasma.

**Metabolism and Excretion**
Albendazole is rapidly converted in the liver to the primary metabolite, albendazole sulfoxide, which is further metabolized to albendazole sulfone and other primary oxidative metabolites that have been identified in human urine. Following oral administration, albendazole has not been detected in human urine. Urinary excretion of albendazole sulfoxide is a minor elimination pathway with less than 1% of the dose recovered in the urine. Biliary elimination presumably accounts for a portion of the elimination as evidenced by biliary concentrations of albendazole sulfoxide similar to those achieved in plasma.

**Special Populations:**
**Patients with Impaired Renal Function:** The pharmacokinetics of albendazole in patients with impaired renal function have not been

studied. However, since renal elimination of albendazole and its primary metabolite, albendazole sulfoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients.

**Biliary Effects:** In patients with evidence of extrahepatic obstruction (n=5), the systemic availability of albendazole sulfoxide was increased, as indicated by a 2-fold increase in maximum serum concentration and a 7-fold increase in area under the curve. The rate of absorption/conversion and elimination of albendazole sulfoxide appeared to be prolonged with mean $T_{max}$ and serum elimination half-life values of 10 hours and 31.7 hours, respectively. Plasma concentrations of parent albendazole were measurable in only one of five patients.

**Pediatrics:** Following single-dose administration of 200 mg to 300 mg (approximately 10 mg/kg) albendazole to three fasted and two fed pediatric patients with hydatid cyst disease (age range 6 to 13 years), albendazole sulfoxide pharmacokinetics were similar to those observed in fed adults.

**Elderly Patients:** Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data in hydatid cyst patients (up to 79 years) suggest pharmacokinetics similar to those in young healthy subjects.

**Microbiology:**
The principal mode of action for albendazole is by its inhibitory effect on tubulin polymerization which results in the loss of cytoplasmic microtubules.

In the specified treatment indications albendazole appears to be active against the larval forms of the following organisms:

*Echinococcus granulosus*
*Taenia solium*

**INDICATIONS AND USAGE**
ALBENZA is indicated for the treatment of the following infections:

Neurocysticercosis. ALBENZA is indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by

larval forms of the pork tapeworm, *Taenia solium*.

Lesions considered responsive to albendazole therapy appear as nonenhancing cysts with no surrounding edema on contrast-enhanced computerized tomography. Clinical studies in patients with lesions of this type demonstrate a 74% to 88% reduction in the number of cysts; with 40% to 70% of albendazole-treated patients showed resolution of all active cysts.

Hydatid disease. ALBENZA is indicated for the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of the dog tapeworm, *Echinococcus granulosus*.

This indication is based on combined clinical studies which demonstrated non-infectious cyst contents in approximately 80-90% of patients given ALBENZA for 3 cycles of therapy of 28 days each. (See **DOSAGE AND ADMINISTRATION**.) Clinical cure (disappearance of cysts) was seen in approximately 30% of these patients, and improvement (reduction in cyst diameter of $\geq$ 25%) was seen in an additional 40%.

NOTE: When medically feasible, surgery is considered the treatment of choice for hydatid disease. When administering ALBENZA in the pre- or post-surgical setting, optimal killing of cyst contents is achieved when three courses of therapy have been given.

NOTE: The efficacy of albendazole in the therapy of alveolar hydatid disease caused by *Echinococcus multilocularis* has not been clearly demonstrated in clinical studies.

**CONTRAINDICATIONS**

ALBENZA is contraindicated in patients with known hypersensitivity to the benzimidazole class of compounds or any components of ALBENZA

**WARNINGS**

Rare fatalities associated with the use of albendazole have been reported due to granulocytopenia or pancytopenia. (See **PRECAUTIONS**.) Blood counts should be monitored at the beginning of each 28-day cycle of therapy and every 2 weeks while on therapy with albendazole. Albendazole may be continued if the total white blood cell count and absolute neutrophil count decrease appear

modest and do not progress.

Albendazole should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be, the patient should be apprised of the potential hazard to the fetus. Patients should not become pregnant for at least 1 month following cessation of albendazole therapy. If a patient becomes pregnant while taking this drug, albendazole should be discontinued immediately.

**PRECAUTIONS**

**General:** Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids should be considered to prevent cerebral hypertensive episodes during the first week of anticysticercal therapy.

Cysticercosis may, in rare cases, involve the retina. Before initiating therapy for neurocysticercosis, the patient should be examined for the presence of retinal lesions. If such lesions are visualized, the need for anticysticercal therapy should be weighed against the possibility of retinal damage caused by albendazole-induced changes to the retinal lesion.

**Information for Patients:**

Patients should be advised that:

- Albendazole may cause fetal harm, therefore, women of childbearing age should begin treatment after a negative pregnancy test.
- Women of childbearing age should be cautioned against becoming pregnant while on albendazole or within 1 month of completing treatment.
- During albendazole therapy, because of the possibility of harm to the liver or bone marrow, routine (every-two-weeks) monitoring of blood counts and liver function tests should take place.
- Albendazole should be taken with food.

**Laboratory Tests:**
**White Blood Cell Count:** Albendazole has been shown to cause occasional (less than 1% of treated patients) reversible reductions in total white blood cell count. Rarely, more significant reductions may be encountered including granulocytopenia, agranulocytosis, or pancytopenia. Blood counts should be performed at the start of each 28-day treatment cycle and every 2 weeks during each 28-day cycle. Albendazole may be continued if the total white blood cell count decrease appears modest and does not progress.

**Liver Function:** In clinical trials, treatment with albendazole has been associated with mild to moderate elevations of hepatic enzymes in approximately 16% of patients. These have returned to normal upon discontinuation of therapy.

Liver function tests (transaminases) should be performed before the start of each treatment cycle and at least every 2 weeks during treatment. If enzymes are significantly increased, albendazole therapy should be discontinued. Therapy can be reinstituted when liver enzymes have returned to pretreatment levels, but laboratory tests should be performed frequently during repeat therapy.

Patients with abnormal liver function test results prior to commencing albendazole therapy should be carefully evaluated, since the drug is metabolized by the liver and has been associated with hepatotoxicity in a few patients.

**Theophylline:** Although single doses of albendazole have been shown not to inhibit theophylline metabolism (see **Drug Interactions**), albendazole does induce cytochrome P450 1A in human hepatoma cells. Therefore, it is recommended that plasma concentrations of theophylline be monitored during and after treatment with **ALBENZA**.

**Drug Interactions:**
*Dexamethasone:* Steady-state trough concentrations of albendazole sulfoxide were about 56% higher when 8 mg dexamethasone was coadministered with each dose of albendazole (15 mg/kg/day) in eight neurocysticercosis patients.

*Praziquantel:* In the fed state, praziquantel (40 mg/kg) increased

maximum serum elimination half life and area under the curve of albendazole sulfoxide by about 50% in healthy subjects (n=10) compared with a separate group of subjects (n=6) given albendazole alone. Mean $T_{max}$ and mean serum elimination half life of albendazole sulfoxide were unchanged. The pharmacokinetics of praziquantel were unchanged following coadministration with albendazole (400 mg).

*Cimetidine:* Albendazole sulfoxide concentrations in bile and cystic fluid were increased (about 2-fold) in hydatid cyst patients treated with cimetidine (10 mg/kg/day) (n=7) compared with albendazole (20 mg/kg/day) alone (n=12). Albendazole sulfoxide plasma concentrations were unchanged 4 hours after dosing.

*Theophylline*: The pharmacokinetics of theophylline (aminophylline 5.8 mg/kg infused over 20 minutes) were unchanged following a single oral dose of albendazole (400 mg) in 6 healthy subjects.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**
Long term carcinogenicity studies were conducted in mice and rats. In the mouse study, albendazole was administered in the diet at doses of 25, 100, and 400 mg/kg/day (0.1, 0.5, and 2 times the recommended human dose based on body surface area in $mg/m^2$, respectively) for 108 weeks. In the rat study, albendazole was administered in the diet at doses of 3.5, 7, and 20 mg/kg/day (0.04, 0.08, and 0.21 times the recommended human dose based on body surface area in $mg/m^2$, respectively) for 117 weeks. There was no evidence of increased incidence of tumors in the treated mice and rats when compared to the control group.

In genotoxicity tests, albendazole was found negative in an Ames Salmonella/Microsome Plate mutation assay with and without metabolic activation or with and without preincubation, cell-mediated Chinese Hamster Ovary chromosomal aberration Test, and *in vitro* mouse micronucleus test. In the *in vitro* BALB/3T3 cells transformation assay, albendazole produced weak activity in the presence of metabolic activation while no activity was found in the absence of metabolic activation.

Albendazole did not adversely affect male or female fertility in the rat at an oral dose of 30 mg/kg/day (0.32 times the recommended human dose based on body surface area in $mg/m^2$).

**Pregnancy:Teratogenic Effects Pregnancy Category C:**
Albendazole has been shown to be teratogenic (to cause embryotoxicity and skeletal malformations) in pregnant rats and rabbits. The teratogenic response in the rat was shown at oral doses of 10 and 30 mg/kg/day (0.10 times and 0.32 times the recommended human dose based on body surface area in $mg/m^2$, respectively) during gestation days 6 to 15 and in pregnant rabbits at oral doses of 30 mg/kg/day (0.60 times the recommended human dose based on body surface area in $mg/m^2$) administered during gestation days 7 to 19. In the rabbit study, maternal toxicity (33% mortality) was noted at the 30 mg/kg/day. In mice, no teratogenic effects were observed at oral doses up to 30 mg/kg/day (0.16 times the recommended human dose based on body surface area in $mg/m^2$), administered during gestation days 6 to 15.

There are no adequate and well-controlled studies of albendazole administration in pregnant women. Albendazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

**Nursing Mothers:** Albendazole is excreted in animal milk. It is not known whether it is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when albendazole is administered to a nursing woman.

**Pediatric Use:** Experience in children under the age of 6 years is limited. In hydatid disease, infection in infants and young children is uncommon, but no problems have been encountered in those who have been treated. In neurocysticercosis, infection is more frequently encountered. In five published studies involving children as young as 1 year, no significant problems were encountered, and the efficacy appeared similar to the adult population.

**Geriatric Use:** Experience in patients 65 years of age or older is limited. The number of patients treated for either hydatid disease or neurocysticercosis is limited, but no problems associated with an older population have been observed.

**ADVERSE REACTIONS**
The adverse event profile of albendazole differs between hydatid disease and neurocysticercosis. Adverse events occurring with a frequency of ≥1% in either disease are described in the Table

below.

These symptoms were usually mild and resolved without treatment. Treatment discontinuations were predominantly due to leukopenia (0.7%) or hepatic abnormalities (3.8% in hydatid disease). The following incidence reflects events that were reported by investigators to be at least possibly or probably related to albendazole.

**Adverse Event Incidence ≥1% in Hydatid Disease and Neurocysticercosis**

| **Adverse Event** | **Hydatid Disease** | **Neurocysticercosis** |
|---|---|---|
| Abnormal Liver Function | 15.6 | <1.0 |
| Abdominal Pain | 6.0 | 0 |
| Nausea/Vomiting | 3.7 | 6.2 |
| Headache | 1.3 | 11.0 |
| Dizziness/Vertigo | 1.2 | <1.0 |
| Raised Intracranial Pressure | 0 | 1.5 |
| Meningeal Signs | 0 | 1.0 |
| Reversible Alopecia | 1.6 | <1.0 |
| Fever | 1.0 | 0 |

The following adverse events were observed at an **Incidence of <1%**:

**Hematologic:** Leukopenia. There have been rare reports of granulocytopenia, pancytopenia, agranulocytosis, or

thrombocytopenia. (See **WARNINGS**.)

**Dermatologic:** Rash, urticaria.

**Hypersensitivity:** Allergic reactions.

**Renal:** Acute renal failure related to albendazole therapy has been observed in one patient.

**OVERDOSAGE**

Significant toxicity and mortality were shown in male and female mice at doses exceeding 5,000 mg/kg; in rats, at estimated doses between 1,300 and 2,400 mg/kg; in hamsters, at doses exceeding 10,000 mg/kg; and in rabbits, at estimated doses between 500 and 1,250 mg/kg. Clinical symptoms were demonstrated in a dose response relationship and included diarrhea, vomiting, tachycardia, and respiratory distress. One overdosage has been reported with ALBENZA in a patient who took at least 16 grams over 12 hours. No untoward effects were reported. In case of overdosage, symptomatic therapy (e.g. gastric lavage and activated charcoal) and general supportive measures are recommended.

**DOSAGE AND ADMINISTRATION**

Dosing of *ALBENZA* will vary, depending upon which of the following parasitic infections is being treated.

| Indication | Patient Weight | Dose | Duration |
|---|---|---|---|
| Hydatid Disease | 60 kg or greater | 400 mg bid, with meals | 28-day cycle, followed by a 14-day ALBENZA-free interval, for a total of three cycles |
| | less than 60 kg | 15mg/kg (maximum dose 800 mg/day), given bid with meals | |
| | NOTE: When administering ALBENZA in the pre- or post-surgical setting, optimal killing of cyst contents is achieved when three courses of therapy have been given. | | |
| Neurocysticercosis | 60 kg or greater | 400 mg bid, with meals | 8-30 days |
| | Less than 60 kg | 15 mg/kg (maximum dose 800 mg/day), given bid with meals | |

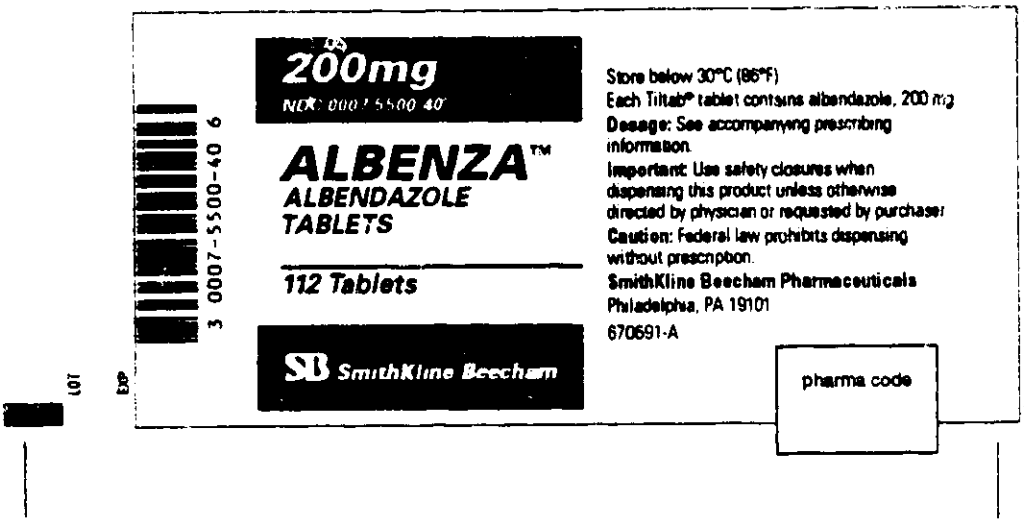
Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids should be considered to prevent cerebral hypertensive episodes during the first week of treatment.

**HOW SUPPLIED**
**ALBENZA** is supplied as 200 mg, white to off-white, circular, biconvex, bevel-edged, film-coated Tiltab® tablets in bottles of 112.

NDC 0007-5500-40 Bottles of 112
Store below 30°(86°F).

**SmithKline Beecham Pharmaceuticals**
Philadelphia, PA 19101

**ALBENZA - ALBENDAZOLE TABLETS**
**200mg/112 Tablets**
**3/5/96**
**670691-A**
**PROOF #4 dl/dt**




Top band prints solid
PANTONE WARM RED
Type reverses to white
out of BKGD

Rule-PANTONE WARM RED

Bottom band prints solid PMS 328
(corp green)
Logo reverses to white
out of BKGD

All type prints BLACK
Except where indicated

Pharma Code No.:XXX
Color breaks -

Size: 2" x 5"
(See Printing Spec.)

Spot Varnish - Magenta die line does
not print, guide for varnish only

Div. D.I.R.
memo

June 11, 1996

Division Director's Memo

NDA 20-266
(ALBENZA) Albendazole 200 mg tablets

This application consisted of 2 indications for the use of Albendazole in the treatment of (1) Hydatid Disease and (2) Neurocysticercosis.

The review was completed as a priority application in its scheduled time frame and a final approval decision was made for both indications with the following restrictions:

1. Hydatid Disease

The data presented was primarily derived from literature publications and compassionate use programs totalling over 3,000 patients in several countries including the U.S. and U.K. The rationale for use was based on in vitro effect of the drug on Echinococcus granulosus as well as observed clinical response rates. Following treatment Echinococcus granulosus cyst contents were found to be non-infectious in 80-90% of cases. Although cure and improvement rates varied widely, combined results indicated cure in 30% and improvement (decreased cyst diameter of less than or equal to 25%) in an additional 40%. The observed response rates in bone and brain were deemed to be inadequate to support approval for treatment at these sites. Treatment guidelines for the approved regimen were expanded to include pre- and post- surgical situations where the decrease in infectiousness of spillage at the time of surgery would minimize the potential for recurrence.

The data provided for Echinococcus multilocularis was different in nature as is the disease process caused by this organism. There was no clear demonstration of drug effect on the organism itself and the clinical data provided included a very small number of patients and demonstrated cure rates as low as 13.9%. Thus Albendazole was not approved for treatment of Echinococcus multilocularis based on inadequate data to support either safety or efficacy.

2. Neurocysticercosis

The data used to support this indication consisted of publications, compassionate use experience in the U.S. and a clinical study in Peru. The clinical study in Peru was

inspected and found to have major procedural problems which invalidated its inclusicn as a pivotal trial. These included the absence of primary clinical and CT scan data as well as unblinded reading of the CT scans. When these were read by members of the division of medical imaging at the FDA the cure rates were considerably lower than those reported by the investigator ie 0% for 7 day therapy compared to 57.6% and 12% for 14 day therapy vs 78.8%, respectively.

The primary source of data used in reaching this decision was provided via 2 metaanalyses of studies and clinical observations stratified according to adequacy of the study design. This yielded observed cure or improvement rates measured by CT scan in the range of %. Compassionate study results showed cure or improvement rates of 74.4%. Clinical responses were higher.

The area of treatment of neurocysticercosis is frought with disagreement among experts. The use of therapy has been shown to be most effective for active lesions (non-enhancing, cysts without surrounding edema on CT scan) and would scientifically be supported by the mechanism of action of this drug which is to kill the larval forms of Taenia Solum, the cause of Neurocysticercosis.

Thus, the indication given is for the treatment of active lesions as defined above.

Mary M. Fanning, M.D., Ph.D.

cc: Orig. NDA 20-266
HFD-520
HFD-520 (PCoyne)
HFD-520 (BLeissa)
HFD-520 (DKing)
HFD-520 (DKatague)
HFD-520 (MAdeyemo)
HFD-520 (PFogarty)
HFD-104 (DFeigal) 6-9-95

S. mor

memo

**Supervisory Medical Officer's Memorandum**

# NDA 20-666

**Date:** 3 June, 1996

**Drug:** Albenza® (albendazole)

In the applicant's proposed labeling for Albenza®, they request approval for the following treatment indications:

"*Albenza* is indicated for the treatment of:
(1) hydatid disease (cystic echinococcosis due to *E. granulosus* or alveolar echinococcosis due to *E. multilocularis* larvae). *Albenza* has shown greatest efficacy in the treatment of liver, lung and peritoneal cysts;
(2) neurocysticercosis due to larval *T. solium*."

In this submission, the applicant submitted very little information (in the form of clinical trial data or literature references) to address the purported efficacy of albenazole in the treatment of alveolar echinococcus due to *E. multilocularis*. Therefore, approval for this infection and its associated pathogen should not be granted at this time.

Similarly, insufficient information was submitted to assess the efficacy of albendazole against hydatid disease localized to the brain and bone.

Thus, for this treatment indication, approval should be limited to: "the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of the dog tapeworm, *Echinococcus granulosus*."

I concur with the reviewing medical officer's recommendation to approve albendazole for the treatment of parencyhmal neurocystosis due to *Taenia solium* and cystic hydatid disease of the liver, lung, and peritoneum due to *Echinococcus granulosus*.

Brad Leissa, M.D.
Supervisory Medical Officer

**CC:** NDA 20-666
HFD-520
HFD-520/MO/Coyne
HFD-520/SMO/Leissa
HFD-520/DepDir/Gavrilovich
HFD-520/Biostats/Jiang
HFD-520/CSO/Fogarty
HFD-520/Chem/Katague
HFD-520/Micro/King
HFD-520/Pharm/Adeyemo
HFD-520/Biopharm/Colangelo
HFD-344/Thomas

**Concurrence Only:**
HFD-520/Dir/DFeigal


mor

NDA 20-666

# MEDICAL OFFICER REVIEW OF ORIGINAL NDA

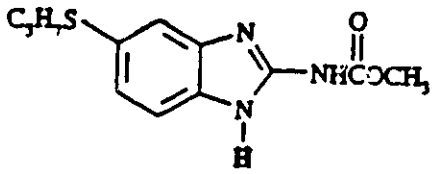
Date of submission: 8 December 1995
Date of receipt: 11 December 1995
Date review completed: 1 June 1996

Name of drug:
Generic: Albendazole
Proprietary: Albenza

Applicant: SmithKline Beecham Pharmaceuticals
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101
POC: Debra Hackett, Manager, US Regulatory Affairs

Class of drug: benzimidazole antiparasitic
Dosage form: 200 mg tablets for oral administration

Molecular formula: $C_{12}H_{15}N_3O_2S$
Molecular weight: 265.33
CAS Registry Name: CAS-54965-21-8
Chemical name: Methyl 5-(propythio)-2-benzimidazole carbamate
Structural formula:



Materials reviewed:
1. NDA 20-666, volume 1.1 and volumes 1.107-1.120
2. Amendment 1 to NDA 20-666, submitted 22 February 1996. 24 volumes.

# Table of contents

## .iistry, Manufacturing, and Controls

The CMC review of NDA 20-666 was performed by the Reviewing Chemist, David Katague. This document should be referred to for complete information on CMC aspects of this NDA.

Albendazole is a white to off-white powder which is hydrophobic and practically insoluble in water (aqueous solubility of 0.530 mg/L at pH 7.0). It has no known stereoisomers or polymorphic forms. It has a coefficient of partition ($CHCl_3/H_2O$) of 52.2 at 20°C. Albendazole is not hygroscopic (based on 10 year stability data).

The structure of albendazole has been verified by elemental analysis, infrared and UV spectroscopy, NMR and mass spectometry. The compound is chemically synthesized in stages. One-year stability data for three lots stored at room temperature were submitted with NDA 20-666 and found to be acceptable. Additional stability data was submitted from previously manufactured lots, which demonstrate the stability of albendazole at room temperature (approximately 25°C) for up to five years.

The applicant proposes to manufacture albendazole at a facility in Juitepec, Mexico. This facility was inspected by Office of Compliance, and is the subject of an acceptable EER (#9340) dated 3/22/96.

The manufacturing process involves the following:

# Preclinical Pharmacology/Toxicology

*The reader is referred to the complete review* by Oluwadare M. Adeyemo, Reviewing Pharmacologist, HFD-520. In the conclusion to his review, he states:

"The pharmacokinetics of albendazole have been studied in the rat, dog, and rabbit, while the biotransformation has been studied in the rat and mouse. Following oral dosing in all species examined, albendazole (ABZ) was rapidly converted to ABZ sulfoxide, such that ABZ concentrations in plasma were negligible or below detectable limits. The systemic anthelminthic activity of ABZ was attributed to the primary metabolite, ABZ sulfoxide. Studies with oral [$^{14}$C] ABZ in the rat and mouse indicated that ABZ was moderately well absorbed. In the mouse, approximately 20% of the administered dose was recovered in the urine following administration of [$^{14}$C] ABZ. In studies in the rat, radioactivity excreted in the urine ranged from 30 to 70% of the administered dose following single oral doses of [$^{14}$C] ABZ (10-13.25 mg/kg).

"The absorption of ABZ followed first-order kinetics in the rat, probably due to passive diffusion with no evidence for a saturable mechanism. Maximal plasma concentrations of ABZ-sulfoxide (ABZ-SO) occurred between 2 and 6 hours following oral dosing in the rat, rabbit, and dog. The extent of ABZ-SO bioavailability appeared to be lower in the dog compared with the rat and rabbit. ABZ-SO mean $AUC_{(0-t)}$ in the dog was 10.6 µg.h/mL compared to 32.9 and 31.9 in the rat and rabbit, respectively, following single oral doses of ABZ at 10 mg/kg. However, in all species, ABZ-SO was the primary circulating metabolite with plasma concentrations consistently higher ( than those of the sequential metabolite, ABZ sulfone. The pharmacokinetics of ABZ-SO appeared to increase in a dose-dependent manner between mg/kg following single oral doses in the rabbit.

"ABZ-related metabolite was rapidly eliminated from tissues and blood following a single oral dose of [$^{14}$C] ABZ at 10 mg/kg to male and female Wistar rats. Maximal radioactivity was observed in organs and blood 2-3 hours after dosing. The highest amount of drug-related metabolite was observed in the liver and kidneys. Radioactivity in the blood declined with a half-life of about three hours. After 10 days of treatment with ABZ at 10.6 mg/kg/day in rats, ABZ-SO $AUC_{(0-18)}$ decreased by about %, while plasma concentrations of ABZ-sulfone were increased %) compared with single dose administration. These data seem to suggest auto-induction of metabolism following repeated administration of ABZ to rats. Other studies showed that increases in cytochrome P450 enzyme activity in vitro fold increase in 7-ethoxyresorufin-0-deethylase) and results of immunoblotting assays suggest that the increased sulfonation observed in vivo can be attributed to the induction of rat liver cytochrome P450IA. Another important metabolic route reported in both the rat and mouse was hydroxylation of the propyl group to hydroxysulfone metabolites. In the rat, an additional pathway of importance was hydrolytic cleavage of the carbamate to the 2-amino derivative. The cleaved intermediate comprised about 14.8% of the total extractable radioactivity. However, the formation of the 2-amino derivative was less important in the mouse, and comprised only 3.7% of the total extractable radioactivity."

"The acute toxicity of ABZ in the mouse, rat, and dog appeared to be low and the sponsor speculated that acute poisoning in man may be remote. Subacute studies in the mouse, rat, and dog showed that the testes, kidneys, liver, and the hematopoietic systems are targets of toxicity. Recovery studies showed that ABZ-associated effects significantly reversed following cessation of treatment. In the presence of testicular toxicity, fertility in males and females appeared not to be affected by treatment with ABZ. Benzimidazole compounds, e.g. ABZ, are known to be teratogenic but there may be a NOEL level for this effect for ABZ."

"ABZ was evaluated for its mutagenicity potential in several in vitro and in vivo systems, but considered not mutagenic. Also, carcinogenicity studies in mice and rats showed ABZ not to be carcinogenic in animal models."

"In common with other benzimidazole compounds, ABZ has been shown to be teratogenic in rats, rabbits, and hogs."

"Based on the preclinical data...ABZ was shown to be teratogenic in several animal species. Therefore it is recommended that ABZ be classified as 'Pregnancy Category C'."

# Microbiology

The reader is referred to the microbiology review completed by James R. King, reviewing microbiologist, HFD-520.

In summary, the mechanism of action of ABZ is via its ability to bind to the cytoskeletal protein matrix, inhibiting the polymerization of tubulin to form the microtubulin matrix of the eukaryotic cell. *Tubulin and microtubules are universally* present in eukaryotic cells, and the lower toxicity to mammalian cells is related to the reversibility of tubulin binding of the benzimidazole; this reversibility is not demonstrated in parasite cells.

The spectrum of activity of ABZ appears to be wide among helminths, including various species of nematodes, cestodes, and trematodes. Furthermore, limited clinical data indicate that ABZ has activity against protozoa, to include species of microsporidia as well as the intestinal flagellate *Giardia lamblia*. Given the paucity of in vitro systems of culturing and *susceptibility testing*, the spectrum of activity of ABZ can only be judged by observations of clinical and veterinary trials.

Although resistance to ABZ has appeared in animals exposed to high parasite burdens and repeated treatment courses, this has not been apparent in the clinical use of ABZ.

# Clinical Pharmacology and Biopharmaceutics

The reader is referred to the review of NDA 20-666 by Philip Colangelo, Ph.D., OCPB reviewer, HFD-520. In his synopsis, Dr. Colangelo states the following:

"In nearly all studies, plasma ABZ concentrations were not quantifiable and the pharmacokinetic estimates for ABZ-SO were comparable between subjects and patients. The sulfoxide metabolite attained maximal plasma concentrations within ~ 2 hours and has an average half-life in both subjects and patients of ~ 8 to 12 hours. The presence of a high fat meal increased the systemic exposure to ABZ-SO by fold when compared to fasted conditions. The plasma protein binding of ABZ-SO was ~ 70%, and plasma concentrations of ABZ-SO were reported to be fold higher than those in cysts and -fold higher than those in cerebrospinal fluid. Bioconversion of ABZ to ABZ-SO by the liver appeared to be rapid and extensive, as evidenced by the results of *in vitro* studies in both rat and human microsomal preparations. In rat intestinal preparations, the contribution of intestinal metabolism to ABZ-SO was minimal ( %) compared to that of the liver. A route of ABZ-SO excretion appeared to be biliary, with urinary excretion of ABZ-SO accounting for only ~ 1% of the administered ABZ dose over a 24-hour period and no ABZ detected in human urine. Fecal excretion of either ABZ or ABZ-SO was not studied in any of the literature reports.

"No significant alterations in ABZ-SO pharmacokinetics were apparent with coadministration of ABZ and either intravenous aminophylline or oral cimetidine. However, coadministration with either oral praziquantel or oral dexamethasone substantially increased systemic exposure to ABZ-SO, although no side effects or biochemical abnormalities were noted with the combination of ABZ and praziquantel.

"The sponsor submitted results of *in vitro* multi-point dissolution testing between the tablet manufactured at the China facility, which was used for compassionate use for hydatid disease and neurocysticercosis in the US, and the formulation to be manufactured and marketed in the US. The two formulations are identical in composition, and dissolution for the to-be-marketed US formulation was comparable to that of the China tablet (i.e., Q % at min for the to-be-marketed US tablet vs % for the China tablet). The sponsor also performed dissolution testing between the to-be-marketed US formulation and the tablet manufactured at its French facility, which was used for compassionate use in the World Health Organization studies for hydatid disease and in the neurocysticercosis clinical trial conducted in Peru. Dissolution at minutes for the French (i.e., Q %) and to-be-marketed US formulations were acceptable."

# Foreign marketing experience

The following chart describes the dates of filing, approval, launch, and approved indications for formulations of albendazole worldwide, as described in NDA 20-666:

| Country/ formulation | Date of | | | Indications approved | | | Comments |
|---|---|---|---|---|---|---|---|
| | filing | approval | launch | NCC | Echino-coccosis | Other | |
| **Australia**<br>200 mg tab (Zentel®)<br>400 mg tab (Eskazole®) | 8/92<br>6/92 | 2/94<br>12/93 | | X | *E. granulosus* only | Intestinal nematodes and cestodes. CLM. *Chlonorchis, Opisthorchis, Capillaria* | CLM = cutaneous larva migrans<br>NCC = neurocysti-cercosis |
| **Holland**<br>400 mg tab | 5/91 | 11/92 | | | Both species | | |
| **France**<br>200 mg tab<br>400 mg tab | 3/80<br>1/87 | 7/81<br>7/87 | | | | Intestinal nematodes and cestodes. | |
| **Germany**<br>400 mg tab | 6/90 | 8/92 | | | Both species | *Trichinella, Strongyloides* | |
| **India**<br>?? mg tab | | | | | Both species | Intestinal nematodes, cestodes. *Giardia* in children | |
| **Japan**<br>?? mg tab | 3/93 | 1/94 | | | *E. multilocularis* only | | |
| **Spain**<br>200 mg tab<br>400 mg tab | 7/86<br>2/91 | ??<br>5/94 | | | Both species | | |
| **South Africa**<br>?? mg tab | 3/82 | 8/89 | | | | Intestinal nematodes and cestodes, *Opisthorchis* | |
| **United Kingdom**<br>200 mg tab<br>400 mg tab | 3/89<br>3/89 | 6/92<br>6/92 | | | Both species | | |

# Albendazole in the treatment of neurocysticercosis

A. Introduction

1. Life cycle and mode of transmission. (See Figure 1.) Neurocysticercosis (NCC) is a cestode infection of the central nervous system caused by the larvae of the pork tapeworm, *Taenia solium*. The adult tapeworm resides in the small intestine of the human definitive host. It has a head with hooklets (referred to as an armed scolex) with which it attaches to the wall of the small bowel. The adult worm can attain a length of 2 to 7 meters, and is composed of a chain of individual segments called proglottids. Maturation of the proglottids occurs in a conveyor belt-like fashion; the most immature ones are directly behind the scolex, and the most mature proglottids are found at the terminal portion. As proglottids attain maturity, they frequently become separated from the worm (referred to as the strobila) and are passed, either passively or via active migration, through the anus and to the external environment. Mature proglottids contain infective eggs. Each adult strobila is composed of roughly 1000 proglottids of all stages of maturation, and each mature proglottid can hold up to 50,000 eggs which are released into the environment. These eggs are fully mature and infective upon escape from the gravid proglottid and they remain infective for many weeks after passage.

Ingestion of infective eggs by pigs causes the typical pig-man-pig life cycle to be continued. The infective eggs liberate a larval stage (the oncosphere) following exposure to digestive enzymes. The oncosphere penetrates the wall of the small bowel and enters a mesenteric venule, via which it is hematogenously carried to various tissues of the porcine intermediate host. Any tissue can be potentially infected, though striated muscle is the most common site of encystation. Over a period of 60 to 70 days following ingestion, the oncosphere matures into the cysticercus stage. The cysticercus is a subspherical to ovoidal, milky-white bladder with a minute head invaginated into the bladder on one side. This "measle" or "bladder worm" measures 5 X 8-10 mm. In areas endemic for *T. solium*, meat from slaughtered hogs can contain such high numbers of cysticerci that they can be seen grossly, imparting an appearance that is referred to as "measly pork". If such infected pork is inadequately cooked prior to consumption by man, the viable cysticercus is digested out of the pork flesh, evaginates, and attaches its head to the wall of the small intestine. In 5 to 12 weeks, the worm has grown to maturity and gravid proglottids are passed, completing the life cycle.

If this were the extent of man's involvement with the life cycle of *T. solium*, there would not be much need for concern. Infection with the adult strobila can cause vague and relatively mild gastrointestinal symptoms (such as abdominal discomfort, indigestion, diarrhea and/or constipation). In rare cases, the bulk of the strobila in the lumen of the small bowel can cause intestinal obstruction, or the armed scolex may perforate the bowel causing peritonitis.

The important pathologic stage of the *T. solium* life cycle in human disease is the cysticercus. Unlike the similar-appearing beef tapeworm, *T. saginata*, eggs of the pork tapeworm are infective to humans when ingested. The parasite is not able to differentiate when it has gained access to a human, as opposed to a porcine, host. Thus, the *T. solium* egg releases an oncosphere in the lumen of the human small bowel, and the hematogenous spread of larvae can lead to the development of cysticerci in all tissues of the human host. The nature and severity of symptoms are a function of the number and location of the cysticerci. (See *Clinical Manifestations*, below.)

2. Epidemiology and public health significance. Human cysticercosis and taeniasis (infection with the adult stage of *Taenia solium*) is endemic throughout most of the developing world where swine husbandry is practiced (see Figure 2). Two conditions are necessary for continuation of transmission of cysticercosis: human consumption of inadequately cooked pork products, and swine husbandry practices which favor consumption of human waste by hogs. Inadequate sewage treatment with subsequent contamination of human food and water sources is also an important factor in the epidemiology of this disease. Direct person-to-person transmission is also possible; eggs have been demonstrated on the clothing, under the fingernails, and elsewhere on the body of tapeworm carriers. Household clustering of cases of taeniasis/cysticercosis has been described, particularly in Mexico. In a dramatic demonstration of such clustering, a recent study by Schantz et al (NEJM 327(10): 692-5, 1992) described an outbreak of neurocysticercosis among a community of non-pork-eating, orthodox Jews in New York City. Two domestic household workers, both recent immigrants from Latin America, were found to have either direct or indirect evidence of *Taenia solium* infection and were considered to be the likely sources of this urban household outbreak.

In some Latin American countries, the prevalence of *T. solium* infection among hogs approximates 5% and human infection (as defined by serological survey using the highly sensitive and specific enzyme-linked immunoelectro-transfer blot [EITB]) is in the 10% range (Sarti E., et al, Am J Trop Med Hyg 46(6): 677-85, 1992). Neurocysticercosis is a major cause of epilepsy and headache in such countries and can account for 10-12% of neurological hospital admissions and up to 50% of cases of adult-onset epilepsy (Bryan, R., 1992).

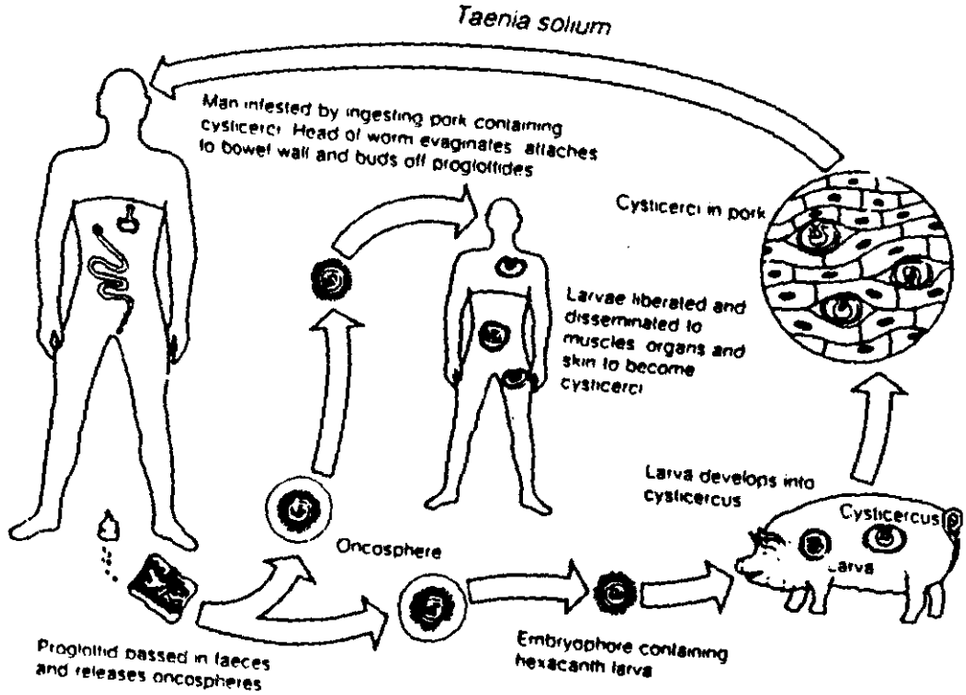



**FIGURE 1:** Life cycle of *Taenia solium*
Adapted from volume 1.107, page 082 of NDA 20-666

# Figure 2

From Bryan, R.T. Current issues in cysticercosis: Proteins, Proglottids, Pigs, and Privies
In: Walker DH (ed): Global Infectious Diseases: Prevention, Control, and Eradication.
Vienna: Springer-Verlag, 1992. Page 189.

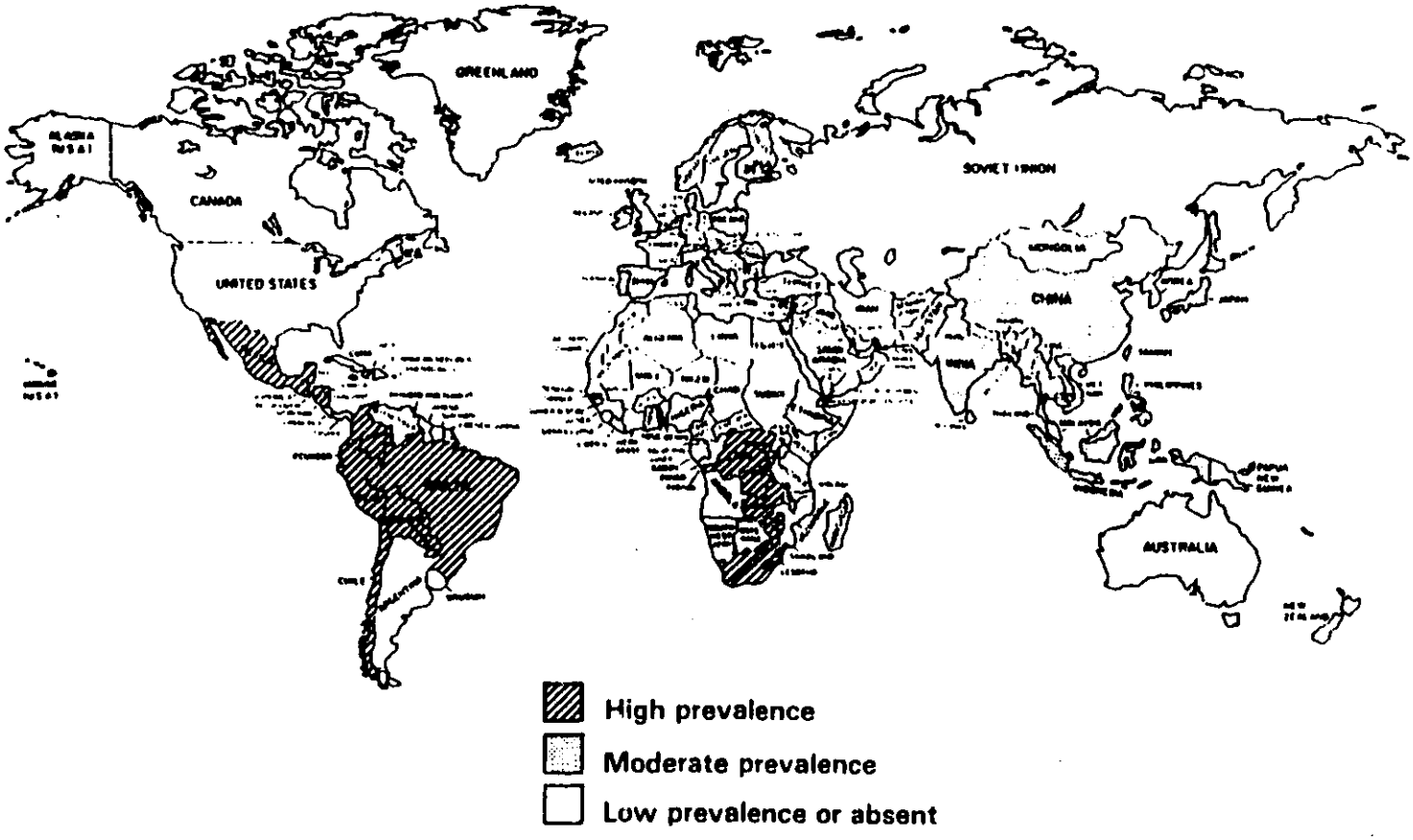



Fig. 2. Geographic distribution of *Taenia solium*

The relative prevalence of cysticercosis and taeniasis in Central- and South Americans, coupled with the large numbers of people from these countries immigrating to the United States in recent years, have significantly increased the public health significance of this infection in the US. Furthermore, as demonstrated by the New York City outbreak (above) as well as an intensive surveillance system in Los Angeles County (Sorvillo F, et al, Am J Trop Med Hyg 47(3): 365-71, 1992), as the prevalence of infection rises among the immigrant population, the possibility of locally-acquired disease also increases.

As Bryan (1992) states, "It is difficult to assess the overall public health and socioeconomic impact of cysticercosis. Flisser has estimated that 75% of patients with neurocysticercosis fall within productive age groups, thereby making a significant socioeconomic impact due to inability to work. Flisser also estimates that in 1986 over 14.5 million US dollars were spent in Mexico alone to treat approximately 2700 newly hospitalized patients with neurocysticercosis." Similar sorts of estimates concerning dollar costs for treatment in the US, and costs of lost productivity, are not immediately forthcoming. Nonetheless, particularly in the current climate of health care cost containment, the prevention and non-surgical treatment of the neurologic complications of cysticercosis would seem to be important goals.

3. Clinical manifestations. Given the fact that the hematogenous spread of oncospheres can lead to implantation and development of a cysticercus in any anatomic site, it is not surprising that this disease can manifest with a number of different clinical signs and symptoms. It is not only the location of the cysticerci, but their number, size, morphology, and the presence or absence of associated inflammatory response that affect the clinical picture in an individual patient. The most common site of anatomic localization is the subcutaneous tissues, followed by the eye, brain, skeletal muscle, heart, liver, and lungs (Faust et al, Clinical Parasitology 8th ed., Lea and Febiger, 1977).

Of specific interest in this application is neurocysticercosis, which is the most commonly recognized and clinically significant form of the disease. In decreasing order of importance, the following are the most prominent manifestations of neurocysticercosis: seizures; headache; increased intracranial pressure; personality changes; and focal neurologic deficits (Faust, 1977). The range of neurologic symptoms results from the variety of pathophysiologic lesions: discrete or multiple intraparenchymal or intraventricular lesions; chronic arachnoiditis; acute encephalitis; or intraocular lesions. The parasite may also grow in one of two ways: either as a discrete, bladder-like cyst (the 'cysticercus'), or as a more amorphous, spreading form referred to as the 'racemose' cyst. Racemose cysticercosis can occur in anywhere from 10 to 33% of cases (Nash T and Neva F, NEJM 311: 1492-6, 1984) and is found most commonly in the ventricles, basal cisterns, and subarachnoid space.

4. Clinical disease factors which influence process of regulatory review. Neurocysticercosis (NCC) is a disease which does not lend itself easily to the type of clinical studies usually submitted to the U.S. Food and Drug Administration. Such factors include the following:

- Little or no autochthonous disease. In the United States, NCC is a disease of immigrants. Those medical centers which see cases of NCC, predominantly those states and cities in the US that have large populations of Hispanic immigrants, do not see large enough numbers of cases to enable the conduct of a well-designed, prospective investigation. Therefore, almost all of the medical literature on the treatment of NCC is non-US in origin. The US data consist of a series of individual compassionate-use cases compiled by the sponsor.

- Incompletely understood natural history of the disease. As mentioned in the above discussion of clinical manifestations, there is a wide range of signs and symptoms that a particular patient with NCC may manifest. Such variation is thought to be caused by a combination of host factors (for example, individual host's immune response, underlying health status, and number of *Taenia solium* eggs ingested) and parasite factors (such as predilection for certain tissues at encystment, and predilection for formation of racemose cysts). Not only is the natural history of intraparenchymal lesions considered to be quite different from that of intraventricular or meningeal lesions; the natural history of intraparenchymal lesions is considered to be quite variable as well. There may also be strain-to-strain variability in susceptibility to antiparasitic drugs, although this has not been adequately studied. Because these factors and others combine to determine clinical outcome, it becomes vitally important to perform clinical studies on as homogeneous a group of NCC patients as possible.
  Since CT scanning is currently the primary diagnostic modality for diagnosing NCC, the appearance of NCC lesions on CT scanning is of primary importance in determining a homogeneous patient population at study entry.

The consensus of the medical literature is that the earliest clearly visible lesion of NCC is the cystic stage; when viable and 'active', this lesion does NOT demonstrate any surrounding edema and does not ring-enhance when contrast media are utilized. The presence of either ring enhancement or surrounding edema is considered to be evidence of a host immune response and thus the beginning of eventual cyst demise. Once an effective host response has been mounted, the lesion transforms to the 'nodular enhancing' stage, then eventually becomes calcified. The end result of this process is the calcified nodule, which is considered to be the final stage observable on neuroimaging prior to total resorption.

- Lack of gold standard for diagnosis. The gold standard for diagnosing NCC is histopathologic diagnosis via brain biopsy. For numerous reasons, this is an almost universally unavailable option (although biopsy of musculocutaneous cysts, if present, can assist in the presumptive diagnosis of NCC if brain lesions are present as well). Therefore, in the great majority of cases the diagnosis of NCC is made by indirect means. Serologic diagnosis has been attempted via a number of methodologies, none of which were recognized as adequately sensitive, specific, and reproducible, until the advent of the Immunoelectrotransfer blot (IETB) developed by Tsang and coworkers at the CDC (Tsang V et al, J Inf Dis 159: 50-59, 1989).

*Medical officer comment: This methodology has not yet been widely adapted, and the clinical data submitted as part of this NDA were in large part collected without the prospective use of such a sensitive and specific serologic test.*

Neuroimaging studies are currently the primary method of indirect diagnosis of NCC. However, the sensitivity and specificity of CT and MRI have not been precisely determined. As Bryan (1992) points out, "CT images are rarely, if ever, pathognomonic for cysticercosis and negative scans do not necessarily rule out the presence of cysticerci" but, having so stated, he goes on to say, "Immunologic testing for cysticercosis will likely always be used as an adjunct to, rather than a replacement for, radiologic diagnosis." For the purposes of regulatory review, such vagaries of diagnosis underscore the importance of solid clinical trial design. Clear criteria for patient entry and randomized assignment to treatment groups are important.

- Lack of reliable clinical endpoints. Most patients with intraparenchymal NCC present with seizures. In practically all of the clinical trials submitted with the literature section of this NDA, patients are treated with anti-seizure medications (ASM) as part of their initial clinical management. Once the diagnosis of NCC is made, the patient is usually maintained on ASM during and after anticysticercal therapy. Most studies will maintain subjects on ASM during the entire period of post-therapy follow-up; therefore the presence or absence of seizures post-therapy cannot be utilized as a valid clinical endpoint. Additionally, there will always be a theoretical possibility that the site of an adequately treated and eradicated NCC lesion, because of residual scarring, may continue to serve as a seizure focus. Therefore it is not reasonable to require that eradication of seizures be demonstrated for a potential antiparasitic agent to found efficacious in the treatment of NCC. On the other hand, it is reasonable to ask what clinical benefit is derived from anticysticercal treatment of NCC.

- Need for long-term follow-up. Clinical and radiographic evidence of response/nonresponse to therapy must be collected over a protracted period of time. NCC lesions are relatively slow-growing. Once they have attained a stable size, they may remain as such, or (particularly in the case of intraparenchymal lesions) gradually succumb to the host immune response. Because some intraparenchymal lesions may gradually resolve over time in the absence of any specific antiparasitic therapy, it is important for clinical trials to incorporate patients with CT lesions that are considered to be stable. Optimally, such stability of lesions can be demonstrated in patients by repeated CT studies over years. In such patients, the response of these previously-stable NCC lesions to specific antiparasitic therapy will be the most objective evidence of efficacy that can be obtained.

B. Information submitted in support of indication

1. Supporting literature

a. Description of submitted literature. The applicant has submitted a total of 65 references (volume 1.115 of NDA submission) in support of the NCC indication. These references include articles from the published literature (both English-language and other), abstracts of posters and/or presentations from scientific meetings, and several manuscripts of papers that have not yet been published. The applicant states, "Sixty-five publications and/or manuscripts have been identified, which refer to the use of albendazole in the treatment of cysticercosis. Total exposure to albendazole in these studies is 1044 patients." It is not clear how these references were assembled (i.e., what medical literature database was used, what search strategy was utilized). A search done by the Medical Officer using the SilverPlatter ® MEDLINE search, combining the keywords "albendazole" and "cysticercosis", resulted in 86 references. Some of these are more recently published and would have appeared after the applicant's literature search was performed and prepared for NDA submission. Overall, the major clinical studies of albendazole in the therapy of NCC appear to be included in the submitted literature.

b. Applicant's review process. The applicant totaled the patients reported in each of these 65 sources and generated a series of tables based on the entire 1044 patients. These tables are found in Volume 1.115, pages 21 thru 83. The applicant provides the following evaluation of these literature references (Volume 1.115, pages 10-16):

The applicant's text follows. Please note that all tables referred to in the applicant's text can be found in volume 1.115 of the NDA. Applicant's text appears in ARIAL 12 POINT font:

3.3.1.1. Overview

This section presents a review of available published data relating to the treatment of cysticercosis with albendazole. In addition to these peer-reviewed publications there are also presented details from other, as yet unpublished, manuscripts. The majority of these papers are the result of unsponsored studies undertaken by physicians with an (sic.) personal interest in cysticercosis.

Evaluation of these data is difficult because the pattern of disease varies widely - in number and site of cysts, leading to widely differing clinical syndromes. Furthermore, the numbers of patients involved in these studies are small and the methods used to monitor the disease also vary from centre to centre.

Sixty-five publications and/or manuscripts have been identified, which refer to the use of albendazole in the treatment of cysticercosis. Total exposure to albendazole in these studies is 1044 patients.

Details of the individual studies are presented in Table 1. Demographic data are

presented in Table 2. Details of treatment regimens and numbers of patients treated are provided in Table 3. Summaries of treatment outcome are presented in Tables 4 and 6. Details of treatment outcome, by study, are presented in Table 5 and Table 7. Safety data reported in these papers are provided in Table 8 and summaries of these data are provided in Tables 9 and 10.

In evaluating this material, it should be recognised that some duplication of patient data is likely to have occurred and some repetitive publication by individual groups has also been noted. As far as possible cases of repetitive publication or overlap of patient data sets have been identified and are indicated in the tables. In such cases the latest or most detailed paper has been used as the prime reference and other related papers quoted to provide a complete picture.

3.3.1.2. Treatment

Table 2 summarises the breakdown of treatment regimens used in these papers.

A total of 922 patients are reported to have received treatment with albendazole. The vast majority of patients received a single course of treatment. All remaining patients received between two and three courses of treatment.

*Medical officer comment: on the previous page, the total number of patients exposed to albendazole is reported to be 1044. This discrepancy is not explained by the applicant.*

All patients received albendazole treatment within the dose range 10-25 mg/kg/day[1]. The majority of patients received albendazole 15 mg/kg/day or 800 mg/day, in divided doses.

[1] 6 patients - dose not stated

Duration of treatment varied to a greater extent. The treatment duration historically recommended was 30 days and this was the duration used most frequently in these studies (407; 44.1%). More recently shorter courses of treatment have been adopted and treatment durations of 15, 8 and 3 days were reported for 77 (8.4%), 220 (23.9%) and 20 (2.2%) patients respectively.

*Medical officer comment: if this breakdown of patients by treatment duration is added, one arrives at 407 + 77 + 220 + 20 = 724. It is unclear why this total is different from the previously reported total of 922, or the initially-reported total of 1044.*

A number of papers compare albendazole with praziquantel. A total of 441 patients received treatment with praziquantel, the most common treatment regimen being 50 mg/kg/day for 15 days (291; 66.0%).

Thirty-one patients received treatment with albendazole in combination with praziquantel (either sequential or concurrent). In addition, reports are provided for 280 patients who acted as controls or for whom historical pre treatment data is available

The duration of follow-up to the time of data collection ranged between 2 weeks and 14 years.

### 3.3.1.3. Treatment Outcome

In the majority of papers, treatment outcome is assessed in terms of changes to the numbers of cysts or their radiological appearance (as detected by computer tomography), whilst a smaller number of papers examine changes in clinical symptoms. Tomographic response data and clinical response data, following albendazole treatment, are provided for 702 (75.3%) and 603 (65.4%) patients respectively.

3.3.1.5.1. Tomographic response

Table 4 summarises tomographic response data, by treatment regimen and Table 5 presents details of tomographic response data by study. These data are derived from 55 publications which report tomographic responses either in terms of overall changes or more quantitatively in terms of changes to individual cysts.

Overall the treatment regimens reported 85.5% of patients improved/were cured following treatment with albendazole compared with 76.2% of patients following treatment with praziquantel.

Five research groups - Cruz-Alcala et al , Escobedo, Sotelo, Vasquez et al , Puri et al, Medina et al - report comparative data from studies in which albendazole and praziquantel were compared directly. In three of these studies (Cruz-Alcala, Medina, and Sotelo) albendazole and praziquantel are compared at equivalent treatment durations. The results of these studies suggest a greater benefit from treatment with albendazole with an 18-52% greater proportion of patients cured than were following treatment with praziquantel.

A variety of treatment durations are evaluated. More than 70% of patients improved/were cured following treatment with albendazole 15 mg/kg/day for three days or more. Three studies investigate directly the effect of treatment duration on response to treatment with albendazole (Alarcon 1990, Cruz, and Sotelo 1990). No detrimental impact upon treatment response is observed upon a reduction in treatment duration from the 30 days historically recommended.

Eleven papers provide data for patients treated with albendazole administered in combination with praziquantel (sequentially or concomitantly). Overall 50% of patients improved/were cured in response to combination therapy.

Overall more than 74% of patients with untreated non-ring enhanced lesions remained unchanged or worsened during the period of follow-up (generally > 3 months).

Overlap of patient data has been noted by some research groups, most notably Escobedo, Sotelo and Vasquez et al.

3.3.1.5.2. Clinical Response

Table 6 summarises clinical response data by treatment regimen and Table 7 presents details of clinical response data, by study. These data are derived from 50 publications which report treatment outcome in terms of global changes in clinical symptoms.

Overall, almost 90% of patients improved/were cured following treatment with albendazole compared with 7.9% of patients following treatment with praziquantel.

*Medical officer comment: '7.9%' is clearly a typographical error; Table 6 of the NDA submission (page 058, vol 1.115) shows an overall clinical response rate of (cure + improved) 41.5% + 36.4% = 77.9%.*

In three studies (Cruz-Alcala 1990, Medina 1993, and Sotelo 1990) albendazole and praziquantel were compared directly, over equivalent periods of treatment. The results of these studies indicated a greater benefit from treatment with albendazole, with an 18-70% greater proportion of patients improved/cured than were following treatment with praziquantel.

More than 70% of patients improved/were cured following treatment with albendazole 15 mg/kg/day for three days or more. Three studies investigate directly the effect of treatment

duration on response to treatment with albendazole (Alarcon 1990, Cruz, and Sotelo 1990). No detrimental impact upon response to treatment was observed as a result of reduction in treatment duration. In contrast, in the one study which examines the effect of treatment duration both albendazole and praziquantel therapy (Sotelo 1990) the proportion of patients showing improvement decreased by more than 35% with a reduction in treatment duration from 15 to 8 days.

*Medical officer comment: it is unclear how this figure of 35% was calculated by the applicant, after careful review of the reference cited.*

Ten papers provide data for patients treated with albendazole administered in combination with praziquantel (sequentially or concomitantly). Less than 50% of patients improved/were cured in response to combination therapy.

Overall more than 90% of patients with untreated non-ring enhanced lesions remained unchanged or worsened during the period of follow-up (generally > 3 months).

Perhaps the most interesting data is contained in a paper by Vasquez and Sotelo, which compares the outcomes of patients treated with chemotherapy, surgery and those given no treatment (including a group of patients with ring-enhanced lesions). Of specific interest are the responses of seizure syndromes to these varying approaches. The study clearly showed that, during the three-month follow up no treatment leads to continued seizures (10.9 ± 3.0 per annum), with only 22% of patients able to reduce their use of anticonvulsants. Patients with ring-enhanced lesions showed evidence of cyst clearance in 83% of patients and their seizure rate fell (to 2.7 ± 0.9 per annum) - 36% were able to reduce their use of anticonvulsants. Surgery to accessible cysts resulted in a reduction in the annual seizure rate but only 10% of patients were able to reduce their use of anticonvulsants. The greatest reduction in the use of anticonvulsants was seen (44%) in the patient group treated with chemotherapy.

Overlap of patient data has been noted by some research groups, most notably Escobedo, Sotelo and Vasquez et al.

3.3.1.4. Safety and Tolerability

The total exposure to albendazole in these studies is 1044 patients.

Table 8 provides a detailed breakdown of the adverse events reported in these papers. However a number of papers do not provide safety data. Safety data is provided for a total of 801 patients but in some cases this data is only qualitative. Quantitative adverse event data are summarised in Table 9.

*Medical officer comment: please refer to pages 071-083 of volume 1.115 of the NDA for these tables.*

Headache was the most commonly reported adverse event. Eighty-eight (11%) of patients reported headache during treatment with albendazole.

Nausea/vomiting was the next most frequently reported adverse event with 50 (6.2%) cases reported. Meningeal symptoms were reported for 12 (1.5%) patients: meningeal signs, 2; meningeal reaction, 7; relapse of cysticercotic meningitis, 3. Raised intracranial pressure was reported by 8 (1.0%) patients. All other adverse events reported occurred at an incidence of < 1%.

In eight papers, adverse events during treatment with albendazole are quoted in combination with those occurring during treatment with praziquantel. These papers constitute the only source of safety data for a total of 88 patients. These combined

albendazole/praziquantel safety data are tabulated separately in Table 10.

### 3.3.1.5. Discussion

The data presented here represent the results of a series of unsponsored, and for the most part unrelated, studies which have been undertaken by physicians with a personal interest in cysticercosis. The 65 publications/manuscripts considered provide data for a total of 922 patients, treated with albendazole.

Interpretation of these data is problematic and must be undertaken with care since cysticercosis is a complex disease, varying widely in its presentation, the methods adopted to monitor disease progress vary (radiological and clinical) and most of these studies involve a small number of patients.

Treatment outcome in these studies is evaluated in terms of changes to number or size of cysts (assessed by computer tomography) and/or clinical response. Unfortunately, the complex nature of the disease means that the number and size of cysts do not necessarily relate to clinical symptoms and these data have therefore been considered separately.

Tomographic response data and clinical response data are available for 702 and 603 patients respectively. Overall more than 85% of patients improved/were cured following treatment with albendazole, in terms of both tomographic and clinical responses.

The treatment duration historically recommended was 30 days but, no reduction in effectiveness is observed in studies where shorter treatment durations have been compared directly with the recommended treatment period.

In studies where albendazole and praziquantel have been compared directly, at equivalent treatment durations, albendazole is shown to be of greater benefit with 18-70% and 18-

52% more patients showing improvement/cure, in terms of tomographic and clinical responses respectively.

Overall the studies analysed, albendazole appears to be more effective and more consistent than praziquantel, in terms of both tomographic and clinical responses to treatment. This may be explained in part by the widespread use of corticosteroids in these patients, which have been shown to reduce the bioavailability of praziquantel and increase the bioavailability of albendazole. In contrast, earlier studies with praziquantel rarely used steroids to suppress cerebral reactions.

Total exposure to albendazole in these studies is 1044 patients but safety data are provided for only 801 patients. The most commonly reported adverse effect noted was headache, affecting 11% of patients. Nausea and/or vomiting was the next most frequently reported adverse effect, with an incidence of 6.2%. Other adverse effects reported at an incidence of >1% were: meningeal symptoms and raised intracranial pressure. It is difficult to assess the relationship to treatment of adverse effects related to the central nervous system, since these symptoms may arise during the normal course of the disease. Headache, the most commonly reported adverse effect, is a common clinical manifestation of cysticercosis but may also arise as a result of the death of the parasite in response to treatment.

### 3.3.1.6. Conclusion

Albendazole 15 mg/kg/day is shown to be an effective treatment for cysticercosis, with > 85% patients improved/cured following therapy. A reduction in treatment duration from the 30 day treatment period historically recommended does not appear to reduce its effectiveness.

Overall albendazole appears to be a more effective and more consistent treatment than praziquantel. This may be attributable, in part, to the increased use of steroids in these patients which have been shown to reduce the bioavailability of praziquantel whilst increasing the bioavailability of albendazole.

Albendazole appears to be well tolerated in this group of patients. Clinical symptoms are relatively uncommon and are not treatment-limiting. The most common adverse event reported is headache which may arise as a result of the death of the parasite in response to treatment. These symptoms may be avoided by concomitant administration of steroids.

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*Medical Officer comments on Sponsor's literature review:*

*1. The technique utilized by the sponsor involved the combination of a widely disparate variety of references: conference abstracts, unpublished manuscripts, single case reports, case series, retrospective reviews, and prospective trials (either randomized or nonrandomized). These references included a variety of clinical types of NCC. This technique attempts to maximize the number of treated patients under consideration. This may be appropriate for assessing the safety of albendazole, but it would seem to be a suboptimal way of assessing the clinical efficacy.*
*2. The source of albendazole utilized in the treatment of these patients is infrequently mentioned in these references. There appear to be other manufacturers of albendazole throughout the world, aside from the sponsor. In the context of an NDA submission, it is normally the responsibility of the sponsor to provide information which verifies that the drug product used in a particular clinical study is either identical to, or has been shown to be bioequivalent to, the drug product for which marketing approval is being sought. This issue is discussed further in the biopharmaceutics review of Dr. Philip Colangelo, HFD-520.*

c. Medical Officer findings. In order to systematically review published neurocysticercosis studies that include albendazole-treated patients, a more systematic method must be undertaken to combine studies. In essence, a meta-analysis-like approach must be used so that the results of combining data across studies can be done in as valid a manner as possible. The following factors will be used in applying such an approach to the submitted literature:

- Studies must have been published, so that some degree of external peer review has been applied to the manuscript. Therefore, unpublished manuscripts and conference abstracts will not be included.
- Case reports will not be included, as these commonly consist of unusual cases with a variety of relatively unconventional clinical presentations. Furthermore, the sites of cyst localization in these case reports are usually not brain parenchyma.
- Prospective studies with random assignment of patients to treatment groups are considered to be the best; retrospective studies will also be considered but are not as well designed.
- Ideally, only similar patients with similar-appearing CT lesions (non-enhancing, non-edematous cystic lesions in the brain parenchyma) should be combined, since the natural history of some types of NCC lesions (particularly those with surrounding edema and/or contrast enhancement on CT) is considered by many experts to be one of gradual resolution.

- Source of albendazole should ideally be mentioned in the materials and methods section of the study. There are numerous worldwide manufacturers of albendazole; thus not all studies which appear in the literature can be assumed to have utilized the SK/B product.

- Duration of follow-up should be adequately long (at least 3 months post-therapy) to document adequate and persistent clinical and parasitologic response to therapy.

Given the above considerations, a subset of the 65 references submitted by the sponsor will be considered for further analysis. Two groups of references are defined. The first group ("Group A") has the best overall study design, but each has its own individual weaknesses. The second group ("Group B") includes studies whose designs are suboptimal but nonetheless include useful information. These groupings and their design characteristics can be found in Tables One and Two, below. A brief synopsis of each of the design of these studies will follow:

# TABLE

## GROUP A

## LITERATURE STUDIES SUBMITTED IN SUPPORT OF NEUROCYSTICERCOSIS INDICATION

| Ref | Site | Study design | | | | Definition of lesion on CT | | | | | Source of Albendazole | | | Dose & duration | N | Length of F/U | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Prospective entry* | Randomized assignment* | Controlled trial* | Type of diagnosis | Presence of cysts* | Non-enhancing | Non-calcified | Non-cystic | No. allowed | SK/A | other | not mentioned | | | | |
| Alarcon 1989 | Quito Ecuador | Y | Y* | Y | Dose ranging & no Rx | Y | Y | Y | | 1-3, >10 mm | | | X | 1)AL 15mkd x 3 days<br>2)AL 15mkd x 30 days<br>3) No Rx | 9<br>9<br>5 | 3 months | |
| Alarcon 1990 | Quito Ecuador | Y | Y* | Y | Dose ranging & no Rx | Y | Y | Y | | 1-3, >10 mm | | | X | Same as above | 30<br>30<br>?* | 1 year | Expansion of ref #1 |
| Cruz-Alcala 1990 | Guadalajara Mexico | Y | N | Y | No Rx, active | Y | * | * | cystic | not mentioned | | | X | 1) PZ 50mkd x 15 days<br>2)AL 15mkd x 15 days<br>3) No Rx | 76<br>30<br>18 | 3 months | |
| Escobedo 1987 | Mexico City Mexico | N | N | Y | Historic (self) | Y | Y | Y | cystic | | | | X | AL 15 mkd + dd x 30 days | 7 | 3 months | |
| Sotelo 1990 | Mexico City Mexico | Y | Y | Y | Active; Dose ranging; Self | Y | Y | Y | | | | | X | 1) PZQ 50mkd x 15 days<br>2) PZQ 50mkd x 8 days<br>3) AL 15mkd x 30 days<br>4) AL 15mkd x 8 days | 52<br>13<br>25<br>24 | 3 months | Extension of #4) |
| Takayanagui 1992 | Sao Paulo Brazil | Y | N | Y | Active; No Rx | Y | Y | Y | cystic | | drug purchased by patients | drug purchased by patients | drug purchased by patients | 1) PZQ 50mkd x 21 days + DEX<br>2) AL 20mkd x 21 days + DEX<br>3) DEX x 21 days | 22<br>21<br>16 | 6 months | |
| Vazquez 1992 | Mexico City Mexico | N | N | Y | Retrospective cohort | Y | Y | Y | cystic | | | | X | 1) AL 30 mkd<br>2) PZ 15 mkd<br>3) AED only<br>4) " + lesions - AED only<br>5) Surgical excision | 42<br>60<br>49<br>58<br>15 | ≥1 year | |

AL = albendazole

PZ = praziquantel

AED = antiepileptic drug

DEX = dexamethasone

RE = ring-enhancing

*GROUP A*

**1. Alarcon, F. et al. Neurocysticercosis: Short course of treatment with albendazole. Arch Neurol 46(11): 1231-6, 1989.** This was a prospective, open-label study of albendazole at a dose of 15 mg/kg/day, given once daily in two different regimens (either 3 days or 30 days) to NCC patients in Quito, Ecuador. There were nine patients in each of the treatment arms. Assignment to treatment group was claimed to be by random allocation. A comparison group of five patients served as controls; these patients were treated symptomatically but were not given anti-cysticercal therapy. Lesions were required to be nonenhancing, nonedematous, parenchymal cystic lesions by CT. Concomitant steroids were not administered. Length of follow-up post-therapy was 3 months. **Major criticisms:** Although this unblinded study claims to have randomly allocated patients to one of the three treatment arms, it also claims that the five contol patients were "selected" at the time of diagnosis. Although the authors state, "It was necessary to administer analgesics to 7 patients during the taking of albendazole", no safety data are presented. The source of albendazole is not stated. Numbers are small, consistent with a preliminary investigation. Patients were not enrolled if they had more than three NCC lesions.

**2. Alarcon, F., et al. Albendazole therapy for neurocysticercosis (letter). Arch Neurol 47(12): 1278-9, 1990.** This letter to the editor provides follow-up information on the data presented in the previous citation, and expands the study to include 20 patients in each of the treatment arms. The length of follow-up has been extended to one year. The study design is identical and brings into question the same issue of how the patients were assigned to the different treatment groups.

**3. Cruz-Alcala, L., et al. Antihelminthic treatment in cerebral parenchymatous cystic cysticercosis. Compend Invest Clin Latinoam 10(2): 60-67, 1990.** This prospective sequential cohort study reports the experience of investigators in Guadalajara, Mexico during a six-year time period ( March 1984 thru March 1989). The first 76 patients evaluated (1984 thru 1986) who had cystic, parenchymatous lesions were given praziquantel (PZ) and the last 30 patients (1987 thru 1989) were given AL. A control group of 18 patients with identical-appearing NCC lesions were treated symptomatically and observed. Follow-up CT studies were done at 3 months post-therapy. Concomitant steroids were not utilized. **Major criticisms:** Unblinded non-randomized study. Method of selection of control group not mentioned. CT criteria do not specifically mention nonenhancing, nonedematous lesions. Source of AL not mentioned.

**4. Escobedo, F., et al. Albendazole therapy for neurocysticercosis. Arch Intern Med 147(4): 738-41, 1987.** This small study of seven patients seen in Mexico City reported on the use of AL in patients with known, stable NCC lesions. Six of the seven patients had parenchymal lesions that had been documented to be clinically stable for 6-24 months before AL treatment; therefore, the patients served as their own controls. These were nonenhancing, nonedematous, cystic lesions. Steroids were not routinely co-administered. Patients were given a follow-up CT scan at 3 months post-therapy. **Major criticisms:** Small study. Unblinded, without concurrent control arm. Two patients with prior PZ therapy. Dose of AL was standard 15 mg/kg/day, but was administered as a TID regimen. No safety data presented. Source of AL not mentioned.

**5. Sotelo, J., et al. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J Neurol 237(2): 69-72, 1990.** This study was performed by the same Mexico City group as the above study, but is considerably larger and better-designed. This is a prospective, randomized, four-armed study which compares two PZ regimens (50 mg/kg/day for 8 or 15 days) to two AL regimens (15 mg/kg/day for 8 or 30 days) in patients with nonenhancing, nonedematous, parenchymal NCC. Study size was large: there were 65 PZ patients and 49 AL patients. Follow-up was done at 3 months post-therapy. Steroids were not routinely co-administered. **Major criticisms:** Study claims random allocation, yet size of each arm (52/13/25/24) uneven and no explanation given. Unclear whether patients in reference #4 are included in this study. Source of AL not mentioned.

**6. Takayanagui, S., et al. Therapy for neurocysticercosis: comparison between albendazole and praziquantel. Arch Neurol 49(3): 290-94, 1992.** This prospective study was performed in Brazil. A total of 59 consecutive patients with nonenhancing, nonedematous, parenchymal NCC were enrolled and divided into three groups: 22 received PZ at a dose of 50 mg/kg/day for 21 days; 21 received AL at a dose of 15 mg/kg/day for 21 days; and 16 were treated symptomatically with steroids. Patients were followed with CT scans at 6 months post-therapy. **Major criticisms:** Method of assignment of patients to treatment groups is not mentioned and cannot be assumed to be random. All patients received concomitant steroids. Anticysticercal drugs were not supplied by the investigators and had to be purchased by each study subject. AL dose was unusual (20 mg/kg/day for 21 days).

**7. Vazquez, V., and Sotelo, J. The course of seizures after treatment for cerebral cysticercosis. N Engl J Med 327(10): 696-701, 1992.** This is a retrospective cohort study of all patients treated for NCC at the authors' Mexico City location. These patients had all been reported on previously in other journal articles. Parenchymal lesions without surrounding edema or enhancement were required for enrollment. A total of 118 patients are included in the cohort treated with anticysticercal medication (PZ, AL, or both). A separate cohort of 49 patients had been treated with anti-seizure medications only. A third cohort of 58 patients was included who had ring-enhancing lesions that were treated with anti-seizure medications only. Finally, a cohort of 15 patients was included who had had their NCC lesions surgically removed. Patients were required to have at least one year of post-therapy follow-up to be included in the analysis. Concomitant steroids were not routinely used. **Major criticisms:** Retrospective study. Source of AL not mentioned.

## TABLE TWO

## GROUP B

## LITERATURE STUDIES SUBMITTED IN SUPPORT OF NEUROCYSTICERCOSIS INDICATION

| Ref | Site | Study design | | | | Definition of lesion on CT | | | | | Source of Albendazole | | | Dose & duration | N | Length of F/U | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Prospective? | Randomized? | Controlled? | Type of controls | Parenchymal? | Non-enhancing | Non-calcified | Non-calcific | No. allowed | SK/B | other | are mentioned | | | | |
| Bruera 1993 | Medellin, Colombia | N | N | N | | Y | Y | Y | cystic | | | | X | AL 15mg/kg bid x 8 days | 20 | 6 months | |
| Chotmongkol 1993 | Thailand | Y | N | N | | Y | ? | ? | ? | | | | X | AL 15mg/kg bid x 14 days | 10 | 3 months | 6/91-6/92 |
| Chotmongkol 1992 | Thailand | Y | N | N | | Y | N | N | ? | | | | X | AL 15mg/kg bid x 30 days | 12 | 2 months | 10/88-5/[illegible] |
| Cruz 1991 | Quito, Ecuador | Y | N | Y | appointed cohort | N | N | N | all types and loca-tions | Parenchymal: PZ 37 AL 42 | | | X | 1) PZ 50mg/kg x 15 days<br>2) AL 15mg/kg x 30 days | 50<br>50 | 3 months | cystic phase:<br>24 PZ<br>10 AL |
| Medina 1993 | Mexico City, Mexico | Y | N | Y | Comparative | ? | Y | Y | | | | | X | 1) PZ 50mg/kg x 6 days<br>2) AL 15mg/kg x 8 days | 11<br>5 | 3 months | |
| Padma 1994 | Delhi, India | Y | Y | Y | DB, placebo | Y | N | N | ? | | | | X | 1) AL 15mg/kg + tid x 7 days<br>2) placebo x 7 days | 40<br>35 | 3 months | ?? Was pla-cebo identical?? |
| Sihota 1994 | Delhi, India | Y | Y | Y | placebo | N | | | extra-ventricular lesions | | | | X | 1) AL 15mg/kg x 30 days<br>2) MVI x 30 days | 12<br>12 | 6 months | |

AL = albenazole

PZ = praziquantel

DB = double blind

*GROUP B*

**8. Botero, D., et al. Short course albendazole treatment for neurocysticercosis in Columbia. Trans Roy Soc Trop Med Hyg 87: 576-7, 1993.** This study is a retrospective review of the authors' experience using AL in Medillin, Columbia, between 1989 and 1991. A total of 20 patients with nonenhancing, nonedematous parenchymal NCC lesions are included. They were treated with an AL regimen of 15 mg/kg/day for 8 days, and had follow-up at six months post-therapy. Routine administration of steroids was not practiced. **Major criticisms:** Retrospective review of open-label, uncontrolled administration of AL.

**9. Chotmongkol, V. Treatment of neurocysticercosis with a two week course of albendazole. SE Asian J Trop Med Public Health 24(2): 396-99, 1993.** This paper reports the open-label, prospective experience using AL for treatment of NCC in Thailand. Ten patients with 'characteristic' parenchymal cysts were given AL at 15 mg/kg/day dosed BID for two weeks. Follow-up CT scans were obtained 3 months following treatment. No source of AL was identified. **Major criticisms:** Small number of patients, open-label study with no control group. Lesions not specifically identified as nonenhancing and nonedematous; therefore a proportion of these lesions could be expected to resolve spontaneously.

**10. Chotmongkol V. Albendazole treatment of neurocysticercosis. SE Asian J Trop Med Public Health 23(2): 344-47, 1992.** This study is similar in design to the previous reference by the same investigator. This paper reports the investigator's initial experience with AL, in patients enrolled between 10/88 and 5/90 (reference #9, above, included patients enrolled from 6/91 to 6/92). This study used the 30 day AL regimen at the same 15 mg/kg/day dose. Total number of patients enrolled was 12. **Major criticisms:** As above for reference #9. Text of article specifically mentions that on CT, lesions in 5 of the 12 cases revealed "single, ring-like enhancement with perilesional edema".

**11. Cruz, M., Cruz, I., and Horton, J. Albendazole versus praziquantel in the treatment of cerebral cysticercosis: clinical evaluation. Trans Roy Soc Trop Med Hyg 85: 244-47, 1991.** This was a study performed in Ecuador of 100 consecutive patients with NCC of all types (parenchymatous, ventricular, and/or arachnoidal). The authors claim to have 'randomly' assigned them to either PZ or AL (15 mg/kg/day for 30 days), then state that the first 50 patients were *assigned* to the PZ group and the second 50 *assigned* to the AL group. All stages of NCC by CT appearance were enrolled. Patients were imaged at 3 months following completion of therapy. **Major criticisms:** Although study abstract calls this a randomized trial, it sounds more like an open-label sequential cohort study. Although 42 of the 50 AL patients had solely parenchymal lesions, it is impossible from this paper to determine which of those actually had nonenhancing, nonedematous lesions so that comparison with Group A studies can be done. Even though one of the authors (J. Horton) is a SmithKline Beecham employee, the paper does not specifically mention where the AL was obtained and whether it was the SK/B product.

**12. Medina M. T., et al. Effect of anticysticercal treatment on the prognosis of epilepsy in neurocysticercosis: a pilot trial. Epilepsia 34(6): 1024-27, 1993.** This prospective study was performed in 16 patients with NCC in Mexico City. Lesions were nonenhancing and nonedematous, ranging from one to 127 per patient. Eleven patients received AL at a dose of 15 mg/kg/day for 8 days, and 5 received PZ at 50 mg/kg/day for 8 days. Along with CT scanning at 3 months post-therapy, patients were followed for seizure activity for 10-18 months post-therapy. **Major criticisms:** Small numbers. Method of allocation to treatment group is not specified and cannot be assumed to be random. No mention of source of AL.

**13. Padma, M.V., et al. Albendazole in single CT ring lesions in epilepsy. Neurology 44: 1344-46, 1994.** This Indian study was a randomized, double-blind, placebo-controlled investigation in 75 patients with single, ring-enhancing parenchymal lesions. As the authors point out, these lesions are known to resolve spontaneously. The purpose of this study was to determine whether treatment with AL (15 mg/kg/day given TID for 7 days) might accelerate the resolution of these "SSEL" (single, small, enhancing lesions). Follow-up CT scanning was done at 1 and 3 months post-therapy. **Major criticisms:** No mention made of efforts to obtain identical-appearing placebo; thus, integrity of double-blind nature of study is uncertain. Lesion studied is not lesion of interest in this review, but study is important because it points out need to consider only those studies which exclude such patients from enrollment.

**14. Sihota, R., and Honavar, S.G. Oral albendazole in the management of extraocular cysticercosis. Br J Ophthalmol 78(8): 621-23, 1994.** These authors studied the efficacy of AL (15 mg/kg/day for 30 days) in the treatment

of extraocular cysticercosis in India. They conducted a prospective, randomized, open study of AL versus placebo in 24 patients with symptomatic (proptosis or ocular motility disorders) extraocular cysticercosis. Patients were followed by clinical examination, ophthalmologic testing, and ultrasonography for six months following completion of study drug. No mention of source of albendazole is made. **Major criticisms:** This study did not enroll patients with parenchymal NCC lesions, although four of the 24 enrolled had NCC detected on initial CT scanning. Despite the different clinical setting, this study is included because it demonstrates the efficacy of AL in treating *Taenia solium* cysts in a well-designed, prospective manner. Clinical benefit was clearly demonstrated in this study.

The main distinguishing characteristic of Group A is that each study defines the target lesion as a nonenhancing, nonedematous parenchymal lesion. All have at least three months of post-therapy follow-up. Furthermore, each study has some sort of control group: a concurrent no-treatment group, a comparative active treatment group (either dose-ranging or with a different anticysticercal agent), or a retrospective cohort. None of these studies specifically state from where the albendazole was obtained.

*Medical officer comment: in order to utilize these studies in this manner, in the context of this NDA, the sponsor should document that the drug used in these studies was actually the sponsor's own ZENTEL brand of albendazole, or be able to demonstrate bioequivalence between the formulation used in the publication and the sponsor's product.*

In order to combine the efficacy results in these references, the Medical Officer expressed the results of each treatment arm as number of cysts per patient at entry and at follow-up, along with the number (percent) of patients cured in each treatment arm. 'Cured' means disappearance of all lesions on repeat CT scanning, and does not address clinical cure (specifically, eradication of seizures).

## Medical Officer's Efficacy analysis of pooled studies, Group A

(See table on next page.)

**GROUP A COMBINED RESULTS**

| Study | | entry r Ao study | | 3 month follow-up | | |
|---|---|---|---|---|---|---|
| group | N | #cysts | #/pt | #cysts | #/pt | #cured |
| #1 Alarcon 1989 | | | | | | |
| AL 3 days | 9 | 11 | 1 22 | 4 | 0 44 | 5 (56%) |
| AL 30 day | 9 | 16 | 1 78 | 6 | 0 67 | 6 (68%) |
| control | 5 | 10 | 2 00 | 9 | 0 90 | 0 (0%) |
| #2 Alarcon 1990 | | | | | | |
| AL 3 day | 20 | 34 | 1 70 | 9 | 0 45 | |
| AL 30 day | 20 | 39 | 1 95 | 10 | 0 50 | |
| #3 Cruz-Alcala 1990 | | | | | | |
| AL 15 day | 30 | 69 | 2 30 | 13 | 0 43 | 22 (73%) |
| PZ 15 day | 76 | 375 | 4 93 | 62 | 0 82 | 42 (55%) |
| no drug | 18 | 104 | 5 78 | 100 | 5 56 | 0 (0%) |
| #4 Escobedo 1987 | | | | | | |
| AL 30 day | 7 | 157 | 22 43 | 22 | 3 14 | 3 (43%) |
| #5 Sotelo 1990 | | | | | | |
| AL 8 day | 24 | 329 | 13 71 | 49 | 2 04 | 16 (67%) |
| AL 30 day | 25 | 239 | 9 56 | 37 | 1 48 | 16 (64%) |
| PZ 8 day | 13 | 263 | 20 23 | 136 | 10 46 | 4 (31%) |
| PZ 15 day | 52 | 392 | 7 54 | 158 | 3 04 | 21 (40%) |
| no drug | 37 | 314 | | | | |
| #6 Takayanagui 1992 | | | | | | |
| AL* 21 day | 21 | 101 | 4 81 | 12† | 0 57 | 11 (52%) |
| PZ 21 day | 22 | 178 | 8 09 | 89† | 4 05 | 3 (14%) |
| Dex | 16 | 113 | 7 06 | 106† | 6 63 | 1 (6%) |
| #7 Vazquez 1992 | | | | | | |
| AL/PZ 30/15 | 118 | 591 | 5 01 | | 0 9‡ | 84 (71%) |
| no drug | 49 | 195 | 3 98 | | 4 6‡ | 2 (4%) |

FOOTNOTES

Empty cell signifies data not available in text of reference
"Cured" at 3 month follow-up means eradication of all lesions on CT scanning, thus is not meant to imply *CLINICAL* cure

* albendazole dosed at 20 mg/kg/day in this study
† follow-up scans at 6 months post-therapy
‡ follow-up scans at one year (or longer) post-therapy

If the above chart is combined by treatment group rather than by study, one can compare the relative efficacy of albendazole vs. praziquantel vs. control.

# POOLED RESULTS OF GROUP A STUDIES BY TREATMENT ARM

**1. Albendazole (≥ 8 days of therapy)#:**

| Ref # | Entry | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | N | Total cysts | # cysts/pt | Total cysts | # cysts/pt | pts cured (%) |
| 2 | 20 | 39 | 1.95 | 10 | 0.5 | |
| 3 | 30 | 69 | 2.30 | 13 | 0.43 | 22 (73%) |
| 4 | 7 | 157 | 22.43 | 22 | 3.14 | 3 (43%) |
| 5 | 24 | 329 | 13.71 | 49 | 2.04 | 16 (67%) |
| 5 | 25 | 239 | 9.56 | 37 | 1.48 | 16 (64%) |
| 6 | 21 | 101 | 4.81 | 12 | 0.57 | 11 (52%) |
| | **Σ 127** | **934** | **7.36** | **143** | **1.13** | **68/107* (64%)** |

Notes # Study #1 (Alarcon 1989) is not included, as these patients are incorporated in study #2.
* Denominator in total patients cured is 107 rather than 127 because number of patients cured was not available for first study cited.

**2. Praziquantel (≥ 8 days of therapy):**

| Ref # | Entry | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | N | Total cysts | # cysts/pt | Total cysts | # cysts/pt | pts cured (%) |
| 3 | 76 | 375 | 4.93 | 62 | 0.82 | 42 (55%) |
| 5 | 13 | 263 | 20.23 | 136 | 10.46 | 4 (31%) |
| 5 | 52 | 392 | 7.54 | 158 | 3.04 | 21 (40%) |
| 6 | 22 | 178 | 8.09 | 89 | 4.05 | 3 (14%) |
| | **Σ 163** | **1208** | **7.41** | **445** | **2.73** | **70 (43%)** |

**3. No active treatment (controls):**

| Ref # | Entry | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | N | Total cysts | # cysts/pt | Total cysts | # cysts/pt | pts cured (%) |
| 1 | 5 | 10 | 2.00 | 9 | 0.90 | 0 |
| 3 | 18 | 104 | 5.78 | 100 | 5.56 | 0 |
| 5 | 33 | 314 | 9.52 | - | - | - |
| 7 | 49 | 195 | 3.98 | - | 4.6 | 2 (4%) |
| 6 | 16 | 113 | 7.06 | 106 | 6.63 | 1 (6%) |
| | $\sum$ 121 | **736** | **6.08** | **215** | **5.51** | **3 (2.5%)** |

*Medical Officer comments: When the seven studies in Group A are pooled in this manner, treatment differences can be discerned. Interestingly, at study entry the three groups (Albendazole, Praziquantel, and Controls) had a similar parasite burden when expressed as average number of cysts per patient at entry. (This is important, as patients with 'massive disease' are thought to have a less favorable response to therapy than patients with more limited [sometimes defined as ≤ 10 cysts] disease.) At follow-up, the untreated controls were found to have a relatively unchanged degree of parasite burden, whereas the study arms receiving anticysticercal therapy showed a decrease in the number of cysts per patient. Albendazole appears to be more efficacious than praziquantel, both in terms of average number of cysts per patient at follow-up, as well as the proportion of patients in whom all CT evidence of neurocysticercosis is eradicated at follow-up.*

The second group of studies ('Group B'), by the nature of their design, do not lend themselves to pooling in the same manner as the Group A studies. Some are retrospective reviews of uncontrolled, open-label experience; most do not rigorously define the CT lesion at enrollment as nonenhancing and nonedematous. One study included in Group B (Sihota and Honavar, 1994) studied patients with extraocular cysticercosis but was nonetheless included because of the relatively tight (placebo-controlled, prospective) study design and striking results (12/12 cures in the treated patients vs. 0/12 in the placebo arm).

In general, all but one of these studies tend to support the findings of the pooled Group A studies as displayed above. One of the references in Group B has negative findings (#13, Padma et al, 1994): it concludes that albendazole is of no benefit over placebo in the therapy of 'SSEL' (single small enhancing lesions). This study is included in Group B because it serves to demonstrate the importance of restricting entry to lesions that are NON-enhancing. The entry criteria for this study specified that lesions *must* be enhancing; in the placebo arm of this study there was a 94% (33/35) cure rate at 3 months post-therapy.

In order to ascertain whether the collection of literature references submitted by the applicant might preferentially include references which cast albendazole in a favorable light, the Medical Officer performed a Silver Platter® MEDLINE search. All Medline references dating back to 1985 were searched, combining the terms 'ALBENDAZOLE' and 'CYSTICERCOSIS'. An additional 24 references were found in this manner. These are listed and briefly characterized in Table Three, on the following page. In general, these references are letters to the editor, reviews, or editorials. Four of the articles are pharmacokinetic studies. Some are retrospective analyses of surgical treatment of NCC. Overall, none of these additional references contradict the conclusion of the above analysis of Group A studies: that is, that albendazole is effective in eradicating nonenhancing, nonedematous parenchymal NCC cysts.

**Medical Officer's Table 3**
**Additional References: 'Albendazole' X 'Cysticercosis'**
**Silver Platter® Medline Search**

| Author | Reference | Type of article | Comments |
|---|---|---|---|
| Martinez et al | J Neurol Sci 130(1): 25-34, 1995 | Clinical trial<br>Mexico | Prospective, non-controlled study<br>Lesions defined by MR, not CT ∴ impossible to compare to Group A |
| Aubry et al | Med Trop Mars 55: 79-87, 1995 | Review | -- |
| Del Brutto | J Neurol Neurosurg Psych 58:247, 1995 | Retrospective study<br>Ecuador | single enhancing parenchymal lesion<br>N = 54 |
| Del Brutto | Arch Neurol 52: 102-4, 1995 | Editorial | Author is proponent of Albendazole therapy for parenchymal NCC |
| Del Brutto | Neurology 44 1706-9, 1994 | Clinical trial<br>Ecuador | Clinical outcome following withdrawal of seizure meds post-Albendazole therapy |
| Del Brutto | Neurology 44: 777, 1994 | Letter to editor | Response to reference 43, vol 1.116 of NDA |
| Webbe | Pharm Ther 64: 175-200, 1995 | Review | -- |
| Colli | Arq Neuropsiquiatr 52: 166-186, 1994 | Retrospective study<br>Brazil | Review of surgical outcome<br>N = 180 |
| Anonymous | N Engl J Med 328: 566-73, 1993 | Clinico-Pathological Conference (CPC) | Discussion of case of racemose NCC |
| Del Brutto | N Engl J Med 329: 813, 1993 | Letter | Response to CPC |
| Despommier | N Engl J Med 327: 727-8, 1992 | Editorial | Comment on Group A study (Vazquez, ref 58, vol 1.115) |
| White et al | N Engl J Med 327: 1955-6, 1992 | Letter | Comment on Group A study (Vazquez, ref 58, vol 1.115) |
| St. Geme et al | Pediatr Inf Dis J 12: 455-61, 1993 | Consensus statement | Authors conclude that Albendazole is drug of choice for NCC |
| Sanchez et al | Clin Neuropharmacol 16: 77-82, 1993 | Clinical PK study<br>Mexico | Randomized crossover study, N = 10 |
| Overbosch | Schweiz Med Wochenschr 122: 893-98, 1992 | Review | -- |

Table 3, continued

| Author | Reference | Type of article | Comments |
|---|---|---|---|
| Carpio et al | Neurosurgery 31: 968-9, 1992 | Letter | Comment on article by Couldwell (below) regarding surgical management of NCC |
| Couldwell et al | Neurosurgery 28: 231-7, 1991 | Retrospective review California | Review of surgical management of NCC (N = 237) |
| Jung et al | J Neurol 237: 279-80, 1990 | Clinical PK study Mexico | Drug interaction study with dexamethasone (N = 8), showed that Albendazole sulphoxide levels go up when dex is coadministered |
| Jung et al | J Clin Pharmacol 32: 28-31, 1992 | Clinical PK study Mexico | 5 mg/kg tid vs. 7.5 mg/kg bid, N = 8 |
| Jung et al | Clin Neuropharmacol 13: 559-64, 1990 | Clinical PK study Mexico | Comparative study of serum and CSF levels of Praziquantel vs. Albendazole |
| Davis | Eur Neurol 31: 229-40, 1991 | Review | -- |
| Frohberg | Acta Leidensia 57: 201-15, 1989 | Review | Review of comparative toxicology of Albendazole vs Praziquantel and several other antiparasitics |
| Kramer et al | Radiology 171: 459-62, 1989 | Retrospective review California | Description of natural history of NCC by CT |

d. Conclusions: When the submitted literature is examined critically, one finds seven studies (Group A)which, in the opinion of the reviewing Medical Officer, are appropriate for pooling. These studies all utilized identical CT criteria for entry, and were conducted in what appears to be a well-controlled manner. The CT lesions found in patients on entry into these studies are acknowledged to be the type of stable, 'active' NCC lesions that are not known to spontaneously remit.

These studies, when pooled, indicate that albendazole therapy eradicated all CT evidence of neurocysticercosis in 64% of patients treated with 8 or more days of therapy at a dose of 15 mg/kg/day. Studies which utilized an active control arm treated patients with praziquantel at a dose of 50 mg/kg/day; patients treated with this regimen, again for 8 or more days, had an eradication rate of 43% when these studies were pooled. Pooled results for the no-treatment arms of these studies revealed that very few (3%) of such patients might be expected to spontaneously resolve their lesions within the timeframe of the study.

In addition to the seven references included in 'Group A', there were seven references in 'Group B' as well as an additional 24 references found in the Medial Officer's Silver Platter® Medline search. The consensus of these references appears to support the findings of the pooled Group A studies: that albendazole is efficacious in the eradication of 'active' (nonenhancing, nonedematous) parenchymal neurocysticercosis.

Among the investigators who do *not* agree with this is Kramer. In the final reference listed in Table 3 above, Dr. Kramer and colleagues attempt to describe the natural history of NCC by CT criteria. In their concluding comments, these authors state: "It is not currently possible to evaluate the efficacy of therapeutic agents because double-blind, comparative studies using clinical and radiographic end points have been lacking." In a subsequent editorial entitled "Medical Treatment of Cysticercosis--Ineffective" (Arch Neurol 52: 101-2, 1995), Kramer reiterates her call for randomized, placebo-controlled, prospective, long-term studies utilizing both radiographic and clinical endpoints. She does, however, concede that treatment

with antihelminthic drugs appears to hasten larval demise.

Whether the hastened demise of intracerebral *T. solium* larvae actually translates into clinical benefit is an important question. The only study to address this issue in a satisfactory manner is the seventh study listed in 'Group A': Vazquez and Sotelo, N Engl J Med 327: 696-701, 1992. This reference was included in Group A precisely because of its importance in addressing this issue. In this paper, the authors convincingly make the link between treatment of nonenhancing, nonedematous parenchymal NCC lesions (with either albendazole or praziquantel), accelerated disappearance of lesions on CT, and subsequent resolution of seizure activity. This important paper was published by the group of investigators which includes Sotelo and others in Mexico City (who contributed two other papers included in 'Group A'); thus, patients in the Vazquez paper who were shown to benefit clinically from anticysticercal treatment were those presenting with nonenhancing, nonedematous parenchymal lesions only. ***The clinical benefit of albendazole in the treatment of other types of parenchymal lesions (ring-enhancing lesions, those with surrounding edema, calcified lesions, etc.), or cysticercosis lesions located outside of the brain parenchyma (intraventricular, arachnoidal, racemose, osseous, etc.) has not been established.***

2. Gilman study: "Albendazole therapy for neurocysticercosis: a prospective double blind trial comparing 7 vs 14 days of treatment."

a. Description of study. The following description of the Gilman study is excerpted from Volume 117, pages 4-6:

The applicant's text follows in ARIAL 12 POINT font:

## ABSTRACT

Two regimens of albendazole therapy for neurocysticercosis (7 and 14 days) were compared in a prospective, randomised, double blind trial. Effectiveness of ABZ was 78% (decrease in total number of cysts), but there were no significant differences in the groups when compared three months after therapy. Complete cure was obtained in 38% of patients. Patients with massive infections (more than twenty cysts) had poorer responses to therapy, even with re-treatment courses of 30 days. The clinical course and EEG evolution improved in most patients. Two patients died in the first year after therapy both because of aggregated infections of ventriculo-peritoneal shunts. Side effects related to the drug were present in 38% of patients, mainly mild, transient gastrointestinal symptoms. Therapy was also associated with exacerbation of neurologic symptoms. One year follow up CT scans showed the existence of lesions of three of ten patients presumed to be cured. Extension of ABZ therapy for more than 7 days adds no benefits for the patients.

## INTRODUCTION

Human cysticercosis is a common cause of morbidity and mortality in developing countries[1,2], accounting for 10-12% of neurological hospital admissions in endemic areas[3,4]. The life cycle of the cestode *T. solium* includes the pig as the normal intermediate host, harbouring the larval vesicles of cysticerci, and man as the definitive host, harbouring the adult form or tapeworm. Humans can also serve as the intermediate host and develop the cystic form by accidental ingestion of Taenia eggs[5]. Cysticercosis causes a variety of neurological symptoms, most commonly seizures due to cysts in the brain parenchyma[1,2,6]. Subarachnoidal or intraventricular cyst may cause intracranial hypertension[2].

For many years, therapeutic approaches to neurocysticercosis (NCC) were limited to steroids and surgery for intracranial hypertension[1,5]. In 1978 praziquantel (PZQ) was introduced as the first effective parasite-specific drug for NCC[7,11]. Albendazole (ABZ) was reported to be useful in 1989[12] and became widely used in the following years because of its efficacy and low cost[12-18]. Initially, the suggested duration of ABZ therapy was 30 days[12], but shorter schedules of 15 and 8 days were successfully used[13,14].

Previous drug studies in NCC have been limited by open designs and short duration of follow up. In this double blind study, Peruvian patients were randomised to either 7 or 14 days of albendazole therapy and followed by clinical Electroencephalography (EEG) and

Computed Tomography (CT) criteria for at least three months (n=50), or one year (n=36) after treatment as overall determinants of treatment efficacy.

## MATERIALS AND METHODS

Fifty five patients from different public and private clinics in Lima, Peru, diagnosed with NCC on the basis of a positive CT scan with active lesions and a positive serological test (immunoblot) were consecutively included in the study. "Active" lesions included live cysts with or without contrast enhancement and nodular enhancing lesions[2]. Patients with no "active" lesions (i.e. calcifications only or hydrocephalus) were excluded as were pregnant or lactating women. Patients were dropped from the analysis if they refused to follow the study protocol, or if they did not return on the 90th day follow-up visit. One case had to be excluded because medication was not given appropriately.

Initial evaluation of the patients included clinical history and standard 8-channel EEG tracings. Three stool exams and a perianal scotch tape examination were performed as previously described[19]. Niclosamide treatment (2gm given as a single oral dose followed by a purge with castor oil 1½ hours later) was given in order to increase the detection of intestinal taeniasis[20] and simultaneously eliminate adult worms, Niclosamide is not absorbed, therefore not affecting cerebral cysticerci and has minimal side effects[21]. Purged stools were also examined for the presence of *Taenia* eggs or proglottids[19].

Informed consent was obtained from all patients. Patients were allocated to one of two treatment groups using a previously assigned randomised schedule. Group A received ABZ 400mg BID orally for 14 days, while Group B received ABZ 400mg BID orally for 7 days, followed by seven days of a similar appearing placebo. Both groups received dexamethasone 1.5mg tid given orally for 5 days, tapered to 0.5mg tid in days 6 and 7 and then withdrawn. Patients receiving antiepileptic drug (AED) therapy were maintained on their current drug regimen.

All patients were hospitalised during treatment. Daily evaluations were performed while in hospital by a study physician. EEG and CT scans were repeated at days 15, 90 and 360 after the initiation of treatment. Patients had clinical follow-up visits at the above dates as well as on days 30, 180 and 270.

CT scans were read by an experienced reader, blinded to the therapy used. Lesions were recorded as follows: 1) Cysts, hypodense, rounded lesions visible in non contrasted CT series, 2) Nodular enhancing lesions, isodense zones which became hyperdense after the injection of contrast, and 3) Calcifications, hyperdense images which did not change with contrast. The patient's scans were read in sequential order by date. In some cases the day 15 images showed lesions not visible in the initial scan. These lesions were categorised as present pre-treatment. The baseline number of active images (cyst, nodular enhancing lesions) was compared with the number present at 90 and 360 days

after treatment. If a single lesion was visible in consecutive slices of the same CT, it was counted only one time. The presence of ventricular dilation or cerebral atrophy were also recorded. Follow up scans showing no active images (cysts or nodular lesions) were recorded as "radiologic cure".

Paroxysmal activity and alterations of the baseline rhythm in the EEG were classified as local or generalised[22]. EEG recordings were read by the same reader (JA) who was unaware of the patient's therapy and the date of the EECG examination.

The treatment code was broken one year after the last patient has been included in the study. The study was approved by the ethical review boards of the Universidad Peruana Cayetano Heredia, Lima, Peru and the John Hopkins University Baltimore.

Statistical Analysis

Efficacy of therapy was defined as the proportion of cysts which disappeared after treatment. Chi square test and Fisher's exact test were used to analyse associations for discrete variables, and Student's t test or Mann Whitney test for continuous variables.

b. Value of study to application. This study is the only clinical study submitted with NDA 20-666 which was funded by the applicant. This is the only NCC study for which the primary data (i.e., case record forms, informed consent documents, and original study materials including CT scans) is available for FDA review. Furthermore, this study is the only one which underwent IRB review and oversight by a US-based IRB (Johns Hopkins University). Consequently, this study takes on considerable importance in the regulatory review of this indication.

c. Applicant's results of Gilman trial: The following description of the results of the Gilman study is taken from pages 6-14 of volume 117, NDA 20-666 (again, Applicant's text follows in ARIAL 12 POINT font):

## RESULTS

50 (initially 55) patients who were originally randomised and treated completed the three months evaluation. One patient refused to continue, two patients did not return after the day 30 visit, in one the medication was given incorrectly, and in one case the scans were lost.

Group Distribution

The total number of patients assigned to Group A (14 days) was 27 and 28 to Group B (7 days). Of the five patients dropped out of the study, two were from Group A, and three from Group B. As shown in Table 1, the groups were similar for all parameters with

exception of the mean number of calcifications. The difference was due to two cases with 25 and 30 calcified lesions, respectively.

*Medical officer comment: the applicant apparently is referring to the category "massive infections", but this is not clearly explained.*

**Table 1 Comparative Characteristics of ABZ treatment groups in Peruvian Patients with Neurocysticercosis (n=50)**

| | Treatment Group A - 14 days (n=25) | B - 7 days (n=25) | P |
|---|---|---|---|
| **General** | | | |
| Male/female | 14/11 | 13/12 | NS |
| Age | 29.4±15.8 | 39.7±17.7 | NS |
| **Antecedents** | | | |
| Pig raising | 17 | 16 | NS |
| Teniasis | 11 | 10 | NS |
| **Symptoms** | | | |
| History of seizures | 19 | 22 | NS |
| Intracranial Hypertension | 4 | 3 | NS |
| **Baseline CT findings** | | | |
| Cysts* | 3.3±3.1 | 3.9±3.7 | NS |
| Nodular enhancing lesions* | 0.4±0.7 | 0.7±1.3 | NS |
| Massive infections | 2.1±3.1 | 6.4±8.55 | <0.05 |

*Medical officer comment: the meaning of the asterisks in this table is unclear. No footnote appeared in the text of the applicant's study report.*

Presenting Symptoms

The most frequent symptom at study entry was headache (45 patients, 90%) followed by seizures (82%). Headache or seizures were also the initial manifestation in 21 and 20 patients respectively. Memory loss was reported in 14 patients, but was the initial symptom in only three of them. Seven patients had symptoms related with intracranial hypertension. Two other patients reported subcutaneous nodules, both of whom had demonstrated cysticerci on histological examination (Table 2). The duration of symptoms ranged from 8 days to 30 years, with a mean of 51.6 ± 69.2 months (mean ± SD).

**Table 2 Main Presenting Symptoms in Peruvian Patients with Neurocysticercosis (n=50)**

| Symptom | N (%) | Initial Symptom* |
|---|---|---|
| Headache | 45 (90) | 21 |
| Seizures | 41 (82) | 20 |
| Cranial nerve deficit | 19 (38) | 6 |
| Memory loss | 14 (28) | 3 |
| Sensitive alterations | 12 (24) | 2 |
| Motor deficit | 12 (24) | 1 |
| Intracranial hypertension | 8(16) | 1 |
| Subcutaneous nodules | 2 (4) | 1 |

* in some cases there was more than one presenting symptom.

Baseline Physical examination

Eighteen patients had abnormal neurological and other findings on examination. These included all seven patients with intracranial hypertension syndrome (100%), and 10/42 (26%) of the remaining patients (Table 3).

**Table 3 Findings at baseline physical examination in Peruvian Patients with Neurocysticercosis (n=50)**

| Sign | Symptoms of intracranial hypertension | |
|---|---|---|
| | Positive (n=7) | Negative (n=42) |
| Ataxia | 5 (63%) | 0 (0%) |
| Disorientation | 3 (38%) | 1 (2%) |
| Memory loss | 3 (38%) | 2 (5%) |
| Papilledema | 4 (40%) | 1 (2%) |
| Cranial nerve paresis | 2 (25%) | 2 (5%) |
| Motor paresis | 2 (25%) | 3 (7%) |
| Extrapyramidal signs | 0 (0%) | 1 (2%) |
| Subcutaneous nodules | 0 (0%) | 2 (5%) |
| Total* | 7(100%) | 11(26%) |

*p<0.001 Fisher's exact test

Parasitological examinations

Eggs of *Taenia sp.* were found in the stools of only two patients (4%). The scotch tape test was negative for both. After niclosamide treatment one of these two patients passed an adult *T. solium* tapeworm while only eggs of *Taenia sp.* but no proglottids or eggs after niclosamide treatment.

Side Effects

Side effects apparently related to ABZ were present in 19/50 patients (38%). Fourteen of them had nausea, three had abdominal pain and/or discomfort and four had diarrhoea. In four patients a transient cutaneous rash appeared, on treatment days 3, 4, (2 patients) and 7 (2 patients). One patient had persistent hiccough on days 4 to 8 of ABZ therapy, and another had mild hair loss persisting for one month after ABZ treatment. In no case did therapy need to be interrupted.

Neurological symptoms during treatment

Most patients (46/50, 92%) complained of headache during treatment. Headache began in the first two days in 17 cases, between the 3rd and the 5th day in 11 cases, and between days 8-10 (following steroid withdrawal) in 12 cases. Twelve patients, all with a previous seizure history, had motor seizures during treatment.

One patient had a worsening of her extrapyramdial signs developing generalised rigidity. This diminished after day 12, and improved in the next months. Her control CT at day 90 showed moderate hydrocephalus, not present on her baseline CT. Another patient had a crisis of intracranial hypertension three days after the end of treatment. In this patient the 15th day CT showed significant inflammatory reaction around multiple enhancing images, with cerebral oedema. The symptoms remitted with the reintroduction of steroids and infusion of mannitol.

No patient died during the 15 days of therapy. Two patient, both with intracranial hypertension at baseline, died during the first year of follow up (fourth and sixth months). Both deaths were associated with bacterial ventriculitis secondary to the placement of ventriculo-peritoneal (VP) catheters.

15th Day CT

13 out of 50 patients showed at the 15th day CT "new" images (a total of 7 cysts and 11 nodular enhancing lesions). Seven were from Group A and six from group B.

Efficacy of Treatment

a) Three months evaluation - There were 37 patients with less than 20 viable cysts, 20 from Group A (14 days) and 17 from Group B (7 days). At the end of three months of follow up, efficacy of therapy (diminution in the number of cysts) was similar for both groups (Group A: 51/66, 77%, Group B: 52/66, 78%). In 14 patients, eight from Group A (8/20, 40%) and six from Group B (6/17, 35%) there was radiologic "cure" (p>0.96, chi square test) [Table 4].

**Table 4** **CT Evaluation of Cysticercosis cysts in 37 patients three months after ABZ therapy (Group A: 20, Group B: 17)**

| | CT EVALUATION | | |
|---|---|---|---|
| | **BASAL** | **DAY 90** | **REDUCTION** |
| **Cysts** | | | |
| Group A (14 days) | 60 | 15 | 51 (77%) |
| Group B (7 days) | 66 | 14 | 52 (79%) |

*p=1.00. Chi square test for differences in number of cysts persisting at day 90.

*Medical officer comment: the number of cysts reported at baseline in Group A in Table 4 is 60; in the text which precedes Table 4, Group A is reported to have 66 baseline cysts. This is assumed to be a typographical error on the part of the applicant.*

b) One year evaluation - Twenty four patients (65%) in this cohort had a one-year control CT. At this control there were 21 cysts, eight more than in their day 90 CT (Table 5). Ten "cured" patients, with no active lesions at day 90, had one-year control CT exams. In three of them (two from Group A and one from Group B) day 360 scans showed one active lesion each, a cyst in one case and nodular enhancing lesions in two.

**Table 5** **CT Evaluation of cysticercotic cysts in 24 patients one year after ABZ therapy (Group A:14, Group B:10)**

| | | CT EVALUATION | |
|---|---|---|---|
| | | BASAL | DAY 90 REDUCTION |
| | [n] | [n - % reduction] | [n - % reduction] |
| **Cysts** | | | |
| Group A | 33 | 8 - 76%* | 14 - 58%# |
| Group B | 40 | 5 - 87%* | 7 - 83%# |

*p=1.00. Chi square test for differences in number of cysts persisting at day 90.
#p=0.037. Chi square test for differences in number of cysts persisting at day 360.

*Medical officer comment: This table is confusing. The columns are labeled as 'basal' and 'day 90', yet the title and footnote describe a day 360 timepoint. It is assumed that this is a typographical error, and the table actually shows that of the 14 group A patients who had a year of follow-up, there were 33 cysts at baseline, 8 at day 90, and 14 at day 360; for the 10 group B patients there were 40 cysts at baseline, 5 at day 90, and 7 at day 360. This increase in cysts at the one year timepoint may represent new infection that was acquired during the interveining 9 months, or may represent lesions that were below the limit of detection at the first two scans (baseline and day 90) but were visible by CT at day 360.*

Massive Infections

There were 4 patients with more than 20 cysts visualised at the baseline scan, one from Group A and three from Group B. None of them had radiological cure. Effectiveness of therapy in this subgroup was only 27% (115/421 cysts).

Patients with only nodular enhancing lesions

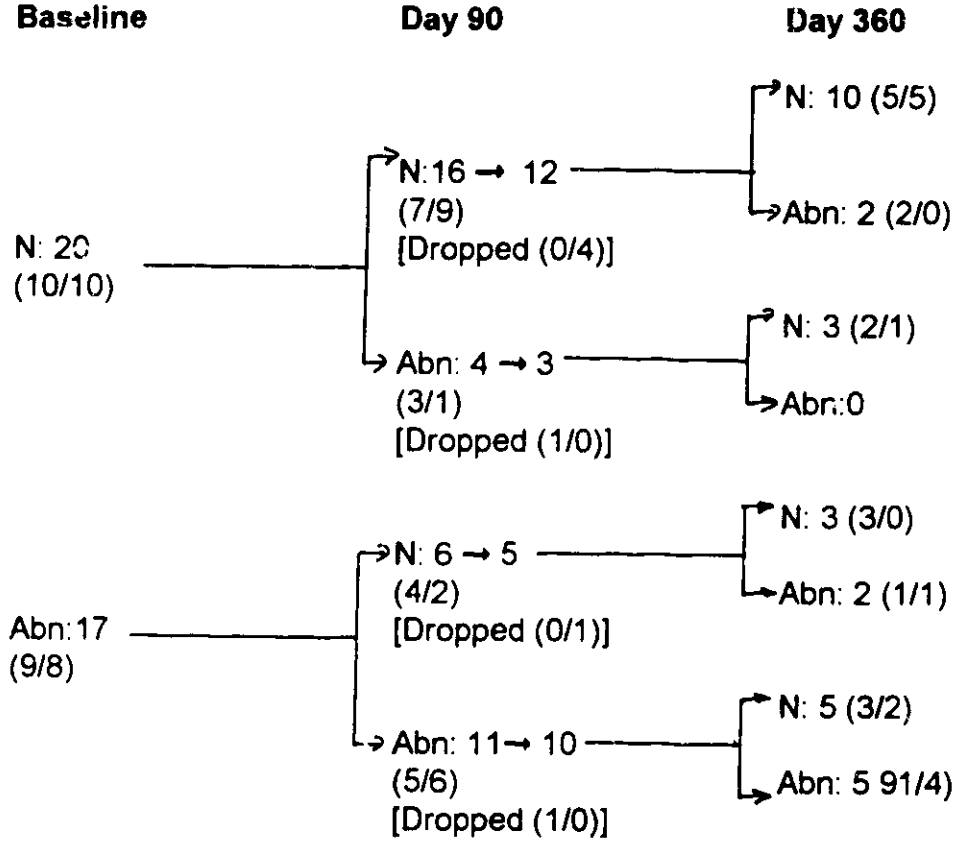
There were 9 patients (four from Group A, five from Group B) with only nodular enhancing lesions, without cysts. Seven of them (78%) still had active lesions on CT at day 90, and three of eight (38%) at the one-year control. There was no difference in the outcome of Group A and Group B patients.

EEG Results

There were serial EEG examinations (basal, day 90 and day 360) in 30 patients (Figure 1). Among 15 patients with normal baseline EEG, 12 (80%) had normal exams at the end of the one year follow up. Among 15 patients with abnormal baseline EEG, 8 (53%) had a normal EEG one year after therapy. There was a greater proportion of patients whose

EEG became normal in Group A (6/8, 75%) than in Group B (2/7, 29%), although it didn't reach conventional statistical significance (p=0.13, two-tailed Fisher exact test).

**Figure 1 EEG Evaluation in 37 Peruvian patients with NCC after either 7 or 14 days of ABZ therapy**




N: Normal; Abn: Abnormal.
Numbers between parenthesis are (Group A/Group B).

*Medical officer comment: following the logic of this Figure is difficult.*

Clinical Follow Up

All the 50 patients had clinical follow up visits at day 90, and 39 had visits until day 360. Sixteen patients (32%) were asymptomatic at day 90. Twelve of these 16 had follow up visits at day 360, and 8 (67%) were still asymptomatic. A further seven patients had no symptoms between day 90 and day 360, giving a total of 15 patients (38%) without symptoms at the end of the one-year follow up (group A=8, group B=7).

Thirty four of 40 patients with motor seizures completed the one year follow up (18 from Group A, 16 from Group B). Twenty four (71%) of them remained seizure-free until day 90, and 15 (44%) persisted without further seizures to day 360. There was no difference between therapy groups in regard to development of seizures. In ten of the 19 cases who had new seizures there was a history of interruption of AED treatment. Of the six patients who did not complete the follow up, 5 had no motor seizures during the first three months. Forty five patients had a history of headache pre-treatment. Only 8 (18%) of them persisted with headache to day 90, and 3 of then until day 360.

Clinical and tomographic follow up in patients with ICH

Five of the seven patients with ICH syndrome had VP shunts placed before the day 90 control. Symptoms remitted in three of them before day 90, and in one other before day 360. The fifth patient was still symptomatic at day 90, and died one month later. Among the other two patients with ICH syndrome one was still symptomatic and had a shunt placed after day 90, but died from infection two months later. In the remaining patient - the only who did not have a shunt -, symptoms remitted after treatment.

Three other cases had hydrocephalus on baseline CT, with no clear ICH syndrome. Two of them had symptoms at day 90, but not at day 360. None required placement of a shunt. The two who had one-year controls still had enlarged ventricles, but no clinical symptoms of ICH. Three further cases developed hydrocephalus on the follow-up, seen on CT (one at day 90, two at one-year), without ICH syndrome.

## DISCUSSION

This study is to our knowledge, the first prospective, double blind study on antiparasitic therapy for neurocysticercosis. The study population was systematically followed, and CT and EEG examinations were performed irrespective of clinical status. Treatment was equally effective whether given for seven or 14 days. Effectiveness against live cysts was high (78%), but only 35 to 40% of patients were lesion-free at three months due to the continued presence of enhancing lesions and some cysts.

Results of therapy were poor when large numbers of cysts were present. Patients with less than 20 cysts cleared over three quarters of the lesions, whereas the four patients with massive infections (over 20 cysts) cleared less than one third. After one year and several courses of therapy one of the four patients with massive infection had complete clearance of lesions on CT, while the other three had a decrease of less than fifty percent in the number of cysts (H.H. Garcia, personal observation). Our study suggests that patients with heavy infections behave differently than those who have small numbers of cysts. These two groups should be stratified in future therapeutical trials. Also, further studies should determine the utility of multiple courses of therapy, drug combinations or new drugs in heavily infected individuals.

Similar to other reported series[23,24], only two patients (5%) had evidence of tapeworm infection but 42% had a prior history of passing proglottids. One of the two carriers had a massive infection with over 100 cysts, suggesting that the presence of an intestinal tapeworm may increase the risk of heavy infection. The use of Graham scotch tape technique has been suggested for tapeworm detection, especially for Taenia saginata[19]. It was not useful in this series, missing the Taenia eggs detected by stool examination in both cases. It also appears ineffective in field studies[25,26].

Therapy appears to either kill cysts directly or to unmask the cyst to the host's immunological response resulting in a granulomatous reaction which eventually calcifies. Commonly, an exacerbation of symptoms occur between the second and the fifth day of treatment, reflecting local inflammation due to leakage of antigen from damaged or dead larvae[2]. Fifteen days after therapy we observed new liaisons on CT in eight patients. We believe that this is due to the local oedema and marked contrast enhancement caused by the inflammation response, increasing the CT detection of lesions. Similarly subcutaneous nodules may become more evident soon after antiparasitic treatment. Nodular enhancing ("colloidal"[27]) lesions are thought to be unresponsive to therapy since the larvae are already dead. However, association between antiparasitic therapy and better evaluation of seizures in patients with enhancing lesions has been reported[28].

We also found cystic and/or nodular enhancing images in CT one year after treatment in several patients who had apparently demonstrated complete cure in their three month control. Since most patients lived in Lima, where teniasis is not endemic, new infection is unlikely. Whether these parasites were simply missed by CT or were present, resisted treatment and then grew in size is not clear. In any case, patients with only calcifications or nodular enhancing lesions at CT who have poor response to antiepileptic treatment and are persistently seropositive to cysticercosis may benefit from ABZ treatment.

*Medical officer comment: Given the quality of the CT scans from this study, which were submitted to the NDA by the applicant, it is not surprising that some smaller lesions were missed.*

Praziquantel concentrations fall to about 50% when steroids are given concomitantly[29]. In contrast, when albendazole is given with steroids, serum concentrations are either not affected or may even increase[30]. In this study, steroids were given for seven days. Overall the efficacy of ABZ was similar to other series, and only one patient had a severe reaction to treatment. Steroids may prevent intracerebral complications and should be used during ABZ treatment.

The presence of hydrocephalus and/or intracranial hypertension has been noted to be related with poor prognosis[31]. The only two deaths which occurred in our study population were in this group of patients. NCC patients develop obstructive hydrocephalus because of intraventrical or cisternal cysts, meningeal fibrosis or ependymal hyperplasia[2,27,31]. Parasite destruction may cause local inflammation and lead to

residual meningeal fibrosis, which may have contributed to the development of hydrocephalus in three patients in this series. Whether long term steroids may prevent the development of hydrocephalus needs to be examined.

The clinical course of most patients was favourable. The majority of those with seizures either were completely controlled or had fewer seizures than before treatment. The electroencephalographic evaluation was also favourable, with the majority of patients with abnormal EEG patterns returning to normal before one year. Whether ABZ or PZQ treatment affects the clinical course of epileptic seizures due to NCC still is open to question since prospective studies are lacking. Recent retrospective studies suggest that NCC patients with seizures treated with ABZ or PZQ have a better evaluation than those receiving only AEDs[28,32].

Therapy with albendazole appears to be effective even when given for only seven days. However, complete disappearance of lesions is not the rule, and comprehensive follow-up must be maintained for at least one year. Despite its great usefulness, the validity and reliability of CT scan are not absolute, and still careful clinical monitoring is essential in the management of NCC patients.

d. Medical Officer comments. The Gilman study, as mentioned in the preceding comments, is an important segment of this NDA submission. It represents the only study conducted with the prospective participation of the applicant. In general, this study has several advantages over any of the studies included in the previous literature review section. The advantages and problems of the Gilman study, as compared to the studies included in Group A or Group B of the submitted literature references, are outlined in the following table:

**ADVANTAGES AND DISADVANTAGES OF GILMAN STUDY**

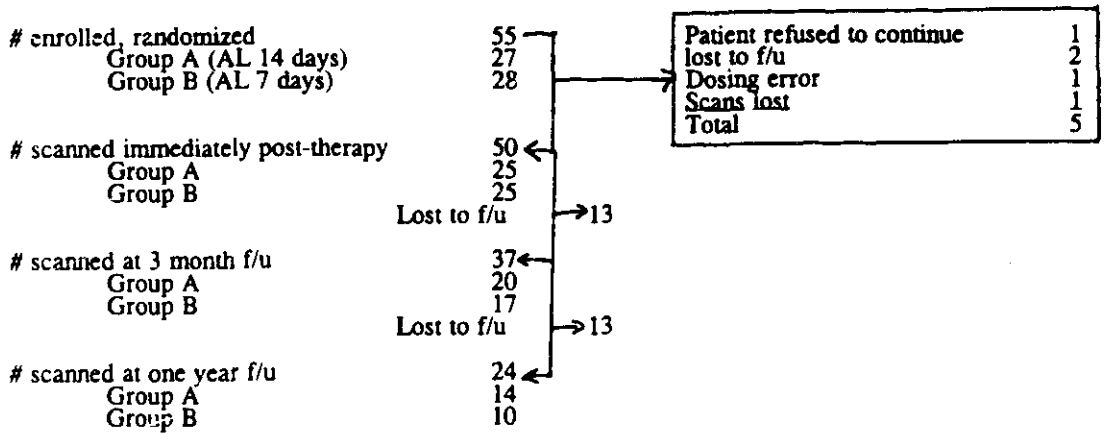
| *Advantages* | *Disadvantages* |
|---|---|
| Conducted under U.S. IRB | NOT conducted under IND; no FDA input |
| Prospective, randomized, double-blinded | Concomitant steroids given to all treated patients |
| Immunoelectrotransfer blot used for serodiagnosis | Enhancing CT lesions included |
| Primary data (CT scans) available for review | No untreated concomitant control group |
| Source of Albendazole (presumably) SK/B | No line listings submitted with NDA |
| Long-term follow-up (3 months and one year) | Quality of submitted CT scans poor |
| CT reader blinded to study group@ | |
| Endpoint = # of lesions before/after therapy | |

@ this may not have been the case. Please refer to Attachment 2 of this portion of the Medical Officer review.

The disadvantages listed in the above table are troublesome insofar as they make the results of this study impossible to pool with the results of the 'Group A' studies. Moreover, the absence of any submitted line listings makes it impossible to critically review the results of this investigation. The CT scans from this trial were not initially submitted with the NDA; they were specifically requested by the Agency at the time of the 45-day fileability meeting. The scans themselves were not available for independent review until Amendment #1 to the NDA was submitted on 22 February 1996 The review of these scans is the suoject of ADDENDUM 1

The reviewing medical officer found it difficult to interpret the sponsor's tabular presentations of the results of the Gilman study as presented above. Without actual line listings for each enrolled subject, it is impossible for the medical officer to accurately reconstruct and present these data. From the data presented, the following can be surmised:

**GILMAN STUDY: ALLOCATION AND OUTCOME OF SUBJECTS**




Thus it can be seen that this study had a 33% (18/55) attrition rate between the time of enrollment and the three month post-therapy follow-up scan. This time point is the most relevant to compare with the literature studies included in the Group A studies. From Table 4 of the sponsor's results, it can be seen that among these 37 patients (20 Group A, 17 Group B) the following table can be constructed which permits comparison with the literature studies reviewed previously:

**GILMAN STUDY: CT EFFICACY RESULTS**

| Gilman, Peru | | entry into study | | 3 month follow-up | | |
|---|---|---|---|---|---|---|
| Group | N | # cysts | # per patient | # cysts | # per patient | # patients cured (%) |
| AL 14 days (Group A) | 20 | 60 | 3.0 | 15 | 0.75 | 8 (40%) |
| AL 7 days (Group B) | 17 | 66 | 3.9 | 14 | 0.82 | 6 (35%) |

*Medical officer's comments:*

*1. Presumably, the above numbers do not include patients with so-called 'massive infections' (see page 37), defined as enrollees with greater than 20 cysts on baseline CT scan. There were 4 such patients enrolled, one in Group A and 3 in Group B; if the statement on page 39 (page 010, volume 1.117 of NDA) can be interpreted correctly, these 4 patients had a total of 421 cysts for an average of 121 cysts/patient. None of these four patients were cured following therapy. In their discussion, the authors agree that "patients with heavy infections behave differently than those who have small numbers of cysts." This phenomenon has been recognized by other investigators as well.*

*2. If the rates of cyst reduction per patient and overall cure rates, as seen in the above table, are compared with the literature studies in Group A (Table One, page 23), it can be seen that the cure rates are somewhat lower in this study. This is surprising, given that patients with enhancing lesions were enrolled in this study and one might expect a certain number of such lesions to resolve spontaneously during the three months of follow-up. On the other hand, this may be a more accurate reflection of the real efficacy of albendazole in NCC, since this study used IETB for confirmation of the diagnosis (whereas the literature references reviewed previously did not). Another possibility is that some of these patients developed new NCC lesions following AL therapy.*

e. Conclusions. The overall results of this study are consistent with the literature reviewed earlier in this document. The CT results have been verified by internal FDA review of the submitted scans (see Attachment 1). The clinical investigator and study site have been audited by ' and the fact that the study was conducted has been verified. Therefore, the medical officer concludes that this study should be considered to be an adequate and well-controlled study for the neurocysticercosis indication.

3. Compassionate use data

a. Description of process and shortcomings of resultant data. The applicant, Smith Kline Beecham Pharmaceuticals (SK/B), has never applied for, and does not currently hold, an Investigational New Drug application for albendazole for either of the two indications sought in this NDA. Therefore, acquisition of albendazole by treating physicians in the United States has been exclusively via individual investigator IND applications, granted on a case-by-case basis by the Division of Anti-Infective Drug Products. This process involves an initial telephone request by the requesting physician to HFD-520 (usually after having called the sponsor initially). A clinical information form is faxed to the requesting clinician, who completes the patient information and returns the form to HFD-520 by fax. The case is then reviewed by the Project Manager in conjunction with the Medical Officer, and, if clinically appropriate, an individual investigator IND number is granted. The requesting physician/investigator is contacted and informed of his/her duties and responsibilities as the holder of an IND, then informed that they can now obtain drug for their patient from SK/B. Upon receipt of a clinical summary and IND number from the physician/investigator, SK/B ships the appropriate amount of albendazole for that individual patient's use. Further follow-up paperwork (including FDA forms 1571 and 1572) is mailed to the investigator for completion after drug acquisition has taken place. The net result of this cumbersome process is the relatively rapid acquisition of an unapproved drug for patients with serious diseases (neurocysticercosis and echinococcosis), with no pre-shipment requirement of regulatory paperwork on the part of HFD-520.

Since drug has been shipped and (usually) administered long before the duties of paperwork completion are brought to the requesting physician's attention, further clinical follow-up has been difficult to obtain. Regulatory reporting requirements for IND holders notwithstanding, the great majority of clinicians to whom drug is shipped fail to provide any clinical follow-up on their patients.

The applicant has attempted to solicit follow-up information from those clinicians to whom albendazole was shipped for the treatment of patients with NCC. The following description of these efforts is taken from volume 1.116 of NDA 20-666, pages 5-10 (applicant's text follows in ARIAL 12 POINT font):

## 3.3.2.1 Introduction

There has not been any previous attempt made to locate and follow up patients with cysticercosis treated under the compassionate use IND process in the United States. In almost all countries where cysticercosis is prevalent, albendazole is licensed and available, although not necessarily with an indication for cysticercosis. The United States is one of the few non endemic countries in which albendazole is not approved where there are significant number of clinical cases . Therefore it is also one of the few countries where compassionate use data might be obtained retrospectively.

After experience with a retrospective follow up of hydatid patients (see section 3.2.4, Compassionate Use Experience in the United States (Hydatid), Volume 1.111), a similar exercise was undertaken with physicians who were identified as having received INDs for cysticercosis. This collection of data was conducted on patients issued with INDs between Jan 1991 and June 1994. The last date of entry for a patient of record

was September 1994, giving adequate time for follow up assessments to be made.

### 3.3.2.2 Methods

The records of drug supplies dispatched under INDs from SmithKline Beecham in the UK to individual physicians in the United States were obtained. Details of physicians who received drug for the treatment of patients with cysticercosis were recorded. A case record form to collect relevant data for efficacy and safety evaluation was devised and dispatched by telefax or by post with a letter to each physician requesting data to be supplied (Appendix 1). Follow up letters/faxes were sent to non responders. Since the data collection was co-ordinated from United Kingdom follow up telephone contacts were not feasible. Responses were received in London and entered to a simple spreadsheet for analysis.

### 3.3.2.3 Results

#### 3.3.2.3.1 Demography

There were 158 physicians who had treated 169 patients under compassionate use INDs were contacted. Forty-four physicians (29.8%) responded with data and 51 of their patients had data which was evaluable. Responses were excluded in addition for the following reasons. Eleven responses from physicians without patient data: 2 not neurocysticercosis, 4 patients refused treatment, 3 drugs not used but no reason given, 1 patient died before drug given, 1 lost to follow up. 6 physicians had moved without leaving a contact address and 97 (61.4%) failed to respond.

The State of origin of the patients is shown in Table 1.

There were 25 males and 26 females, whose mean age was 32.2 ± 15.3 years, ranging from 2-64 years. There was no apparent difference in age between the sexes (male 32.0 ± 11.7 years, female 32.3 ± 18.4 years).

Cysts were located in the central nervous system in all cases, although two patients also had extraneural sites involved (Table 2). The majority of lesions were newly diagnosed (28; 54.9%), but 6 patients were recorded as having recurrent cysts (after either surgery or chemotherapy) and 2 patients had new and recurrent cysts. 14 patients had previous surgery (33 no surgery and 4 not stated). 21 patients had previously received praziquantel, two albendazole and two both drugs. Only 9 patients had no previous drug therapy although in 17 no data was entered.

3.3.2.3.2 Treatment

The majority of patients (40; 83%) received a single course of treatment although 5 received 2 courses and one each, 3, 4, and 6 courses. No data was recorded for 3 patients.

Duration of treatment ranged widely. The majority (22; 43.1%) received 28 to 30 days of treatment, while 7 received 7/8 days, 9 received 14/15 days and 5 received 21 days of albendazole. One patient reportedly received 60 days continuous treatment and no data were recorded for 6 patients.

While treatment duration was variable, and was probably determined by the data provided from the literature and other sources, the dose used varied even more. Although the greatest number of patients received 800mg/day or 15mg/kg/day (27 patients) doses of 300mg (2 patients), 400mg (3 patients), 600mg (5 patients) and in excess of 800mg (8 patients) were also used. Some of the different dose regimens could be explained on the use of a weight based dose schedule: for example some of the youngest patients received the lowest doses. However, other of the lower doses were given to adults. Unfortunately body weight data were not collected.

At the time of data collection 4 of the 51 patients were still recorded as under active follow up, while 2 had died as a result of cysticercosis, one was lost to follow up and 19 had apparently completed follow up.

The duration of follow up to the time of data collection averaged 8.7 ± 9.3 months with a range of 0.25 - 36 months.

3.3.2.3.3 Treatment Outcome

The results of treatment were assessed by radiological means (Computerised tomography, magnetic resonance imaging or both) and also clinically. The average time to radiological/clinical evaluation was shorter than the total available period for evaluation since the management of patients was not scheduled to occur within a specified protocol. The mean time to outcome assessment was 4.9 ± 6.3 months.

Radiological response showed 6 patients cured (all cysts disappeared), 23 patients improved (cysts resolving or some cleared some resolving or calcified), 9 patients without change, and one worse with new lesions. 5 patients did not have data. Clinically 44 (95.6%) of those with data were reported as improved and 2 unimproved.

In addition to a global clinical improvement, the data collection form aimed to identify whether initial or presenting clinical symptoms had improved after treatment. There were a total of 79 symptoms recorded for 41 patients (16: 1 symptom, 16: 2

symptoms, 6: 3 symptoms, 2: 4 symptoms and 1: 5 symptoms). Their resolution or improvement are shown in Table 3. In the patient listings the actual terms reported are listed. However only headache and seizures are recorded as individual terms, and the others are combined into groups of similar terms/ symptoms. Improvement or clearance of presenting symptoms was observed in 94.9% of the evaluable patients. Anticonvulsants were received by 28 patients (24 recorded as having seizures). During follow up, 8 had stopped therapy and 5 reduced the dosage.

3.3.2.3.4 Drug Tolerability and Safety (Table 4)

The physicians assessed the treatment as tolerated in 47 patients and not tolerated in 1 patient (3 no data). Steroids were administered to 40 patients and not used in 9 patients (2 no data).

Twelve patients experienced untoward events of which 3 were classified as severe, 6 mild and 3 not specified. 2 of the severe events and one unspecified (Headache pat#74, headache, nausea and vomiting pat fever/obtundation pat ) appeared to be related to cerebral reactions to treatment and responded to steroid treatment. The other (pat ' with multiple intraventricular cysts) experienced a pronounced rise in liver enzyme levels and treatment was withdrawn after 7 days. 2 patients suffered from dermatological reactions described as mild; one received steroids and antihistamines. One patient suffered from glucose intolerance while on steroids, and this resolved on their withdrawal. Other events were mild and apparently self limiting. Two patients died post treatment, 1 month and 9 months post treatment. In both the cause of death was considered unrelated to albendazole treatment.

3.3.2.4 **Discussion**

The return of data on these patients (40%) is somewhat disappointing given the over 60% response with hydatid disease. The reasons are unclear, and somewhat unexpected given the relatively short duration of follow up required to provide evaluable results. It is possible however that most were lost to follow up quite soon after treatment as the patients typically affected with cysticercosis (newly arrived immigrants from South and Central America and migrant workers) are highly mobile.

Since cysticercosis is more rapidly evolving than hydatid disease, it is not surprising to find some very young children affected, and it is less common in middle to old age. It is interesting to note that a significant proportion of patients had recurrent cysts and had surgical intervention. Previous chemotherapy however was reported in half the patients. This is therefore, fairly typical for a cysticercotic population in Latin America. What is unusual is the proportion of non parenchymal cysts (Table 2) with 23 ventricular, arachnoidal and spinal cystic sites (45.1%) in the total.

It is recognised that non parenchymal cysts, particularly racemose and spinal cysts are difficult to treat and require longer periods of treatment. Eight patients received

more than one course of treatment and half of these had extra parenchymal cysts. Some of the eight patients with doses greater than 800mg/day also had extra parenchymal cysts.

The relatively poor response rate based on radiological criteria may in part be due to the predominance of difficult to treat extra parenchymal and multiple cysts. None the less 71.8% of patients evaluated were 'cured' or 'improved' radiologically. Clinical improvement was more dramatic with 95.6% reported improved.

Although cysticercosis may be life threatening, especially when the lesions are subtentorial, spinal or racemose, most patients suffer debilitating symptoms which can severely reduce quality of life and employability. Thus resolution of clinical signs and symptoms are important. This evaluation was able to collect these data from a high proportion of patients. The commonest presenting symptoms were headaches and seizures, although a number of other central and peripheral nervous system presentations were reported. Nearly two thirds of the patients had two or more symptoms. At the final outcome assessment, on average 5 months post treatment 59.5% had shown clearance and a further 35.4% of symptoms had improved. This improvement is also borne out by the number of patients who were able to stop (8:28.6%) or reduce (5:17.9%) their anticonvulsants.

Twelve patients experienced adverse events attributable to treatment. Three of these were directly related to treatment related cerebral oedema (mass effect) and responded promptly to steroid therapy. One patient experienced a significant rise in transaminases and withdrawn after 7 days. Since this was of rapid onset, this could have been a hypersensitivity type response. Other events were mild. One patient was withdrawn from steroids because of glucose intolerance and two had mild dermatological reactions. Overall therefore, side effects attributable to therapy were easily managed. Two deaths were reported both as the result of cysticercosis complications rather than of therapy.

### 3.3.2.5 Conclusion

This retrospective evaluation of radiological and clinical response to albendazole treatment provides evidence of beneficial effect at both levels. It is disappointing that, given the potentially large and varied population available that so little data could be obtained. The results are also complicated by the inclusion of a relatively high proportion of non parenchymal cystic disease which is known to respond less well to albendazole and is virtually unresponsive to praziquantel. These data provide a useful addition to the published material and represent a probably typical US population of cysticercosis patients.

**Table 1** **State of origin of Patients**

| | |
|---|---|
| New York | 12 |
| California | 7 |
| Texas | 6 |
| Maine | 6 |
| Colorado | 4 |
| Illinois | 4 |
| Connecticut | 2 |
| Idaho | 2 |
| Rhode Island, Montana, Nevada, Virginia, Hawaii, Georgia, Pennsylvania, New Jersey | 1 |

**Table 2** **Sites of Cysticercosis Lesions**

| Site | Number of Patients* Affected |
|---|---|
| Cerebral Parenchyma | 21 |
| Intraventricular | 11 |
| Subarachnoid/Racemose | 5 |
| Spinal | 4 |
| Cerebellar | 3 |
| CNS Site not specified | 9 |
| Extraneurological | 2 |

* Some patients had 2 sites involved.

**Table 3** **Resolution of Presenting Clinical Symptoms**

| Total Symptoms | Symptom | Cleared | Improved | N/C | No Data |
|---|---|---|---|---|---|
| 22 | Headache | 13 | 9 | – | – |
| 24 | Seizure | 15 | 6 | 1 | 2 |
| 5 | Diplopia/Optic Nerve | 2 | 2 | – | 1 |
| 6 | Confusion/Distrurbed Sensorium | 4 | 2 | – | – |
| 7 | Peripheral Nervous System | 2 | 5 | – | – |
| 9 | CNS symptoms various | 7 | 2 | – | – |
| 4 | Dizziness/vertigo | 3 | 1 | – | – |
| 2 | Nausea/vomiting | 1 | 1 | – | – |
| | **Resolution** | 47 (59.5%) | 28 (35.4%) | 1 (1.3%) | 3 |

**Table 4** **Adverse Experiences**

| Patient # | Event | Duration | Severity | Action |
|---|---|---|---|---|
| | Itching | 3 days | Mild | None |
| | Headache, nausea vomiting | 1 day | Severe | Increase steroids; add hydroxyzine |
| | Hepatitis | -- | -- | Intercurrent illness |
| | Elevated WBC & SGPT | ~2 months | -- | Not stated |
| | Epigastric distress | Few days | Mild | None |
| | Fever/obtundation | -- | -- | Add steroids |
| | Headache | 1-2 days | Severe | Add steroids |
| | Urticaria/petechial rash | 5 days | Mild | Increase steroids + antihistamine |
| | Vomited | Once | Mild | None |
| | Glucose intolerance On steroids | -- | Mild | Stop steroids |
| | Nausea | First day | Mild | None |
| | Liver enzymes increase LDH 1302, AST 417, ALT 499 | -- | Severe | Discontinue |

b. Value of these data to application. These data are of marginal value to the overall application, at least in terms of evaluating the efficacy of albendazole in the treatmen. of NCC. Given that only 30% of the requesting physicians responded to the applicant's requests for clinical follow-up, it is impossible to discern whether the data obtained are representative of the US experience overall. Furthermore, as can be seen from table 2, only 21 of the 51 patients included in this compassionate use dataset had intraparenchymal NCC lesions which are the focus of this review. The precise CT appearance of these lesions (enhancing/nonenhancing, edematous/nonedematous) is not mentioned. These shortcomings are compounded by the wide variability in reported dosing regimens both in terms of total daily dose and duration of therapy.

Because of these shortcomings, these compassionate use data do not contribute greatly to the evaluation of efficacy of albendazole in the treatment of NCC. The efforts of the applicant to obtain follow-up information on these patients do, however, contribute to the safety dataset. In this regard, follow-up regarding the clinical tolerability of albendazole was obtained for 48 patients.

c. Medical Officer's review process. The completed data collection forms from the individual physicians are not included in the NDA submission; the data from these forms have been organized into tabular spreadsheets that are found on pages 21-33 of volume 1.116. These tables were reviewed and correlated with the text of the sponsor's document (included above). The great majority of the information contained in volume 1.116 (from page 35 to end of volume, page 252) is the curricula vitae of the 44 responding physician/investigators.

d. Findings. The applicant's findings from the analysis of these compassionate use data are found on pages 46-49, above. In general, the medical officer's review of these data found no inconsistencies. Therefore, the applicant's findings and conclusions are accepted.

In an attempt to tease out information on the compassionate use patients with intraparenchymal disease, the medical officer reviewed Appendix 3 (volume 1.116, page 23), "Demography and Disease Details" for the subset of patients with descriptions of lesions that could be considered intraparenchymal. A total of 21 patients were found to have lesions listed that could be construed as 'intraparenchymal'. Of these 21, 15 patients had treatment outcomes described in Appendix 5 (vol 1.116 page 28, "Details of Treatment Outcome") that are specifically based on CT or MRI results, as noted by the respondents. Of these 15, three patients (20%) were considered 'cured' by radiographic imaging, eleven (73%) were considered to have 'improved' following albendazole therapy, and one patient (7%) with intraparenchymal disease was noted to have no change in lesions by CT imaging. (No objective criteria were provided by which the respondents were to make such judgements.) These results can be compared to the overall radiographic response noted by the sponsor: 6/39 cured (15%); 23/39 improved (59%); and 10/39 no change or with new lesions (26%). These poorer overall radiographic outcomes are not surprising, given that patients with intraventricular, spinal, and racemose cysticercosis are included.

Clinical response to AL therapy in these 21 patients with parenchymal disease was also reviewed. Of the 21 patients, 17 were noted to have seizures at presentation. Following AL therapy, seizure activity was noted to have 'improved' in 6 and 'cleared' in 9 (no notation was made in the remaining 2 patient entries). Respondents were also questioned specifically regarding their patients' requirements for anticonvulsant therapy: seizure medications were able to be stopped in only 2, reduced in dosage in an additional 2, but 9 patients required the same dosage as pre-AL therapy (no notation was made in the remaining 4 patient entries). Thus, in general these patients may have suffered from fewer breakthrough seizures following AL therapy, but their physicians did not, for the most part, feel comfortable discontinuing anti-seizure medication altogether.

e. Conclusions. The efficacy results of these compassionate use data are of limited value. Since only 30% of the investigators responded to the applicant's written queries, the likelihood of recall bias is very strong. Furthermore, since the patients described by the respondents are quite heterogeneous in their clinical manifestations of NCC, it is impossible to reach any conclusions on the basis of the entire (albeit small) group of patients. Even if the subset of intraparenchymal patients is examined separately, since there is no description of the CT appearance of these lesions it is not possible to compare their outcome with that of a better-defined, more homogeneous group of intraparenchymal NCC patients as found in the literature references reviewed previously.

These data do provide additional safety information that will be considered separately in the integrated review of safety.

C Conclusions regarding NCC indication

In the opinion of the reviewing Medical Officer, the applicant has submitted adequate information in NDA 20-666 to warrant approval of the neurocysticercosis indication. The results of the Medical Officer meta-analysis of the pertinent literature constitute an adequate and well-controlled investigation; the Gilman study constitutes the second adequate and well-controlled investigation. The submitted compassionate use data are considered supportive.

The labeling for this indication will require specific wording to indicate that albendazole is indicated for the treatment of active parenchymal cysts only. Wording should be included to indicate that the use of albendazole in the treatment of intraventricular, arachnoidal, or racemose neurocysticercosis has not been studied in an adequate and well-controlled manner. The dosage should be 15 mg/kg/day given BID, to a maximum of 400 mg BID. The duration of therapy will need to be expressed as a range, since studies in the literature range from 3 to 30 days. The applicant proposes a range of 8 to 30 days.

See Final Medical Officer conclusions at the end of this clinical review for further discussion of this issue.

Please refer to the labeling review for a complete review of the requested and recommended product labeling.

ATTACHMENT 1

RESULTS OF FDA REVIEW OF SUBMITTED MATERIALS

CT SCANS FROM GILMAN STUDY

Medical officer comment: At the time of the 45 day fileability meeting, the applicant was informed that patient-level data for the Gilman study was felt by the division to be extremely important, since this was the sole clinical study submitted with the NDA. On 22 February 1996, the applicant submitted materials as Amendment #1 to NDA 20-666; these materials included photographic copies of the CT scans that were the raw data from the Gilman study.

In order to have these scans independently reviewed and interpreted, DAIDP sought the assistance of FDA radiologists within HFD-160, the Division of Medical Imaging and Radiopharmaceutical Drug Products.

The attached data sheets were completed by the reviewing radiologists in HFD-160 and returned to the medical officer on 23 May 1996. The tabulation and discussion of these results, dated 5 June 1996, is attached.

HFD-160 CONSULT REVIEW
June 5, 1996

NDA 20-666
ALBENDAZOLE
SMITH-KLINE BEECHAM

Original NDA
Subm date: 12/8/95
Subm recd: 12/11/95

**Indication:** Treatment of hydatid and neurocysticercosis.

**Background:** HFD-520 has requested a review of CT images pre and post treatment found in the NDA. The sponsor believes that the images assess the therapeutic efficacy of albendazole. Photographs of the images were provided for our review.

**Findings:** We have reviewed the photographs of the CT imaging and completed the accompanying Case Report Forms. Our findings describe the patient status based on a comparison of baseline to intermediate and final follow-up images. The results are noted in the table below.

| STATUS | GROUP A | GROUP B | TOTAL | (%) |
|---|---|---|---|---|
| UNCHANGED | 8 | 8 | 16 | (43.2%) |
| WORSE | 4 | 1 | 5 | (13.5%) |
| IMPROVED | 3 | 11 | 14 | (37.8%) |
| CURED | 2 | 0 | 2 | ( 5.5%) |
| TOTAL | 17 | 20 | 37 | (100%) |

**INDIVIDUAL PATIENT RESULTS**
**GROUP A**

| | | |
|---|---|---|
| UNCHANGED---1,4,7,9,10,14,17,21 | | 8 |
| WORSE-------8,11,13,20 | | 4 |
| IMPROVED----5,6,18 | | 3 |
| CURED-------2,3 | | 2 |
| | subtotal | 17 |

GROUP B

| | | |
|---|---|---|
| UNCHANGED--- | 16,26,27,29,30,32,35,41 | 8 |
| WORSE------- | 46 | 1 |
| IMPROVED---- | 25,31,36,37,38,39,40 43,44,45,49 | 11 |
| CURED------- | none | 0 |
| | subtotal | |
| | TOTAL | 37 |

A statistical analysis of the results has not been completed.

Hsien W. Ju, M.D.

Hsien W. Ju, MD
Medical Officer
HFD-160

6/5/96

James R. Cheever, DMD
Acting Deputy Director
HFD-160

cc: HFD-160/CONSULT FILE
HFD-160/JU
HFD-520/FOGARTY

# ATTACHMENT 2

## RESULTS OF DSI INSPECTION OF GILMAN STUDY

## LIMA, PERU

30 MAY 1996

THOMASM
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**Subject:** Albendazole - Peru inspection

Mary and Phil:

Between May 20 and 24, 1996, Ms. Tracy L. Ramseur (CSO, Atlanta- District) and I, performed an inspection of the study titled "Comparison of two dose regimens of albendazole in the treatment of Neurocysticercosis", conducted at Lima, Peru.

We observed that,

There were 58 subjects enrolled, and there was sufficient documentation upport that all study subjects existed.

2. The safety data was not evaluable in at least 37 subjects.

* Hospital Records were NOT available for twenty-five of fifty-eight subjects.

* Of the 15 subject records reviewed (included 3 subjects without hospital records), there was not even a single subject who had all laboratory data on CRFs supported by laboratory reports and/or records.

3. The efficacy data was not evaluable in at least 30 subjects.

* Eight subjects were excluded by the investigators due to protocol deviations or non-compliance.

* Hospital Records were NOT available for twenty- five of fifty-eight subjects.

* Records indicated that subject number was retreated with albendazole for 30 days at about 3 months after baseline, and then again retreated at the end of one-year after baseline.

During a discussion with Dr. Garcia, he also recalled that subjects required retreatment after 1 year, and subject required retreatment after 2 years.

* The CAT scan images for all 58 subjects were reviewed (when available), and it was observed that,

The entire original set of CAT scans (baseline, day 90 and day 360) were not available for four subjects, and baseline original CAT scans were not available for subjects
In both cases, only prints of the CAT scans were available and they were not very clear. Dr. Garcia explained that these subjects had their CAT scans performed at another hospital, and hence the originals could not be retained.

Follow-up CAT scans for subjects were performed only at 1.5 years. Follow-up CAT scans for subjects were performed at two years after baseline. Subject 16 was retreated with albendazole at the 1 year time- point. We do NOT have information about retreatment on the rest of the subjects.

4. There was no study medication accountability. Dr. Garcia explained that he used the unused study medications to either retreat study subjects or to treat additional patients who required Albendazole treatment.

5. The study randomization and blinding procedures are questionable.

* The randomization envelope was not returned to sponsor. Instead investigator (Dr. Garcia) reportedly opened them during data analyses and not retain them thereafter.

* Patients were not blocked for randomization and hence there were "runs" in the enrollment of study subjects.

* Dr. Garcia was also the neurologist who read the CAT scans and was NOT blinded to the sequence of a subject's CAT scans. He also retains a good memory of the study subjects and their clinical progress.

6. There was no documentation to support the consent of four subjects.

In Summary:

All safety data was not evaluable in study subjects. The efficacy data is evaluable for about 18 subjects (10 in group A and 8 in group B). However, the blinding and randomization procedures used in the study would remain questionable.

This list does not include other procedural deviations that were observed in the study. If you have any further questions or comments please call me. I am scheduled to leave for another inspection this Saturday.

Mathew.

# Albendazole in the treatment of hydatid disease

1. Introduction

The following discussion is taken from vol 1.107 pages 76-81 of NDA 20-666:

## 1.1 Hydatid Disease

### 1.1.2 Parasitology (Fig. 1 - overleaf)

Echinococcosis or hydatid disease in man is caused by two species of tapeworm: *E. granulosus* (cystic hydatid) and *E. multilocularis* (alveolar hydatid). The adult *E. granulosus* is an intestinal parasite principally in dogs, both domestic and feral, although other wild canines may also act as a reservoir. The normal intermediate hosts for the larval tapeworm include domestic sheep, cattle, goats and camels together with a number of species of wild ungulates (antelope, deer, etc.). A separate strain occurs in horses. Infection of the intermediate hosts is by ingestion of eggs contaminating the environment. Transmission to the primary host occurs in the wild from feeding on the carcasses of infected animals, while in a domestic situation infection usually occurs as a result of feeding offal to domestic animals. In some areas abattoirs are an important source of infection.

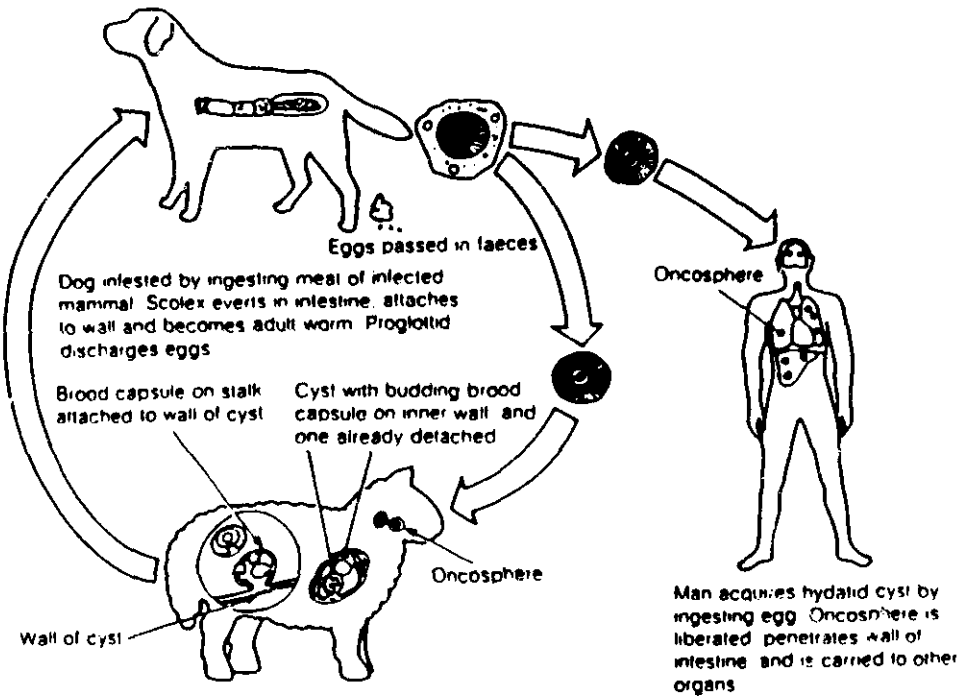
Man is generally considered an end-stage intermediate host, transmission to the primary host only occurring in a few primitive communities. Invariably, the strain affecting man in ungulate-adapted rather than horse-adapted.

The life cycle of *E. multilocularis* is similar *E. granulosus*, the primary host in this case being fox, wolf and wild dog, with the intermediate hosts being a variety of wild rodents. Because the life cycle is less domestic, infection of man is less common.

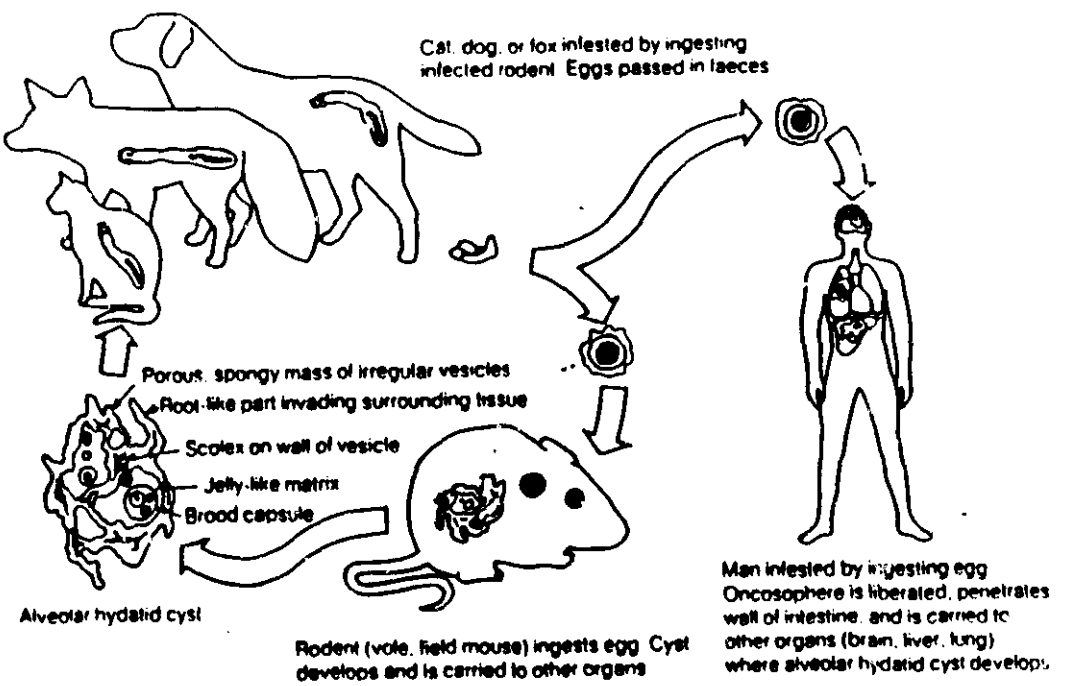
### 1.1.2 Epidemiology

*E. granulosus* is widespread geographically and is found extensively in countries where the domestic intermediate hosts are

*Echinococcus granulosus*




*Echinococcus multilocularis*



raised. Maximum prevalence is probably reached in Northern Kenya (the Turkana), Uruguay and Northwest China. High prevalence rates are also seen in South America (Southern Brazil, Argentina and Chile), the Mediterranean Basin and the Middle East. In Western Europe, infection in man is less common despite an extensive livestock industry. In the United States, the majority of cases of *E. granulosus* infection are acquired abroad, principally by immigrants from the Mediterranean basin. Possible small foci exist in the midwestern states.

*E. multilocularis* is confined to the Arctic regions of North America, over much of the Soviet Union extending south into Eastern Turkey and east to Japan. A focus centered on the European Alps has also been identified. Endemic *E. multilocularis* infection occurs in Alaska, and in animals into the northwestern states (Shantz et al, 1992). Numbers of cases of both infections occurring annually is small, and although figures cannot be obtained reliably, probably does not exceed 200-300 per year.

### 1.1.3 Clinical Features

Echinococcus granulosus infection in man is acquired by contact with infected dogs. Following ingestion of the eggs, these hatch in the intestine and the larvae penetrate through the gut wall and then migrate in the blood to settle principally in the liver or lungs. However, any organ may be involved, and cases of hydatid cysts in the bone, brain, heart, spleen, kidney and orbit are not uncommon. The initial invasive phase is probably asymptomatic. The disease becomes symptomatic when the larval cyst begin to enlarge, this occurring between 5 and 30 years after infection, although cysts may be symptomatic in the brain or spinal cord as early as 2 years after infection. The cysts grow slowly and behave as a slowly expanding tumor, most symptoms and signs being referable to cyst expansion and pressure on neighbouring structures. Occasionally, cysts may rupture with pyrexia, uticaria and a shock-like syndrome. If the cyst ruptures into an abdominal cavity, seeding of the larval protoscolices may occur giving rise to multiple further cysts. While *E. granulosus* infections are rarely fatal, surgical treatment can result in significant morbidity (see below).

*E. multilocularis* has a similar early clinical history. Initial lesions are present in the liver, but the cyst forms a multiloculated or alveolar cyst rather than the simple cyst seen with *E. granulosus*. *E. multilocularis* tends to grow more rapidly, is locally invasive, and

metastasizes to the lung and brain. With active disease, death may occur in 5-10 years.

### 1.1.4 Diagnosis

Cysts of *E. granulosus* are often asymptomatic unless they reach a large size of produce pressure on vital organs. They may be found clinically on routine examinations or may be chance findings at autopsy. When symptomatic, investigation may include X-ray, ultrasound or CAT imaging where a generally simple apparent fluid-filled cyst is identified, sometimes with enclosed daughter cysts. Aspiration is avoided because of the risk of seeding along the needle track or rupture of the cyst. A number of immunological tests are available which may assist in diagnosis. Differential diagnosis is from other cystic or solid lesions of the involved organ. Cysts of *E. multilocularis* are more diffuse and have to be differentiated from hepatoma in the liver. Immunodiagnosis is especially helpful in these cases, and biopsy may show a typical multilaminated cyst wall.

### 1.1.5 Treatment

#### 1.1.5.1 Surgery

To date, the mainstay of treatment has been surgical with removal of the whole cyst or destruction using silver nitrate, formalin or alcohol. Even under ideal conditions, operative mortality at first operation ranges from 0.9-3.6% (Amir Jahed et al 1975, Little 1976) with considerable additional morbidity. The problem however lies principally with recurrence. This may occur due to incomplete removal or destruction of the cyst, with recurrence at the original site, or due to seeding of small amounts of germinal epithelium or protoscolices locally with subsequent local recurrence in the same organ but at other sites. Despite considerable care, cyst rupture may also occur with widespread dissemination in the peritoneal or pleural cavities. It is estimated that up to 11.3% (Mottaghnian and Saidi 1978) or even 30% (Schiller 1966) or patients have recurrences within 5 years of first surgery. Further surgery carries a poor prognosis, with a mortality rate of 6% after second

Despite this, many patients undergo multiple surgery during their lives.

1.1.5.2 Chemotherapy

In view of the not inconsiderable risks of surgery, particularly in patients with extensive local or disseminated disease, or those who are unfit for surgery, some form of chemotherapy would be useful. Furthermore, chemotherapy could have a role in both the pre-treatment of patients prior to surgery to render cysts non-viable or to treat patients post-surgery to reduce the risk of recurrence following cyst removal or spillage of contents.

Effective chemotherapy has been lacking until recently. Studies have centered on one group of compounds, the benzimidazoles. These have been shown to have activity against a wide range of helminth species including cestodes (tapeworms). Thiabendazole, although well absorbed, is too toxic for the long-term therapy required for the treatment of systemic helminth infection such as hydatid. Flubendazole has shown conflicting results in studies (Lassegne et al 1984, Piens et al 1984) largely because there is little systemic absorption, and it is now accepted as of little use. More extensive studies have been conducted with mebendazole and although effective in some cases, treatment has often been at high dosage, up to 130mg/kg/day to 10g/day (Davis et al 1986) and for periods in excess of 3 years (Porat et al 1984). The absorption of mebendazole is poor, and blood levels (<10µg/mL) are inadequate to produce consistent effects in in vitro studies (Morris et al 1987). As a result of these high and prolonged dose levels, and despite poor absorption, severe side effects including major hepatic function disturbance and bone marrow depression are encountered fairly frequently (Bekhti and Pirotte 1987, Davis et al 1986). In addition, glomerulonephritis was reported in 8 of 133 cases treated in Kenya (Kung'u 1982).

There is, therefore, a need for a more consistently effective drug, with better absorption, which can be

2. Clinical disease factors which influence process of regulatory review

This parasitic infection has several features of its epidemiology, life cycle, and clinical manifestations which make it a difficult disease to subject to prospective, controlled investigations which are the norm for submission to the FDA. Such features include the following:

- this disease essentially is not endemic in USA, with the exception of a focus of *E. multilocularis* in Alaska,
- indolent presentation as space occupying lesion of liver, lungs, or abdomen; surgical management is the therapeutic modality of choice.
- clinical heterogeniety of disease due to factors such as
    1. Anatomic location of lesions
    2. Number of lesions
    3. Age of cysts (related to thickness of cyst wall)
    4. Presence of daughter cysts
    5. Previous surgical history
    6. Previous medical therapy
    7. Inherent responsiveness of organism to drug

- unacceptability of placebo-controlled study design given poor prognosis of untreated lesions due to the risks of cyst spillage, traumatic rupture of cysts, etc.
- need for long-term follow-up (at least three years, by most accounts) to ascertain response to therapy

Because of these various factors, the clinical trials which appear in the literature are not generally of a design which is usually encountered by DAIDP. Problematic features of the literature include the following:

- definition of case: compatible anatomic finding on imaging study (either Ultrasound or CT) along with serology of some sort (gold-standard serologic test is not available) in a patient from an appropriate epidemiologic group.
- demonstration of organism pre-therapy is practically never done except for cases of intraoperative spillage of cyst contents.
- studies are generally open-label, nonrandomized.
- heterogeniety of disease (as noted above) makes it difficult to ascertain precise contribution of drug therapy to disease outcome in clinical trials.
- usual study endpoint is soft, non-microbiologic (change in appearance of germinal membrane, reduction in size of cysts, or increased echogenicity of cysts); rarely is post-therapy demonstration of killed organism part of clinical trial.
- since a no-treatment control group is never incorporated into trial design, the contribution of underlying rate of spontaneous stabilization or resolution of hydatid cysts to the overall efficacy result is unknown.

Furthermore, the submitted 'controlled clinical trials' for this indication consists of a compilation of compassionate use experience from the UK, Australia, and the US. Such data are, by definition, the result of open-labeled and uncontrolled studies.

Despite these observations, a substantial literature has developed since the first observation that albendazole may be of benefit in the treatment of human hydatid disease (Morris DL, British Medical Journal 286: 103-4, 1983). It is important to remember that prior to the observation that mebendazole appeared to have some limited degree of efficacy, there was *no* medical therapy for hydatid disease. The only treatment available was surgery. No therapy of any recognized efficacy whatsoever could be offered to patients who had inoperable disease (due to either an inoperable anatomic location, recurrent hydatid disease post-surgery, or debilitated general condition of the patient). Such patients usually succumbed to complications of their hydatid disease.

There are several tests utilized in the literature to ascertain the viability of hydatid cyst contents. (The issue of viability determination will be an important parameter in the Medical Officer review of the applicant's submitted literature.) A brief discussion of these techniques may be helpful to the reader:

When cyst material is obtained, either *in toto* or as the result of *in situ* aspiration of cyst contents, the following measures of parasite viability appear to be commonly employed.

1. Eosin exclusion. When cyst fluid containing 'hydatid sand' is obtained, the sediment (containing booklets, parasite debris, and intact protoscolices) is placed on a microscope slide and wet prep is made. Eosin stain is added to the wet prep, and the protoscolices are observed by direct microscopy. The ability of the protoscolices to resist eosin infiltration is taken to be evidence of an active excretory mechanism, and this ability to exclude eosin is used as an indicator of parasite viability.

2 Flame cell activity. Rather than add eosin to the wet prep of cyst fluid, as described above, the microscopist carefully examines all protoscolices on the slide for the presence of flame cell activity. The flame cell is a primitive excretory organ found in a variety of helminths; it is easily discerned by light microscopy by the presence of an active, flagellated cell. The continued flickering activity of this flagellated cell is taken as a measure of parasite viability.

3. Animal innoculation. Sediment from surgically-obtained cyst fluid and/or membranes is injected intraperitoneally into laboratory animals. Among the animals used are rats, mice, gerbils, and (for *E. multilocularis)* voles. The standard incubation period before necropsy is performed appears to be 6 months. At the time of necropsy, presence of any intraperitoneal cysts is taken as evidence of parasite viability.

4 Germinal membrane appearence by microscopy. When cyst wall material is obtained at the time of surgery, portions are examined by routine H&E and/or electron microscopy. The presence of vacuolization and other signs of membrane disruption is taken as indirect evidence of parasite non-viability.

As will be seen below, viability data of any sort was an infrequent component of published clinical studies of hydatid disease. Therefore, all such data were felt to be of value. The medical officer was not able to find any information that would indicate the relative diagnostic sensitivity, specificity, and positive predictive value of any of the four techniques mentioned above. When available, the animal innoculation technique was taken as the 'gold standard' demonstration of viability.

B. Information submitted in support of indication

1. Supporting literature

a. Description of submitted literature. Volumes 1.108 and 1.109 of NDA 20-666 are a presentation of compiled literature on the medical therapy of hydatid disease. A total of 131 references are included in these 2 volumes, arranged alphabetically by first author. Included in this literature are case reports, abstracts, letters to the editor, and untranslated articles from non-English journals.

b. Applicant's review process and findings. The clinical data presented in these various publications has been tabulated and included in the sponsor's integrated summary of effectiveness. No attempt was made to distinguish between individual case reports, small case series, larger trials (be they prospective or retrospective), or abstracts from scientific meetings. The sponsor admits (vol 1.118, page 008) "As a result of this approach it must be recognised that each of the clinical efficacy and safety sections... may overlap to some extent.... Is is impossible to separate out material which is unique from that which overlaps. It should also be considered that within the publication reports there are instances of repetitive publication of gradually increasing numbers of patients."

The sponsor then proceeds to tabulate the patients reported in these various references. The resulting numbers are included in the various tables generated in the Integrated Summary of Efficacy (ISE). In this way, the tabulated publication data appears as a 'study' alongside the other data sets which appear in the integrated tables (i.e., European MAA, Australian compassionate use, and US compassionate use).

Because different literature references may include variable amounts of patient-specific information, the numbers of patients ascribed to 'Publication' varies widely from table to table in the sponsor's analysis. For example, Table 2 of the ISE (vol 1.118 page 009) "Demographic Details", lists 618 male and 667 female patients (total 1285) under 'Publication data'. Table 4 of the same document (page 13) "Global Response to Treatment", lists 1116 patients as the number evaluable from the 'Publication' dataset

The information extracted from these literature references is incorporated by the sponsor into the various tables generated in the ISE. The reader is referred to Attachment 1 for the sponsor's complete ISE.

*Medical officer comment: The heterogeniety of the literature makes it very difficult to combine studies with any degree of rigor. As outlined in the introductory comments above, there are multiple factors (both study design and disease/patient issues) which would appear to preclude any such attempt at metaanalysis. The sponsor acknowledges this. The information gathered by such a gross overview is nonetheless of value, and the sponsor has done a commendable job of compilating these references into a format that allows comparison with the compassionate-use datasets*

c. Medical officer's review process and findings. As was done with the literature references submitted in support of the neurocysticercosis indication, the MO began by carefully reviewing the submitted literature and extracting the individual articles which appeared to have particular merit. A list of these studies was forwarded to the statistical reviewer for review and, if appropriate, meta analysis. The list of these studies is found on the following page.

As opposed to the neurocysticercosis (NCC) indication, hydatid disease allows for the study of a firm microbiologic endpoint--death of the parasite following drug therapy. In compiling the literature data for NCC, the accepted endpoint was eradication of parenchymal brain lesions by serial CT scanning. Because of the location of the parasite, no microbiologic data were required for this analysis. The improvement on CT was accepted as a surrogate for clinical improvement, with one cumulative long-term follow-up study demonstrating the link between anticysticercal therapy, eradication of NCC lesions, and improvement or cure of seizure disorder.

Hydatid cysts are more accessible to aspiration/biopsy than are NCC lesions. Such a procedure is not without risk, however: percutaneous aspiration of a tense hydatid cyst places the patient at significant risk of intraperitoneal or intrathoracic spillage of viable protoscolices. Therefore, *most* published studies of this disease do not require such a procedure for enrollment and intervention (be it initiation of drug therapy, surgery, or whatever). Nonetheless, information on cyst viability provides an objective microbiologic endpoint that would seem reasonable to combine across studies.

## Important Hydatid references extracted from literature submitted with NDA 20-666

NB. numbers listed are reference numbers assigned by sponsor, as per table of contents to volumes 1.108 and 1.109 of NDA 20-666.

| # | Author | design | comments/reason for inclusion |
|---|---|---|---|
| 5 | Brough et al | 2 cases | PK including intracyst levels, correllation with viability of scoleces |
| 9 | Davis et al | prospective | multicenter WHO study includes 121 pts (30 AL) |
| 10 | --"-- | --"-- | f/u of #9 (paper not included in NDA, but reference is cited in NDA table of contents) |
| 19 | Gil-Grande et al | prospective | randomized controlled study with viability data |
| 19a | Giorgio et al | open study | description of PAIR* technique; provides evidence that one week of pre-aspiration AL is insufficient |
| 20e | Horton | open study | collection of SK/B compassionate experience Includes viability data (N = 47) |
| 21 | Issacs et al | retrospective | review of hydatid experience in New Zealand (N=74); gives overview of long-term outcome of surgical vs medical management |
| 22b | Khuroo et al | prospective | randomized, controlled study has AL only arm (along with AL + PAIR, PAIR alone) |
| 31 | Morris et al | open study | N = 16 given preop AL; viability checked on all 16 |
| 31c | Nahmais et al | open study | N = 68; all have at least 3 years f/u |
| 42c | Teggi et al | open study | N = 337 (AL = 216); viability in 35 cysts (12 AL) |
| 42g | Todorov et al | open study | comparative: Mebendazole N = 30; AL N = 25; |
| 43 | Todorov | open study | comparative; cumulative; AL = 35 |
| 45a | Wen et al | open study | N = 178; viability data in 21 pts with 34 cysts |
| 45b | Wen et al | open study | PK study N = 19; correllates intracystic AL-SO# levels with viability data |
| 46a | Wilson | retrospective | review of 17-year experience with AE§ in Alaska Viability documented in 9 patients on 12 occasions |

footnotes:

* Puncture-Aspiration-Instillation-Reaspiration

# Albendazole sulphoxide

§ AE = alveolar echinococcosis

Since the sponsor had already performed a global assessment of the hydatid literature, the primary focus of the MO analysis was to collect and pool information on cyst viability in patients treated with albendazole.

The following list includes references that were found to provide such information:

## Viability data abstracted from submitted literature

| Reference | dose | duration | method of determination | N(%) pts with non-viable protoscolices | Comments |
|---|---|---|---|---|---|
| Aggarwal Thorax 1991 | 10 mg/ kg/day | 8 weeks | Histopathology of germinal membrane | 0/7 (0%) | Not SK/B product<br>Pts had to purchase own drug<br>Worthless study |
| Brough Aust NZ J Med 1989 | 10 mg/ kg/day | 4 weeks | Flame cell activity<br>Evagination post-digestion<br>Histopath of germ. membrane | 1 / 2 (50%) | – |
| Dellamonica & LeFichoux Path Biol 1986 | 10 mg/ kg/day | 60 days | Mouse innoculation | 1 / 2 (50%) | – |
| Gil-Grande Lancet 1993 | 10 mg/ kg/day | 30 days (n=18)<br>90 days (n=19) | Flame cell activity<br>Mouse innoculation<br>Histopath of germ. membrane | SEE SEPARATE TABLE | excellent study |
| Giorgio J Echo Med Ultrason 1993 | 800 mg/ day | 7 days | Flame cell activity | 0/13 (0%) | – |
| Horton TRSTMH 1989 | 400 mg bid | ≤ 30 days (n=13)<br>> 30 but ≤ 90 (n=34) | Flame cell activity<br>± mouse or gerbil innoculation | SEE TEXT | – |
| Morris Brit J Surg 1987 | 10 mg/ kg/day | 1 week (n=1)<br>3 week (n=1)<br>4 week (n=5)<br>8 week (n=5)<br>12 week (n=4) | Flame cell activity<br>Gerbil innoculation | SEE SEPARATE TABLE | – |
| Rahentulla J Roy Soc Med 1987 | 400 mg bid | 4 weeks (n=1) | Flame cell activity<br>Evagination post-digestion<br>Gerbil innoculation | 1/1 (100%) | – |
| Redzic Arch Gastroentero-hepatology 1993 | 400 mg bid | ?? | Flame cell<br>Rat innoculation<br>Histopath of germ. membrane | 19/25 (76%) | Abstract in English<br>Paper in Slovak |
| Richards & Morris 1990 | 10 mg/ kg/day | 4 weeks (n=2)<br>60 days (n=1)<br>90 days (n=2) | Eosin exclusion<br>Gerbil innoculation | 4 week: ½ (50%)<br>60 d: 1/1 (100%)<br>90 d: ½ (50%) | Decreased efficacy when daughter cysts present. |

## Viability data abstracted from submitted literature (con't)

| Reference | dose | duration | method of determination | N(%) pts with non-viable protoscolices | Comments |
|---|---|---|---|---|---|
| Szpyrt et al J Bone Joint Surg 1987 | 10 mg/ kg/day | 60 days (n=2) | Gerbil innoculation | 2/2 (100%) | Bone hydatid |
| Teggi et al AAC 1993 | 10-12 mg/kg/day | 90 days (n=8) | Neutral red | 4/8 (50%) | – |
| Wen et al TRSTMH 1994 | 15-20 m/k/d | 30 days (10 off) for 3 cycles<br>No Rx controls (n=7) | Eosin uptake<br>Mouse innoculation | 12/13 (94%)<br>0/7 controls | Higher dose<br>(1200 mg/d max) |
| Wilcox & Morris J Roy Soc Med 1988 | 10 mg/ kg/day | 3 weeks (n=2)<br>≥ 30 days (n=4) | Flame cell activity<br>Eosin exclusion<br>Gerbil innoculation | 0/2 at 3 weeks<br>4/4 at ≥ 30 days | – |
| Wilson et al J Am Soc Trop Med Hyg 1987 | 400 mg bid | 28 days (14 o..)<br>for 1 cycle (n=1)<br>for 2 cycles (n=1)<br>for 3 cycles (n=1)<br>for 9 cycles (n=1) | Vole innoculation | 0/1 after 1 cycle<br>1/1 after 2 cycles<br>0/1 after 3 cycles<br>0/1 after 9 cycles | *E. multilocularis* |
| U.S. Compassionate Use data | | variable | ?? | 5/12 | As per sponsor |

The cyst viability results from three studies listed above warrant closer scrutiny:

Firstly, the study by Gil-Grande et al (Lancet 1993; 342: 1269-72) is the only prospective, randomized, controlled study that appears in the literature. For this reason, this study is considered to be very important to this portion of the NDA. In this study (conducted in Spain), adult patients were enrolled who had liver or abdominal hydatid cysts by imaging study, along with a positive serology. Eligible patients were randomized to one of three arms: albendazole (10 mg/ kg/day given BID) followed by surgery after 30 days (Group A); albendazole 10 mg/kg/day given BID followed by surgery after 90 days (Group B); or surgical treatment only (Group C). At the time of surgery, cysts were removed and manipulated under a laminar flow hood. All cysts were assessed for viability using flame cell activity (present/absent), eosin exclusion (present/absent) and intraperitoneal mouse innoculation with necropsy after 6 months of incubation. Also, cyst membrane ultrastructure was assessed by transmission electron microscopy. Cysts were considered non-viable if the protoscolices were non-viable, if there were no protoscolices in hydatid fluid, or if there was lack of hydatid fluid owing to cyst solidification.

The results of these parasite viability studies in this study are shown below, as described in Table 3 of the original paper:

## Parasite pathology results from Gil-Grande et al (Lancet 1993)

| | Group A (N=18) | Group B (N=19) | Group C (N=18) | p* |
|---|---|---|---|---|
| Viability of protoscolices | | | | |
| Present† | 7 | 5 | 12 | |
| Absent | 9 | 6 | 2 | 0.041‡ |
| None found in fluid | 2 | 8 | 4 | |
| Intraperitoneal innoculation in mice | | | | |
| Cysts developed | 5 | 1 | 8 | |
| No cysts developed | 7 | 5 | 4 | 0.167 |
| No protoscolices | 6 | 11 | 4 | |
| Mice died prematurely | 0 | 2 | 2 | |
| Total membrane disruption on EM§ | | | | |
| Present | 14 | 16 | 6 | 0.00006 |
| Absent | 2 | 1 | 12 | |

* Fisher's exact test, two-tailed

† Minimum viability (< 0.1%) in 2 cases from Group A and 3 from Group B

‡ Present/Absent plus no protoscolices, p=0.046

§ Not done for 2 patients from Group A and 2 from Group B.

*Medical officer comment: As mentioned above, this study is the only prospective, randomized study which examines parasite viability following a course of albendazole therapy. As such, this study provides objective evidence which supports the use of albendazole for the sterilization of hydatid cysts. There appears to be a dose-response here as well; although not statistically significant, there were more cysts in the 90-day group (Group B) than the 30-day group (Group A) that had non-viable or absent protoscolices, negative mouse innoculations studies, and total membrane disruption on EM. Unfortunately, no comment was made in this paper on the presence or absence of daughter cysts in the enrolled patients. Other studies have found that hydatids with multiple daughter cysts are more difficult to render non-viable with albendazole treatment.*

The next submitted paper worthy of comment is the study by Horton (Transactions of the Royal Society of Tropical Medicine and Hygiene 1989; 83(1): 97-102), found on pages 333-338 of Volume 1.109 of the NDA. This paper represents a compilation of the compassionate use experience with albendazole for the therapy of hydatid disease, as collected by the sponsor during the years 1983-1993. As such, these data are identical to those included in a separate part of this NDA submission, entitled "Compassionate use Experience in the United Kingdom", found in volume 1.110 of this NDA.

Table 3 of this paper is entitled "Details of treated cases of *E. granulosus* hydatid disease". This table reports the cyst viability information which was available from the total of 253 patients for whom follow-up information was obtained (out of over 500 patients for whom drug was distributed). Because these cases were treated by a variety of clinicians in a variety of healthcare settings, the uniformity and reliability of the viability data is of question. Nontheless, data are presented for the 47 cases in which viability studies were reported. All viability determinations were made on the basis of flame cell activity, eosin exclusion, and/or gerbil or rat innoculation. Patients had been treated with from one to three months of albendazole pre-surgery, at a dose of 400 mg BID. Overall viability of cysts was reported to be 5/47, or 10.6%. Of note, in patients treated for ≤ 1 month pre-surgery, the viability rate was 5/13 (38%); of those patients for whom such data were reported, those receiving greater than one month of albendazole at a dose of 400 mg BID were found to have viable cysts in 0/34 cases

*Medical officer comment. one must be cautious when interpreting such compassionate use data. Nonetheless, these data are consistent with other, better-designed studies such as the Gil-Grande study reviewed above.*

The third study of note was published by D.L. Morris, one of the first investigators to describe a possible theraputic role for albendazole in the treatment of this parasitic disease. This study (British Journal of Surgery 1987; 74(9): 805-6) is a report of 16 patients who had been treated pre-operatively for hydatid disease. Most of these 16 patients had hepatic cysts (12); the remainder had bone, peritoneal, or cerebral cysts. Patients were dosed with 10 mg/kg/day for variable amounts of time. Material obtained at the time of surgery was handled in a uniform manner to assess viability: flame cell activity and eosin exclusion was assessed by light microscopy, then material was innoculated intraperitoneally into gerbils. Table 1 of this paper (found on page 34 volume 1.109 of the NDA) provides the results of these studies (NB: the order of the patients has been re-arranged, in ascending order of duration of albendazole therapy):

## Details of the 16 patients studied (Morris, Brit J Surg 74(9): 805-6, 1987)

| Patient #/Sex | Site of cyst¤ | Diameter (cm) | Albendazole therapy (Weeks) | Viability | | F/U (mo) |
|---|---|---|---|---|---|---|
| | | | | Microscopy (Flame cell) | Gerbil Innoculation | |
| /Male | cerebral | 8 | 1 | + | + | 9 |
| /Male | hepatic/DC | 15 | 3 | + | - | 11 |
| /Male | hepatic/DC | 15 | 4 | - | - | 8 |
| Female | hepatic/DC | 20 | 4 | + | ND | 34 |
| Female | hepatic | 20 | 4 | - | ND | 34 |
| /Female | hepatic/DC | 15 | 4 | - | - | 15 |
| /Female | bone retroperitoneum | 10 | 4 | - | - | 18 |
| /Male | hepatic/DC | 15 | 8 | - | - | 21 |
| /Female | hepatic | 10 | 8 | - | - | 12 |
| /Male | abd. wall | 5 | 8 | - | - | 29 |
| /Male | hepatic/DC | 10 | 8 | - | - | 5 |
| /Female | hepatic/DC | 15 | 8 | - | - | 2 |
| Female | pelvic/DC | 10 | 12 | - | - | 15 |
| /Female | hepatic/DC | 25 | 12 | - | - | 24 |
| Female | hepatic/DC | 25 | 12 | - | - | 21 |
| /Male | hepatic + bone/DC | 10 | 12 | - | - | 14 |

¤ DC = daughter cysts present

*Medical Officer comment: there are several different techniques for ascertaining viability of protoscolices. The fact that practically every study utilizes more than one technique would seem to indicate that there is no one, widely-accepted 'gold standard' for making such a determination. Nonetheless, for the purposes of this review, I will consider these assays in the following hierarchial manner (beginning with what is assumed to be the most sensitive): 1) laboratory animal inoculation of either gerbil OR rodent [vole innoculation is appropriate for* E. multilocularis *only]; 2) evagination of protoscolices following* in vitro *digestion; 3) presence of flame cell activity; 4) eosin exclusion ability; and 5) histopathology of germinal membrane. Given the paucity of viability data that has been extracted and synthesized above, for the purposes of further discussion I will combine all these datapoints.*

These viability data can be combined to examine the dose-response relationship between duration of albendazole dosing and overall success in rendering cysts non-viable. In order to do so, the data from the above studies and tables will be assembled according to duration of albendazole dosing. (NB: With the exception of one study [Wen, TRSTMH 1994], all included studies used a dose of 10 mg/kg/day, which for most adults translates into 800 mg/day. Some studies did not mention whether this was administered as a BID dose of 400 mg or a single 800 mg dose. Despite this, these studies will be combined.)

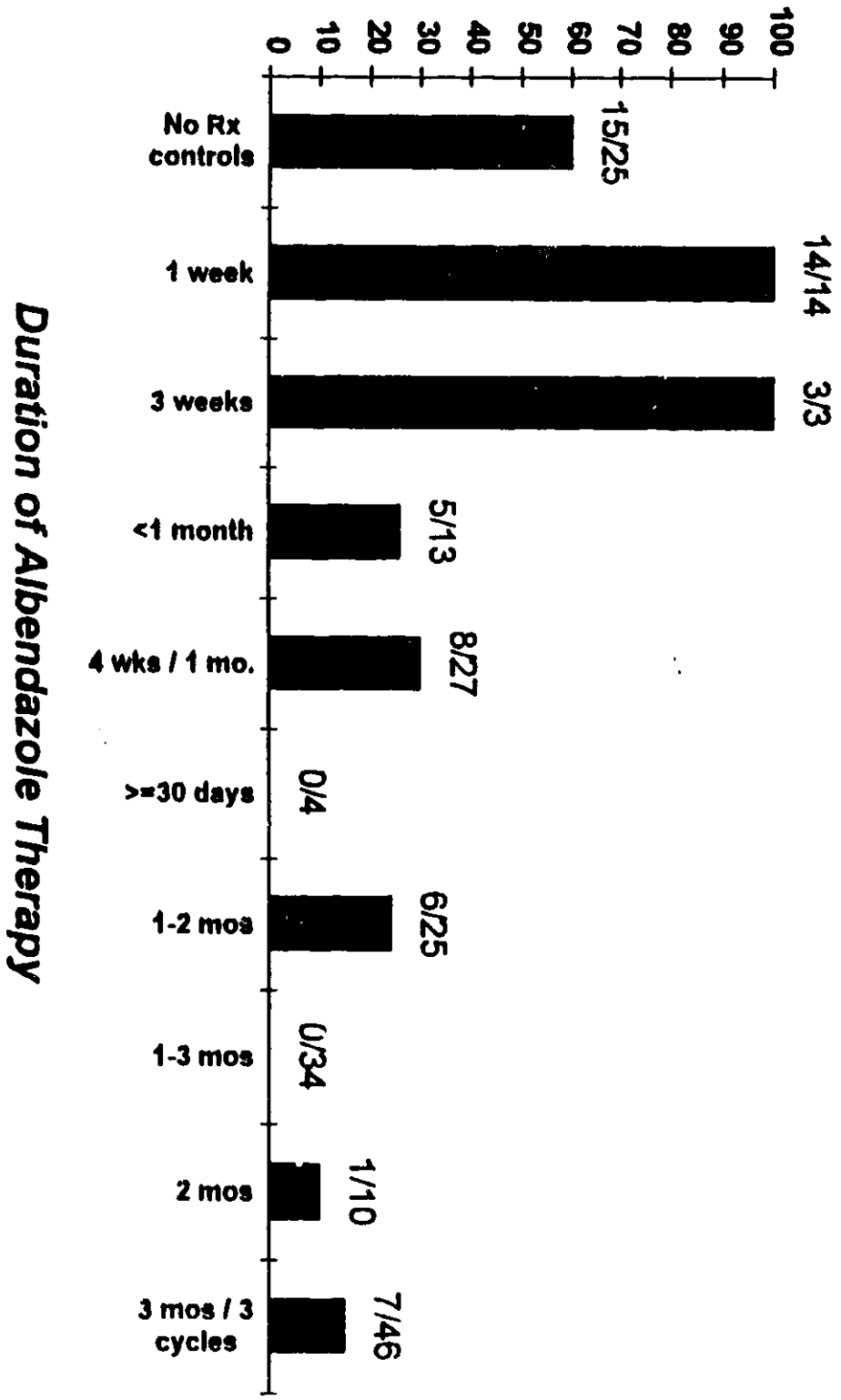
## Composite viability data by duration of albendazole exposure

| Duration of treatment with albendazole | Study | # patients with viable cysts/total group (All definitions) |
|---|---|---|
| NO treatment controls | Wen 1994 | 7/7 |
| | Gil-Grande 1993 | 8/18* |
| 1 week | Giorgio 1993 | 13/13 |
| | Morris 1987 | 1/1 |
| 3 weeks | Morris 1987 | 1/1 |
| | Wilcox & Morris 1988 | 2/2 |
| < 1 month | Horton 1989 | 5/13 |
| 4 weeks/1 month | Brough 1989 | 1/2 |
| | Gil-Grande 1993 | 5/18* |
| | Morris 1987 | 1/5 |
| | Rahentulla 1987 | 0/1 |
| | Richards & Morris 1990 | 1/2 |
| ≥ 30 days | Wilcox & Morris 1988 | 0/4 |
| > 1 month, ≤ 2 months | Redzic 1993 | 6/25 |
| > 1 month, ≤ 3 months | Horton 1989 | 0/34 |
| 8 weeks/2 months | Aggarwal 1991 | 7/7① |
| | Dellamonica & LeFichoux 1986 | 1/2 |
| | Morris 1987 | 0/5 |
| | Richards & Morris 1990 | 0/1 |
| | Szpyrt 1987 | 0/2 |
| 3 months/92 days | Gil-Grande 1993 | 1/19* |
| | Morris 1987 | 0/4 |
| | Richards & Morris 1990 | 1/2 |
| | Teggi 1993 | 4/8 |
| 3 cycles (28/14 X 3) | Wen 1994 | 1/13② |

footnotes: ★ viability by mouse inoculation/total N in group
① by histopathology only; non-SK/B product used, poor study design; excluded from histogram
② used 15-20 mg/kg/day to maximum dose of 1200 mg/day

The above data are presented in graphic format on the following page:

# Cyst Viability by Duration of Albendazole Exposure (metanalysis from literature)



d. Conclusions

i. Sponsor's conclusions. The sponsor has concluded that the literature supports the use of albendazole in the treatment of hydatid disease due to both *Echinococcus granulosus* and *E. multilocularis*. In the proposed labeling (under the DOSAGE AND ADMINISTRATION section) the sponsor seeks language specifically referring to hydatid of the bone and brain. The sponsor further proposes that the labeling allow for pre-surgery, post-surgery, and medical (non-surgical) indications. The proposed dose and duration is 400 mg BID for 3 28-day cycles, each separated by a 14 day period off therapy.

ii. MO conclusions. After review of the submitted literature and the sponsor's global compilation, the medical officer agrees with the sponsor's conclusions regarding cystic hydatid disease of the liver, lung, and peritoneum. This agreement is based on the medical officer's viability assessment as well as the sponsor's synthesis of the literature. The appropriate duration of therapy for sterilization of hydatid cysts should be 3 cycles of 28 days, each separated by a 14-day drug-free interval. The preponderance of the submitted literature utilizes this regimen; furthermore, the viability assessment indicates that this regimen appears to kill somewhere in the vicinity of 80% to 90% of hydatid cysts.

Data regarding the efficacy of albendazole in the therapy of hydatid disease of the brain and bone is insufficient to warrant specific language of this nature in the product labeling. What literature exists would suggest that more prolonged courses of therapy are indicated.

The medical officer further concludes that the literature does not contain an adequate number of studies demonstrating the safety and efficacy of albendazole in the treatment of alveolar hydatid disease due to infection with *Echinococcus multilocularis*. There is only one study which appears in the English language literature (Wilson et al, Clin Infec Dis 15: 234-49, 1992) which includes viability information; this article contains viability data on 9 patients.

2. Compassionate use data: United Kingdom

a. Description of collection process and shortcomings of resultant data. The manner in which these data were collected has been described in the previous review of the neurocysticercosis indication. Basically, the sponsor (in the UK) was the sole source for distribution of albendazole from 1982 to 1987. Although the accumulated data for this indication is more substantial than the compassionate use data for cysticercosis, it nonetheless remains just that: compassionate use data. As such, it has been passively collected from clinicians who chose to provide some degree of post-drug distribution follow-up: therefore these data are subject to recall bias (i.e., the clinicians who witnessed a particularly spectacular clinical response, or whose patients may have had a particularly noteworthy toxicity, were more motivated to respond to the sponsor's requests for clinical follow-up). Furthermore, some degree of repitition exists between these data and the published literature reviewed above. (In fact, these UK compassionate use data comprise the essence of the 1989 Transactions of the Royal Society paper by Horton, referenced in the viability discussion above.)

b. Value of these data to application. Despite the limitations noted above, the compassionate use/UK dataset represents 314 patients. The sponsor has provided line listings on each of these patients, as compiled from the questionnaires completed and returned by the requesting physicians. This set of data not only includes *E. granulosus* patients from the UK; it also contains patients enrolled from Italy, France, Greece, Yugoslavia, Switzerland, Sweden, Germany, Kenya, Chile, South Africa, Dubai, and the USA. Also included in this UK data are *E. multilocularis* patients from France, UK, and Alaska.

c. Review process. The medical officer reviewed the submitted information (volume 1.110 of NDA 20-666) in its entirety. This information included the sponsor's summary (see Attachment 2), the protocols under which albendazole was distributed and clinical information was gathered, line listings compiled from investigator responses, and references (from the protocol bibliographies).

After the initial filing of NDA 20-666, the sponsor was requested to provide case record forms from which these line listings were generated. These were provided under separate cover (volumes 3.1-3.22, submitted 22 February 1996). Volumes 3.2-3.5 contain the CRFs for the compassionate use UK dataset. A random check of 20 CRFs was performed to verify the information contained in the line listings.

d. Findings

i. Sponsor. The results of the sponsor's analysis of these data are included in Attachment 2, which is the summation of the data as presented in volume 1.110, pages 5-21 of the NDA.

ii. Medical officer. The medical officer audited 20 CRFs to cross-check the validity of the line listings (also referred to as CRTs or Case Record Tabulations) from which the sponsor's findings are based. The CRFs and their location in the NDA submission are as follows:

| Number | CRF # | Country | Volume/ page number | CRT location (vol 1.110/page#) |
|---|---|---|---|---|
| | | UK | 3.2/00008 | 105 |
| | | UK | 3.3/00125 | 109 |
| | | UK | 3.4/00128 | 113 |
| | | UK | 3.5/00160 | 117 |
| | | Italy | 3.6/00086 | 120 |
| | | Italy | 3.8/00179 | 126 |
| | | Italy | 3.10/00318 | 130 |
| | | Italy | 3.12/00002 | 134 |
| | | France | 3.13/00213 | 138 |
| | | France | 3.14/00002 | 140 |
| | | France | 3.14/00208 | 142 |
| | | Greece | 3.15/00094 | 145 |
| | | Greece | 3.15/00257 | 148 |
| | | Kenya | 3.17/00002 | 153 |
| | | Kenya | 3.17/00149 | 155 |
| | | Dubai | 3.18/00043 | 158 |
| | | USA | 3.18/00105 | 159 |
| | | USA | 3.18/00139 | 159 |
| | | France | 3.19/00107 | 161 |
| | | USA | 3.20/00212 | --- |

This audit served to verify the reliability of the data as organized by the sponsor in the CRTs in volume 1.110. Some of the photocopied CRF pages were difficult to read, making cross-checking somewhat challenging. The only error detected was a miscalculation of the duration of therapy given to patient the sponsor had listed that 8 weeks of therapy had been administered, whereas the CRF stated 40 days. With that single exception, the tabulated data was found to be an accurate representation of the patient-level data as recorded in the CRFs.

e. Conclusions

i. Sponsor. The sponsor concludes the following (volume 1.110, page 018): "The efficacy data presented provide a rationale for the treatment of inoperable cases of hydatid disease with albendazole. Although cyst response is variable, and not all patients are successfully treated a substantial proportion show evidence of response....

"The use of albendazole presurgically may be beneficial in providing a potentially nonviable cyst, and thus reduce the risk of recurrence."

ii. Medical officer. The data submitted by the sponsor, in its entirety, supports the efficacy of albendazole in the treatment of hydatid disease due to *Echinococcus granulosus*. The combined viability data indicate that three cycles of therapy (one cycle consisting of 28 days of albendazole/14 days off drug) should be sufficient to render protoscolices non-viable in approximately 90% of cases. The composite clinical data from the UK compassionate dataset, as presented by the sponsor, appears to demonstrate a lower rate of efficacy (for liver cysts, 33% cure and 44% improvement) than generally appears in the literature; this may be reflective of the fact that cysts may be rendered non-viable but continue to act as space-

occupying, symptom-producing mass lesions. Cyst response appears to be a function of thickness of cyst wall and presence of daughter cysts; therefore, individual patient and parasite characteristics appear to be important determinants of overall response.

In discussing the calculated rates of clinical and microbiologic efficacy for this disease, it is important to keep in mind that, to date, there is no FDA-approved chemotherapeutic agent for this progressive, debilitating, and sometimes fatal parasitic disease.

3. Compassionate use data: Austrailia

a. Description of collection process and shortcomings of resultant data. Until 1995, availability of albendazole in Austrailia was solely via the so-called "Special Access Scheme" or SAS. This program appears to be similar in nature to the FDA 's Emergency IND program, whereby clinicians are able to obtain albendazole for the individual treatment of a patient with an albendazole-responsive infection. The data collected as part of the SAS were collected and analyzed on an annual basis. Six such reports, covering the period from 1984 to the time of product licensing in 1995, are included in this portion of the NDA submission.

As has been noted for other compassionate use datasets evaluated in this NDA, the Austrailian compassionate use data also relies on the good graces of requesting clinicians to complete and submit clinical follow-up information. As the sponsor states (volume 1.111, page 0003): "The returns in this programme rarely exceed 50% of investigators supplied, and the data even then is often inadequate to evaluate efficacy. Since these reports are essentially 'annual' reviews, there is also an over run from report to report of patients whose treatment continues."

Unlike the UK and US compassionate use data, for which the sponsor was able to provide primary patient data (in the form of actual CRFs completed by the treating physician), similar documentation has not been provided for these Austrailian patients.

b. Value of these data to application. Despite these limitations, these data contribute substantially to the NDA submission. For one thing, there is very little overlap between these data and the submitted literature (in contrast to the UK compassionate use data). Furthermore, because of the large sheep ranching industry in Austrailia, echinococcosis is fairly prevalent there and a substantial number of cases has been accumulated in this SAS. The compilation and analysis of these cases appears to have been done in a more systematic manner than seen in either the UK or USA compassionate data. The safety data appear to have been collected and analysed in a systematic manner but are inherently flawed insofar as the reference ranges are variable (not having been submitted and analysed by a central reference laboratory as would be the case in a prospective, industry-conducted clinical trial).

c. Review process. The submitted materials from Austrailia are found in volumes 1.111 and 1.112 of the NDA. Included are the following documents, all prepared by DataPharm Austrailia: "Albendazole in the treatment of hydatid disease" dated 30 April 1990 and covering the period from July 1984 to February 1990; "Albendazole in the treatment of hydatid disease" dated 23 February 1991 and covering the calendar year 1990; and similarly-titled documents covering calendar years 1991 1992, and 1993-94. There is also a report covering the 1993-94 timeframe which details the SAS experience with albendazole for non-hydatid indications.

The review process involved critically reading these documents. Since none of these data were submitted in computer files for manipulation by the reviewer, no re-analysis was performed. (Given the incomplete nature of such compassionate use data, such secondary analysis was not possible.)

d. Findings

i. Sponsor. The sponsor's synopsis of the Austrailian compassionate use data is found in Attachment 3. This synopsis includes a total of 233 cases of cystic hydatid disease due to E. granulosus. Of these, only a small fraction of patients (81, or 35%) were considered to have enough follow-up information to be considered assessable. Of these 81 patients, a total of 68 (85%) had symptoms that had either improved or resolved following therapy; 4 patients had worsening of symptoms. In terms of cyst responses to therapy (using the standard WHO definition of ≥25% reduction in cyst size to be called 'improved'), these Austrailian data include 72 evaluable cysts, of which 10 (14%) were cured and 24 (33%) were improved. These data are somewhat lower than the accumulated UK compassionate use data, and lower than the response

rates seen in the published literature as well. Please refer to Tables 2 and 3 of the sponsor's synopsis, Attachment 3 pages 11-12.

ii. Medical officer. Each of the SAS reports listed above were reviewed. The data are sketchy at best. The sponsor has tabulated these results as well as can be done; these tables will not be reproduced here.

Particularly disappointing in this dataset was the fact that absolutely no viability data was extractable from the numerous charts, tables, and patient line listings included in these Australian reports.

e. Conclusions

i. Sponsor. The sponsor concludes (vol 1.111 page 010): "The evaluable data is limited and represented only a small proportion (probably about 10%) of all patients treated. Although the total population demography suggests that this is a 'typical' hydatid disese population, it is unclear whether the evaluable population is representative or biased.

"Overall clinical responses are encouraging, with symptom resolution in 58% of those evaluated, and improvement in 26%. However, in terms of cyst responses the results are not as encouraging with only 47% showing improvement or cure and 50% no change. This is a lower figure than reported in the European assessment or in many studies reported in section 3.2.2."

ii. Medical officer. The Australian compassionate use data present the same problems of interpretation that have been confronted with each of the previous such datasets discussed in this NDA review. The observed rates of clinical efficacy, both in terms of symptoms as well as cyst response, are consistent with those seen in other such datasets. Given the problems of such data collection ( low response rates, incomplete reportingof data and, loss of patients to follow-up), the margin of error in these calculated rates of clinical and parasitologic efficacy is very wide.

4 Compassionate use data: United States

a. Description of collection process and shortcomings of resultant data. This section of NDA 20-666 includes the albendazole distribution experience in the US which is conducted via issuance of single-investigator, emergency INDs. Because this program requires issuance of IND numbers, DAIDP has been a participant in this process.

For reasons that remain unclear, the sponsor has never filed for its own IND for the development and distribution of albendazole in the USA. In other countries worldwide, the sponsor maintained standing protocols (either alone, or in conjunction with the WHO) under which distribution of drug to requesting clinicians was conducted.

Up until 1987, this emergency IND program had released albendazole for approximately 50 patients. At that time, the sponsor attempted to capture some of these clinical data in preparation for a marketing application in Europe. Responses were received in only 7 cases.

The albendazole emergency IND program for the five years 1986 through 1990 was summarized in a meeting abstract which was prepared by Dr. Celia Maxwell and colleagues from the Division of Anti-Infective Drug Products, FDA. This was published by the International Society of Travel Medicine in Travel Medicine 2: Proceedings of the Second Conference on International Travel Medicine, Atlanta GA, May 9-12 1991. This publication is included in this portion of the NDA, and the data contained therein are incorporated into the resultant numbers. The authors were able to provide clinical information on 68 patients who received albendazole for hydatid disease during this time period. (NB: this publication did not distinguish cystic vs. alveolar hydatid disease.)

In preparation for submission of NDA 20-666, the sponsor once again attempted to collect clinical information from providers to whom albendazole had been shipped (after issuance of an IND number from DAIDP) between June 1988 and September 1993. Questionnaires were sent to 136 physicians regarding 153 patients. Responses were obtained from 58 (43%) of these physicians, with information on 67 (44%) of the treated patients; evaluable data were obtained regarding 55 of these 67 patients.

These data have the same shortcomings as the other, similarly-collected compassionate use datasets which make up a major portion of this NDA submission.

b. Value of these data to application. Despite the obvious limitations of these data, they are valuable insofar as they reflect usage patterns in hydatid patients seen in the United States.

c. Review process. The medical officer reviewed the entire volume of information submitted. This volume (1.113) of NDA 20-666 is composed of a summary section (Attachment 4) followed by tables and appendices that present the clinical data received in response to the March 1994 solicitation of follow-up data. (The majority of this volume, from page 48 to the end at page 301) is made up of the curricula vitae of these respondants.

d. Findings

i. Sponsor. The sponsor's findings and conclusions are summarized in Attachment 4.

ii. Medical officer. The medical officer has reviewed volume 1.113 in its entirety. It should be noted that no primary data was submitted (i.e., the actual responses from the IND holders who submitted information, not to mention any actual patient-level data that those investigators might have enclosed with their responses to the sponsor's questionnaire). It should also be noted that some of these data are duplications of literature references that have been submitted and reviewed elsewhere in this NDA. (For instance, four of these patients are from Anchorage AK, the investigator listed is Wilson, and the only submitted literature reference which discusses viability assessments of albendazole-treated patients with alveolar hydatid disease is Wilson et al, Clinical Infectious Diseases 1992; 15: 234-49.)

There is, in general, very little that can be extracted from these tables. The sponsor has included the appropriate summary tables in Attachment 4. The medical officer has reviewed these tables and agrees that they are reflective of the spreadsheet data from which they are derived.

The questionnaire sent by the sponsor did request viability information from the investigators. Upon more careful examination of this segment of these compassionate-use data, the Medical Officer found that 23 patients of the 56 patients listed had surgical dates mentioned. Of these 23, there were 9 patients who actually had the listed date of albendazole initiation as preceeding the surgical date. Of these 9, there were 6 patients who had information listed regarding viability of the cyst: two patients were found to have viable cysts at surgery, and four were found to have non-viable cysts. Of the two patients with viable cysts, one (pt received a standard 3-cycle, 28-days/cycle course of 800 mg/day albendazole; the other (pt received a single cycle (exact number of days not listed) at 800 mg/day. The method of viability determination was not mentioned in the three-cycle patient . . nor was any mention made of follow-up for cyst recurrence. The second patient who received a single cycle of albendazole pre-surgery, was found to have viable protoscolices by flame cell assay.

Four of the six patients with viability data provided had non-viable cysts at the time of surgery. These patients had variable courses of albendazole pre-operatively: one had a single 42-day cycle of 800 mg/day; another had a standard (28 days X 3 cycles) course of albendazole, at an adjusted dose of 600 mg/day (the patient was a 13 year-old Native American Zuni from New Mexico); the third had a prolonged course (28 days X 12 cycles) of 400 mg/day; and the fourth patient had no duration of therapy listed.

*Medical Officer comment: the most reliable conclusion that one can draw from reviewing these data is that there is not much data here on which to base any conclusions. It is moderately encouraging to find that more patients were reported to have non-viable cysts post-albendazole than were reported to have persistent, viable ones. It is also of note that, of the two "treatment failures" in this regard, one had a single course of pre-surgical albendazole (which other investigators have demonstrated to be, on the whole, inadequate), and the other was viable by flame cell only (i.e., we are not given any animal innoculation data).*

e. Conclusions

i. Sponsor. (Volume 1.113, page 012): "The data available from US compassionate use IND patients is consistent with that from other sources. In view of the numbers of patients available and the retrospective and fragmentary nature of the data in many cases these data can only be considered confirmatory of other more extensive sources. However, there is nothing in the series to suggest that either efficacy with proposed doses (400 mg BID in cycles of 28 days) or that safety is compromised in this population."

ii. Medical Officer: These data are consistent with the compassionate-use data submitted by the sponsor from other countries around the world. In other words, they are of limited value at best. In general, the Medical Officer concurs with the sponsor's conclusions as stated above. If one can conclude anything from the number of non-responses (aside from the inherently unsatisfactory nature of this sort of 'study design'), it would seem to be that patients treated with albendazole do not routinely experience any readily-identifiable short-term toxicity. Of the 56 patients in this dataset for whom safety data was obtained, only one patient was listed as requiring withdrawal of therapy for reasons of hepatotoxicity (patient The safety data included in this portion of the NDA is sketchier than the other compassionate-use datasets from other countries.

5. French Pharmacovigilence data.

The final segment of clinical data submitted in support of the hydatid indication, NDA 20-666, is a 21-page volume of data (vol 1.114) entitled "French Pharmacovigilence". This volume contains a two-page commentary by the sponsor, followed by an English translation and original French version of a document entitled "Use and tolerance of albendazole at a high dose in France", written by Dr. F. Sallin. This report describes the use and tolerance of high-dose albendazole (i.e., other than the dose used for intestinal helminths, typically 200 mg bid for 3 days) in France from 1989 to 15 October 1993.

The enclosed document discusses distribution data by year and indication, along with reported adverse events both in Germany as well as in France. As such, the information included in this document will be included in the integrated safety review which appears later in this NDA review document. This French document does not address efficacy in any manner. Therefore, it is of no value in determining the approvability of albendazole in the treatment of hydatid disease, from an efficacy point-of-view.

C Medical Officer Conclusions regarding Hydatid indication

1. Regulatory requirement for adequate and well-controlled investigations.

It is the opinion of the reviewing medical officer that the data submitted constitute 'adequate and well-controlled investigations' that document the efficacy of albendazole in the treatment of cystic hydatid disease due to *Echinococcus granulosus*. The manner in which these investigations were conducted, assembled, and submitted for review are somewhat unusual; nonetheless, the data present adequate evidence.

Because of the overlap between datasets, it becomes difficult to identify discreet groups of clinical data that might be considered as separate 'investigations'. The literature *in toto* cannot be utilized as one 'investigation' as was done for the neurocysticercosis indication, since separate papers in the hydatid literature overlap with both the UK and the US compassionate-use datasets. This situation has been summarised by the sponsor in the following table, which appears on page 319 of volume 1.1 of NDA 20-666:

| | Section Number | Content | Overlap |
|---|---|---|---|
| Hydatid | 3.2.1 | Publications | 10-20% may be included in 3.2.2 |
| | 3.2.2 | European MAA | 30-50% may be included in 3.2.1 |
| | 3.2.3 | Australian Compassionate Use | Minimal |
| | 3.2.4 | US Compassionate Use | Only Alaskan alveolar hydatid cases |
| | 3.2.5 | French Pharmacovigilence | Minimal |
| Cysticercosis | 3.3.1 | Publications | None |
| | 3.3.2 | US Data | None |
| | 3.3.3 | Peru Trial | None |

The two datasets that have the least amount of potential overlap (i.e., the Australian Compassionate Use and the French

Pharmacovigilence) also have the minimal amount of useful clinical efficacy information. The US Compassionate Use data, which has been reviewed above, is, at the very least, valuable as a separate 'study' given the involvement of DAIDP in the distribution process. Because of its compassionate use nature, this US 'trial' can be considered as having historical controls. Discounting the alveolar hydatid cases, there is virtually no overlap between the publication dataset and the US compassionate-use dataset.

There were four separate study sites that were included in the WHO Multicenter Clinical Trial, the results of which are part of the literature submitted in this NDA (the reference is Davis et al, Bull WHO 67(5): 503-8, 1989, and is found on pages 202-207 of volume 1.108). The case record forms from two of these sites (Rome and Paris) were submitted as part of the European MAA (also referred to as the UK Compassionate Use) portion of this NDA. Therefore, it would seem reasonable to consider this WHO multicenter study to be the second of the two required adequate and well-controlled investigations. The final results of this study, as presented in the 1989 Bull WHO paper, contain data on 68 (including 46 albendazole-treated) patients with at least 1 year of follow-up who received 3 cycles (or more) for treatment of cystic hydatid disease; since patients were randomized to either albendazole or mebendazole, this study can be considered to have an active, comparative control arm. (NB: mebendazole, although approved in the US, is not indicated for the treatment of hydatid disease). It was considered unethical to have a no-treatment control group in such a study (a viewpoint that the Medical Officer agrees with).

Even though the Medical Officer's assessment of cyst viability was pooled from literature references which may include some WHO data, it would seem to be reasonable to distinguish this analysis as one 'adequate and well-controlled investigation'. These pooled data contain a no-treatment control arm, as well as a dose-ranging design. Most importantly, this analysis demonstrates that the parasite is killed when adequate exposure to drug is achieved.

2. Previous discussions/agreements with DAIDP

The content of this NDA was discussed during a pre-NDA meeting between the sponsor and members of the Division of Anti-Infective Drug Products held on 15 September 1993. Given the ongoing participation of DAIDP in the emergency IND approval process, the problems inherent in the collection and analysis of such data were well known to the participants in this meeting. At that meeting, the sponsor was once again encouraged to file for an IND for the development of albendazole for these two indications. Short of that, the sponsor was encouraged to once again attempt to collect follow-up information on the patients treated in the US under compassionate use IND distribution. The sponsor has made a sincere effort to collect such data.

3. Overall regulatory status and probability of further studies in pursuit of approval

At the present time, the sponsor does not hold an Investigational New Drug exemption for the study of albendazole in the treatment of either of these two indications. This situation has remained unchanged since the late 1980's, when the use of albendazole in patients with either neurocysticercosis or hydatid disease first began to be reported in the literature. At the present time, the reviewing medical officer continues to approve from 5 to 10 emergency IND requests per week; the majority of these (approximately 75-80%) are for the treatment of neurocysticercosis. Given the demographics of the immigrant population in the USA today, and the epidemiology of these two parasitic diseases, this is not surprising.

4. Final Medical Officer comments

The diseases that are the focus of this NDA are, in general, chronic in nature and difficult to diagnose. They are overwhelmingly diseases of persons born outside of the geographic confines of the United States. These two factors create a situation which makes it practically impossible to conduct the type of rigorous, prospective, blinded clinical trials which have become the standard for approval of other anti-infective products in the US.

Should this then lead to the conclusion that it is ***impossible*** to approve albendazole, or any other antiparasitic drug, for either of these indications? I believe the answer to this question is 'no'. Both of these infections affect American citizens. Both are serious infections, potentially fatal, for which no drug therapy is currently approved in the United States. For these reasons, I believe that a more flexible approach to the question of approvability of this NDA is warranted.

With regards to the neurocysticercosis indication, the applicability of the cyst disappearance endpoint is, in my opinion, analagous to the tumor shrinkage endpoints that are used in cancer chemotherapy trials. A single large study has been submitted (from the medical literature) which appropriately links antiparasitic therapy with clinical benefit.

With regards to the hydatid indication, the role of surgery in the management of this disease is acknowledged and is important to include in the albendazole product labeling. In patients for whom surgery is inappropriate or carries an unacceptable risk of morbidity and/or mortality, or in whom intraoperative spillage of cyst contents has taken place, albendazole has, in my opinion, a therapeutic role. Given the consequences of otherwise not treating and merely observing such patients, it is appropriate to utilize an agent such as albendazole, given its known activity in vivo against other human and nonhuman parasites, as well as its in vitro activity against the *Echinococcus* parasite.

**Attachment 1**

**Applicant's Integrated Summary of Effectiveness**

(See NDA submission.)

**Attachment 2**

**Applicant's Summary of Compassionate Use Data from the United Kingdom**

(See NDA submission.)

**Attachment 3**

**Applicant's Summary of Compassionate Use Data**

**Australlia**

(See NDA submission.)

**Attachment 4**

**Applicant's Summary of Compassionate Use Data**

**United States**

(See NDA submission.)

# Medical Officer's safety review of NDA 20-666, Albendazole

A. Background

As has been described in the reviews of efficacy found earlier in this NDA review, the clinical data which form the basis for this NDA are not derived from sponsor-initiated, prospective, controlled clinical investigations. For this reason, the safety database for this NDA is complex. As the sponsor states in the introduction to the ISS (Integrated Summary of Safety), vol 1.118 page 040 of the NDA: "Formal clinical trials of chemotherapy including adequate numbers for statistical analysis of trends in safety parameters have been difficult to obtain....The available data for the evaluation of safety of albendazole...is based primarily not on formal clinical trials but on accumulated clinical reports from small series of patients."

Of relevance in considering the safety profile of albendazole is the fact that the drug has been in clinical use for a number of years. As noted in the introduction to this Medical Officer review, albendazole has been approved in France since 1981 for the treatment of intestinal helminthiases, and since 1992 in the UK for the treatment of hydatid disease. During this time, a large amount of literature has been published regarding albendazole.

B. Sponsor's Analysis of safety

The sponsor has attempted to capture all safety-related information available regarding albendazole. The summary document (the ISS) is included as Attachment 1 for the reader's reference. A summary of the methodology used will be presented here.

1. Clinical Adverse Events

The sponsor has reviewed the published literature as well as the UK, US, Australian, and French Pharmacovigilence datasets for all mentions of adverse events. These have been broken down by body system and by indication: 'low-dose' (i.e., for intestinal helminthiases); cysticercosis; and hydatid. Fatalities have been analyzed separately

Appendix A of the ISS lists literature references of albendazole for the treatment of intestinal helminthiases. The dose for such indications is listed; generally, the duration of therapy is from one to three days, at a dose of 400 mg per day. The references are divided into those which specifically mention adverse events, those in which no adverse events are reported, and those in which "no statement was made on adverse events". The total number of patients in these references is reported (Table 4 of ISS) to be 22,640.

*Medical Officer comment: it is unclear precisely how this number was calculated, but it appears that this 'denominator' for calculation of the rates reported in Table 4 of the ISS is the total number of patients (or 'number of treatments') in* all *of the listed references, even if the reference made no attempt to mention the issue of adverse events. Thus, the rates reported in Table 4 are most likely underestimates. It is acknowledged, however, that if the event 'epigastric pain' has an actual rate of (for instance) 0.5% rather than the reported 0.389%, this is of little clinical relevance. The medical officer agrees that the literature supports the contention that low-dose albendazole is relatively well-tolerated.*

Appendix B of the ISS lists all the hydatid references that appear in volumes 1.108 and 1.109 of the NDA. This table provides the reference, species of Echinococcus, number of patients, dose and duration of albendazole administration, and the adverse events mentioned in the text of the reference. The total number of patients in these references is 1,884; this figure appears in the header of Table 2 of the ISS. Table 5 of this appendix (page 104 of volume 1.118) summarizes the collected AEs from these literature references.

*Medical Officer comment: the accuracy of the entries to this table was checked and verified. The sponsor accurately extracted and categorized all available information provided in these references. It should be pointed out that a total of 55 listed references had "none stated" and an additional 11 had "none" in the adverse event column, out of a total of 131 references. Thus, 50% of the references contributed denominator data with no appreciable contribution to numerator data. This points out the difficulty in attempting to extract safety information from literature references.*

Appendix C of the ISS consists of the line listings compiled from the US Compassionate Use dataset, which is identical to the information submitted in volume 1.110, pages 105-164. The tabulated AEs from this set of patients (for whom CRFs have been submitted) are included in Table 2 of the ISS under the 'MAA' column, numbering 314 patients.

*Medical Officer comment: the accuracy of these entries was crosschecked between the CRFs and the line listings, and found to be accurate.*

Appendix D of the ISS is a tabular presentation of the literature references submitted in support of the neurocysticercosis indication, in a manner similar to the tabular presentation of the hydatid literature.

*Medical Officer comment: of the 61 total references included in this table, there were 18 listed as having 'none stated' and 5 as 'none' regarding AEs. This is roughly 37% of the total references.*

2. Deaths

The sponsor has tabulated all reported deaths from all datasets in Table 3 of the ISS. These are discussed in detail on pages 045-047 of this document. Of the 122 deaths listed in the entire database, 104 occurred in AIDS patients that were enrolled in IND studies of albendazole for the treatment of microsporidiosis.

*Medical Officer comment: This disease, caused by an intracellular parasite that infects lumenal epithelium of the immunocompromised gastrointestinal tract, is an opportunistic infection in late-stage AIDS patients. The disease causes intractable diarrhea and wasting.*

*It is entirely reasonable to consider these deaths separately from the other deaths reported in the database.*

Of the remaining 18 reported deaths, 14 were in hydatid patients, 3 in cysticercosis patients, and one in a patient being treated for giardiasis.

## Non-AIDS deaths reported in Albendazole safety database

| Case ID# | age/sex | Disease | Comments |
|---|---|---|---|
| | 76 male | hydatid | death secondary to aspiration pneumonia; received 2 doses ABZ |
| | 62 male | hydatid | recieved 27 days at 800 mg/day; coma secondary to 'leucoencephalitis' |
| | 25 male | hydatid | ABZ 800 mg/day X 12 days; surgical removal of hepatic cysts; post-surgical hemorrhage unrelated to ABZ |
| | 67 male | hydatid | ABZ 800 mg/day X 7 days; ascites, edema, pancytopenia; had history of cirrhosis |
| | 75 male | hydatid | disseminated echinococcosis; Pseudomonas lung abscess; peritonitis; myocardial infarction |
| | 33 weeks | hydatid | child exposed in utero to ABZ (?dose/duration) for treatment of mother's hydatid disease; born prematurely with respiratory distress; died after 2 days |
| | ?? female | cysticercosis | pancytopenia noted on day 14 of ABZ (?dose); septic shock and respiratory failure ensued |
| | ?? male | hydatid | 'Extremely sick' patient treated with unknown dose/duration ABZ; non-surgical candidate; cause of death unknown |
| | 23 male | hydatid | ABZ 800 mg/day X 28 days; sudden death secondary to obstruction of pulmonary artery by hydatid cyst |

**Non-AIDS deaths reported in Albendazole safety database (continued)**

| Case ID# | age/sex | Disease | Comments |
|---|---|---|---|
| | 84 male | hydatid | ABZ 800 mg/day; while on second course of therapy, pulmonary cyst ruptured and death ensued |
| | 69 female | giardiasis | ABZ 400 mg/day X ?? Days; history of ischaemic heart disease; Loss of consciousness, convulsions; death due to atherosclerosis |
| | 69 male | hydatid | disseminated hepatic cysts; on second course of ABZ 800 mg/day; abdominal pain; ? Intraabdominal bleed due to rupture of cysts |
| | ?? Male | hydatid | following sixth cycle of ABZ therapy, patient developed 'widespread metastases' and subsequently died |
| | 77 male | hydatid | received ABZ for hydatid disease; subsequently died; ABZ reportedly 'well-tolerated'; no causality reported |
| | 43 male | cysticercosis | patient with multiple intracerebral cysts, consequent seizures, strokes; died 9 months following ABZ therapy |
| | ?? Female | ? hydatid | patient treated for presumed CNS hydatid disease, subsequently died and found on autopsy to have an ependymoma |
| | 61 male | hydatid | while on ABZ for hepatic echinococcosis, died of sepsis |
| | 38 male | cysticercosis | patient with racemose neurocysticercosis died from complications of aspiration pneumonia |

*Medical Officer comment: it is difficult to make any definitive conclusions based on such reports, which are basically equivalent to post-marketing Spontaneous Reports rather than prospectively collected reports from sponsor - conducted clinical trials. These cases do point out some important issues:*

*•Surgical therapy of echinococcosis carries significant morbidity and mortality;*

*•Hydatid cysts, particularly in the lungs, may rupture as a result of albendazole therapy;*

*•In the absence of a definitive diagnosis, presumptive therapy may neglect potentially treatable disease.*

*There are also two cases of 'pancytopenia' among these deaths. Both had onset shortly after initiation of albendazole therapy, pointing out the possibility of this toxicity being idiosyncratic rather than strictly cumulative dose-dependent.*

3. Discontinuations

As the sponsor states in the ISS (page 47, volume 1.118 of NDA): "Although in several section of this application there is reference to withdrawal of patients due to adverse events, it is rarely possible to identify the actual cause of the withdrawal. There is often confusion over active withdrawal because of the presence of an event compared to the passive withdrawal at the completion of therapy." In other words, in many cases the exact course (duration) of therapy for hydatid disease is not defined and may last as long as the patient is tolerating the drug and there is evidence (e.g., serial ultrasound images which document intracyst changes) that the disease is responding to therapy.

In the case of liver function test abnormalities, a more definitive estimate of discontinuations can be made. The sponsor states that in the European MAA Hydatid document (volume 1.110, page 015) there are 12 such discontinuations out of 314 patients, or 3.8%; all of these saw normalization of LFTs after cessation of albendazole therapy. The tabulated published literature shows 43 such withdrawals of therapy out of 1116 patients, or 3.8%.

*Medical officer comment: determination of the causal relationship between elevated LFTs and the decision to discontinue albendazole is much more problematic in these literature references. Nonetheless, the coincidence of the same 3.8% figure is of interest.*

The remaining compassionate-use datasets show a small number of discontinuations. In the Australian dataset, three patients were reported to have treatment-associated AEs requiring discontinuation; 2 for alopecia and 1 for LFT abnormalities. One such LFT-associated treatment withdrawal was reported in the US compassionate use dataset. In

the French Pharmacovigilence data, there were 6/479 (1.25%) withdrawals for AEs; of these 6, three were considered drug-related AEs (2 for alopecia and 1 for LFT abnormalities). (NB: The French Pharmacovigilence summary is included as Attachment 2 for the reader's reference.)

There are considerably less data regarding treatment-associated AEs requiring withdrawal of therapy for cysticercosis. The submitted literature, as tabulated by the sponsor, reports 5 patients for whom albendazole therapy was withdrawn. (In all 5 patients the AE appeared to be therapy-induced elevation of intracranial pressure, rather than a direct drug toxicity per se.) One US Compassionate use patient was reported to have LFT elevations requiring discontinuation of cysticercosis therapy, and no such withdrawals were reported in the Gilman study conducted in Peru.

The sponsor concludes: " While data on treatment withdrawal for adverse effects may be considered incomplete for many of the datasets, it is clear that such events are relatively uncommon, occurring in less than 5% of treated patients. The commonest events leading to withdrawal are liver function abnormalities and alopecia. In all cases it appears that the effects disappear after treatment is stopped."

C. Medical Officer's analysis of submitted safety information

After carefully reading and verifying the sponsor's presentation of the safety information discussed above, the Medical Officer concurs with the findings and conclusions of the sponsor. It is difficult to equate this safety database to those typically seen in DAIDP in an NDA application, given their 'postmarketing' nature and reliance on spontaneous reporting by investigator/clinicians. The sponsor has attempted to thoroughly tabulate the AE experience with albendazole from the literature and compassionate-use datasets.

The clinical trial experience with albendazole for the treatment of AIDS-associated intestinal microsporidiosis has also been included in this NDA. Given the multiplicity of concomitant diseases and therapies in these late-stage HIV patients, the contribution of albendazole to the event(s) of interest is difficult to assess. These data are presented as a collection of CIOMS forms and not in any sort of computerized database that would easily lend itself to analysis. The Medical Officer has read each of these CIOMS reports individually and agrees with the sponsor's assessment as reported on page 052 of the ISS (Attachment 1).

One safety issue that has not been addressed by the sponsor concerns the treatment of neurocysticercosis in patients with concomitant retinal involvement. As mentioned in the introductory section of the NCC review, ingested eggs of *Taenia solium* release hexacanth embryos that enter the circulation after penetrating the intestinal wall. These embryos can potentially lodge in practically any anatomic site, but are often clinically silent. In what is considered to be the definitive literature description of the natural history of cysticercosis, Dixon and Lipscomb wrote in 1961 that "cysticerci within the eyeball, though rare, are a recognized manifestation of cysticercosis cellulosae. According to Duke-Elder (1940) they most commonly occur in the posterior segment of the eye, originating in the sub-retinal space and detaching the retina... 8 patients in our series [450 cases] had an eye lesion." This represents 1.8% of the cases in this large series of patients. A chapter on "Taeniasis and Cysticercosis", co-authored by Drs. Botero, Tanowitz, Weiss, and Wittner, appeared in the September 1993 issue of Infectious Disease Clinics of North America (volume 7 number 3, pages 683-696) In this chapter, the authors state: "three to seven percent of cases involve the eye, and the diagnosis is made by funduscopic examination... Antiparasitic therapy should be avoided and surgery is usually indicated."

There are 11 reports of adverse clinical events found in Table 2 of the applicant's ISS under 'Special Senses-Vision': seven of these are reported from the literature and four are from spontaneous reports. The seven literature-associated reports are characterized as 'diplopia' in 3 and 'pain on ocular movement' in four. The four spontaneous reports are characterized as 'retinal detachment', 'retinal disorder', 'vision abnormal', and 'visual disturbance'.

If as many as 7% of cases of cysticercosis involve the eye, one would expect a considerably higher number of treatment-related adverse visual events if antiparasitic therapy were detrimental. It should be kept in mind, however, that the adverse reaction section of this NDA is based on passively-collected compassionate use reports, and synthesis of literature references.

*Medical Officer comment: It is notable that experts in the therapy of NCC, including Drs. Botero and Wittner, recommend routine funduscopic examination of all patients prior to initiation of specific antiparasitic therapy. Despite the absence of specific adverse events in the NDA database, it would seem logical that treatment of intraocular lesions with antiparasitic drugs might increase inflammation around the lesion and cause further harm to the retina or surrounding tissues. Product labeling for albendazole should reflect this theoretical concern.*

# Overall Medical Officer conclusions regarding NDA 20-666

The applicant has submitted an NDA for an NME, the clinical portion of which is made up of the following components (in decreasing order of quantity): literature, to include meeting abstracts and single case reports; compassionate use information from several countries; a French postmarketing 'pharmacovigilence' study; and, finally, a single clinical study which involved 55 patients.

The applicant has never seen fit to file an IND application for albendazole; thus, over the past ten years, albendazole has not been distributed in the US under any sort of established protocol. Rather, individual investigators have obtained emergency IND approval from DAIDP, and the applicant has distributed drug in this manner. These individual investigator/clinicians do not reliably provide clinical follow-up information. The net result of this distribution program has been the inability to capture a significant amount of clinical information. (For example, in the first six months of 1995 DAIDP released albendazole to 76 patients for neurocysticercosis, 40 for hydatid disease, and 4 for other indications.)

The applicant has made an effort to obtain follow-up from these clinician/investigators in the United States by sending out repeated mailings with pleas for follow-up clinical information on the albendazole-treated patients. The results have been a disappointingly low response rate of 46% of the physicians, providing useable clinical information of any sort in 36% of the hydatid patients. For cysticercosis patients, only 30% of the physicians responded, providing evaluable data on 30% of the total patients. The data collected in such a manner is suboptimal.

Compassionate use programs in other countries of the world may yield marginally better response rates, but the resultant data is similarly flawed. However, much of the non-US use of albendazole for the treatment of hydatid disease was conducted within the framework of a WHO-coordinated multicenter comparative study of albend zole vs. mebendazole. In this setting, investigators had a set of standardized case record forms that were completed for each enrolled patient. Thus, these patients had clinical information that was collected in a standardized, prospective manner. These CRFs were submitted by the applicant in Amendment 1 to the NDA. The clinical information contained in the hydatid literature overlaps considerably (estimated by the sponsor to be in the 30-50% range) with the information contained in these CRFs, which make up the 'European MAA' dataset of the hydatid indication.

Comments regarding the specific indications:

## Neurocysticercosis (NCC)

This disease is reported to be the leading infectious cause of seizures worldwide. Particularly prevalent in Latin America, NCC has become an increasingly important disease in the US primarily because of immigration patterns. The incidence of NCC in the US remains sufficiently low to qualify for designation as an orphan disease.

No effective medical therapy currently exists for this disease.

As outlined in the introduction to the NCC portion of the MO review, numerous factors exist which contribute to making the prospective, orderly, well-controlled study of this disease difficult. It is important to keep these factors in mind when weighing the relative merits of this application and its potential approvability.

Factors in favor of approval of this indication include the following:

- In the opinion of this medical officer, the preponderance of medical literature supports the role of anticysticercal therapy in neurocysticercosis. Not all lesions will respond to therapy; the response of an individual lesion will depend on such factors as the age and total number of lesions; the host's immune response (as detected by the CT appearance of the lesion and the surrounding brain parenchyma); and the anatomic location within the central nervous system. In this review, an attempt has been made to define a homogenous population of NCC patients across literature

studies, and compare the response of the NCC cysts to therapy with anticysticercal therapy vs. no anticysticercal therapy. This metaanalysis demonstrates the efficacy of albendazole in the elimination of such parenchymal cysts, when compared to no-treatment controls.

- Albendazole is effective against adult cestodes, including *Taenia* species. It has a definite role in the treatment of veterinary and human infections with the adult form of the parasite which, in its larval stage, causes NCC. It is labeled for such human use in at least four countries (Australia, France, India, and South Africa).

- The *clinical* efficacy of anticysticercal therapy of NCC is an ongoing matter of debate in the medical literature. As mentioned previously in this review, the presence of a residual brain lesion, be it following a response to albendazole or as a result of gradual involution produced by the host's immune response, may serve as a seizure focus. Thus, the direct relationship between anticysticercal therapy and clinical benefit is difficult to establish. The study by Vasquez and Sotelo which appeared in the New England Journal of Medicine (327: 696-701, 1992) makes a convincing case for a link between anticysticercal therapy, reduction in number of brain cysts, and reduction in seizures. This literature reference is an important factor in the recommendation to approve the NCC indication.

- Along with a substantial amount of supporting literature and approximately 9 years of compassionate-use experience, the applicant has submitted a prospectively-conducted, IRB-approved clinical study for this indication, complete with patient-level data for independent review. This study site has been audited by the Division of Scientific Integrity, CDER. Although not without flaws, this site inspection served to validate this study site and the existence of the patients enrolled.

- Albendazole appears to be safe for this intended use when used according to the proposed package insert. It has been approved for use since 1992 for hydatid disease in The Netherlands, Germany, UK, and South Africa at similar doses but for more prolonged durations. It has been approved for lower-dose therapy (for intestinal nematodes and cestodes) since as early as 1981.

*Factors favoring nonapproval of this indication:*

- The literature may be seen to support the use of albendazole for NCC, but one must be wary of such literature. Considerable literature bias may exist which favors the submission and publication of studies reporting a positive result.

- Some recent studies, not captured by the applicant's literature submissions, report negative results. For example, a recent paper published in Archives of Internal Medicine (vol. 155, pages 1982-1988, October 1995) by Carpio et al, reports the results of an open study of albendazole vs. praziquantel, both with concomitant oral steroids, vs. steroids alone. This study, which enrolled 138 patients that were followed for 2 years, concludes "Previous reports of favorable response to treatment of neurocysticercosis with either praziquantel or albendazole are by no means definitive and may be a reflection of the natural history of the condition."

- Is the SmithKline Beecham formulation of albendazole actually used in the literature references of interest? In all of the 14 'pivotal' neurocysticercosis references, no specific reference is made to the identity of the albendazole utilized. The sponsor has been requested to clarify this situation.

- The Gilman study in Peru was audited and found to have multiple deficiencies, to include incomplete patient data, unavailability of some original CT scans, lack of study medication accountability, evidence of nonrandom assignment to treatment groups, and unblinded interpretation of CT scans by the principal investigator. One could argue that these findings invalidate this study.

Medical officer recommendations:

The preponderance of evidence submitted by the applicant supports the contention that albendazole has a role in the therapy of neurocysticercosis. The overall efficacy rates may vary between studies, both in the literature and in the submitted Gilman study; furthermore, the benefits of anticysticercal therapy depend on the nature of the lesions themselves and the status of the host's immune response to them. It is the recommendation of the reviewing medical officer that albendazole should be approved for use in the treatment of intraparenchymal neurocysticercosis caused by active (not ring-enhancing, non-edematous) cysts of the pork tapeworm, *Taenia solium*. The adult dose should be 15 mg/kg/day to a maximum of 800 mg, given in divided doses BID. The duration of therapy should be 8-30 days. (This wide range is representative of the medical literature.)

## Hydatid disease

This parasitic disease is also a disease of immigrants in the United States, although small foci of endemic disease afflict Native Americans in two distinct locations (the Navajo reservation area of New Mexico/Arizona/Utah/Colorado, and in Alaska). The disease is caused by two different species of the genus *Echinococcus*, a cestode parasite whose definitive host is canines. Both species cause a chronic, initially asymptomatic infection that becomes clinically apparent as a space-occupying lesion (for *E. granulosus*) or as a locally-invasive carcinoma-like process (for *E. multilocularis*).

Ideal therapy for both of these infections is surgical excision, but patients often present clinically when the infection has progressed beyond the point of curative surgical intervention. For cystic hydatid disease (*E. granulosus*) this is usually because of the following: the cysts are either multiple in number and/or location; the cysts are located in anatomic sites that make surgery impossible or high-risk; one or more cysts have ruptured, spilling their infectious contents and seeding the anatomic space with protoscolices which are independently capable of growing into new cysts; or the patient is a poor surgical candidate due to age or concomitant underlying medical conditions. For alveolar hydatid disease (*E. multilocularis*), the infiltrative nature of the disease process makes surgical excision practically impossible.

This disease has no currently approved medical therapy in the United States. It, too, qualifies for orphan disease designation.

Factors in favor of approval of this indication include the following:

- The applicant has submitted an extensive literature (including over 160 references) supportive of the contention that albendazole is active in the treatment of hydatid disease.

- The medical officer has extracted portions of this literature that, when combined, demonstrate parasite killing *in vivo* when adequate exposure to albendazole has been accomplished.

- The applicant has submitted similar applications to regulatory authorities in countries where hydatid disease is more prevalent than the US, and has secured marketing approval in at least seven (Australia, Netherlands, Germany, India, Japan, Spain, and the United Kingdom).

- The applicant has participated in a WHO-coordinated multicenter study of hydatid disease therapy, and has submitted case record forms from this study.

- The applicant has submitted compassionate-use information from other countries which had such distribution programs in place prior to marketing approval.

Factors favoring nonapproval of this indication:

- Compassionate-use data is subject to many of the criticisms cited above in the discussion of the neurocysticercosis indication, including recall bias.

- The medical literature is subject to publication bias. Efficacy of any therapeutic intervention, be it medical or surgical, may appear to be more favorable than it really is because investigators tend not to submit manuscripts which report negative results, and, if submitted, journals tend not to publish them.

Medical officer recommendations:

The information submitted by the applicant supports the approval of albendazole in the therapy of cystic hydatid disease due to *Echinococcus granulosus*. The adult dose should be 15 mg/kg/day to a maximum of 800 mg/day, given in divided doses BID. The preponderance of the literature and submitted information (including the integrated safety information) has utilized the 28-day dosing regimen followed by a 14-day drug-free interval; this sequence has most commonly been repeated for a total of 3 cycles. Although the submitted information includes treatment durations of both fewer and greater numbers of cycles, as well as regimens which do not incorporate the 14-day drug-free interval, the product labeling should reflect this standard 28/14 X 3 regimen. The medical officer's viability assessment supports such labeling.

The information submitted by the applicant is considered to be inadequate to support the inclusion of *E. multilocularis* in the product labeling. The literature regarding treatment of this organism is much less extensive; furthermore, there was very little viability information included in the submitted references. Also, since the lesion in this infection is diffuse and infiltrative, the noninvasive methods for assessing response to therapy in this disease are difficult to interpret.

Philip E. Coyne, Jr., MD
Reviewing Medical Officer
HFD-520

cc:
NDA 20-666
HFD-520
HFD-520/SMO/Leissa 6/6/96
HFD-520/MO/Coyne
HFD-520/CSO/Fogarty
HFD-520/Chem/Katague
HFD-520/Micro/King
HFD-520/Pharm/Adeyemo
HFD-520/Biopharm/Colangelo
HFD-520/Stats/Jiang
HFD-344/Thomas

**Concurrence only:**
ODE IV/OD/DFeigal 6-9-96
HFD-520/DivDir/MFanning
HFD-520/DepDivDir/LGavrilovich

EX TY SUMMARY for NDA # 20-666 SUPPL # _____

Tr e ALBENZA Generic Name Albendazole
Applicant Name SmithKline HFD-520

Approval Date 6/11/96

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____ Sponsor will be getting exclusivity based on Orphan status. (Letter Attached)

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. (Not Applicable.)

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.**

## PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /__/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /___/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /___/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /__/ NO /__/ Explain: _____

_____

Investigation #2

IND # ____ YES /__/ NO /__/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

_____ 6/11/96
Signature Date
Title: Project Manager

_____ 6/11/96
Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

SB
SmithKline Beecham
Pharmaceuticals

NDA 20-666

DRUG Albendazole Tablets

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## ITEM 13/14. PATENT INFORMATION

### Information on Any Patent that Claims the Drug

In the opinion and to the best knowledge of SmithKline Beecham Pharmaceuticals there are no United States patents that claim the drug on which investigations that are relied upon in this application are based or which relate to the use of the drug to treat hydatid cyst disease or neurocysticercosis.

U.S. Patent No. 3,915,986 which expired October 28, 1992 claimed the compound albendazole. U.S. Patent No. 3,956,499 which expired May 11, 1993 claimed anthelmintic pharmaceutical compositions containing albendazole and methods of producing anthelmintic activity in animals by administration of albendazole.

DUPLICATE

**SmithKline Beecham**
*Pharmaceuticals*


May 17, 1996

**NDA 20-666**
**Albendazole Tablets**

NEW CORRESPONDENCE

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research IV
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Re: Amendment to pending New Drug Application 20-666**
**Debarment Certification**

Dear Doctor Fanning:

We are writing with regard to our pending New Drug Application for albendazole (NDA 20-666), submitted December 8, 1995.

At this time we wish to amend the application in response to the FDA's request to submit the Debarment Certification for albendazole. A copy of the debarment certification, pursuant to Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act, is located on page 000005.

If there are any questions, please contact me at (215) 751-4455 (telephone) or (215) 751-4096 (FAX).

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ IN A.I. ☐ [illegible]
CSO INITIALS DATE

Sincerely

Debra Hackett
Manager
U.S. Regulatory Affairs

Desk Copy: Ms. Pauline Fogarty (2)

## DEBARMENT CERTIFICATION

Pursuant to section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-666 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade (generic) name/dosage form: ALBENZA (Albendazole)
Action: (AP) AE NA

Applicant SmithKline Therapeutic Class I·P

Indication(s) previously approved _____
_____ Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Neurocysticercosis and Hydatid disease
_____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

X a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

**EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.**

Mary, Project Manager. June 11, 1996
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-666
HFD-520/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**
**5/95**

Stat

# STATISTICAL REVIEW AND EVALUATION

MAY 3 1 1996

| | |
|---|---|
| **NDA:** | 20-666 |
| **Drug Trade Name:** | ALBENDAZOLE™ |
| **Formulation:** | oral |
| **Drug Class:** | 3-P-V |
| **Applicant:** | SmithKline Beecham |
| **Indications:** | 1. Hydatid cyst disease (*E. granulosus* infection and *E. multilocularis* infection)<br>2. Neurocysticercosis |
| **Documents Reviewed:** | NDA volumes 1.1, 1.121-1.134 dated December 8, 1995<br>NDA volumes 2.1-2.24 dated February 22, 1996<br>Electronic data provided by the Applicant on January 19, 1996 |
| **Type of Review:** | Clinical |
| **Medical Officer:** | Philip Coyne, M.D., HFD-520 |
| **Statistical Reviewer:** | Joel Jiang, Ph.D., HFD-725 |

Throughout the review, the following terms are abbreviated and referred as:

Albendazole: ALB; computerized tomography: CT; *Echinococcus granulosus*: E.G.; *Echinococcus multilocularis*: E.M.; *Echinococcus vogeli*: E.V.; electroencephalography: EEG; magnetic resonance imaging: MRI; Mebendazole: MEB; Flubendazole: FLUZ; neurocysticercosis: NCC; Praziquantel: PRZ; *Taenia solium*: T.S.

# I. INTRODUCTION

ALB is a benzimidazole carbamate that has a broad spectrum anthelmintic activity. A 200 mg tablet has been available in Europe and other international markets for the treatment of intestinal parasites since 1982. A 400 mg dosage form became available in Europe in 1992 for the treatment of hydatid disease. One ALB suspension made by the Applicant was approved in the US to treat animal helmintic infections.

In this NDA, the Applicant seeks the approval of ALB for the treatment of hydatid cyst disease and NCC. Hydatid cyst disease is caused by larvae of E.G. (cystic hydatid) and E.M. (alveolar hydatid), and NCC is caused by larvae T.S. The rationale of this proposal claimed by the Applicant is that ALB has been proved as an effective anthelmintic against a wide range of intestinal helminths. This suggests that ALB could be used for the treatment of system helminth disease. In addition, ALB has been available for treatment in the US on a "compassionate use" IND base since 1986 for hydatid cyst diseases and later for NCC. The Applicant proposes the following medication of ALB in the treatment of cystic echinococcosis caused by E.G., alveolar echinococcosis caused by E.M., and NCC caused by T.S.:

1. Cystic echinococcosis caused by E.G. and alveolar echinococcosis caused by E.M.: For patient weight 60 kg or more, 400 mg b.i.d. taking with meals for 28 days, or for weight less than 60 kg, 15 mg/kg (maximum dose 800 mg/day) given in two divided doses, taken with meals for 28 days.

2. NCC caused by T.S.: For patient weight 60 kg or more, 400 mg/day b.i.d. taking with meals, or for weight less than 60 kg, 15 mg/kg (maximum dose 800 mg/day) given in two divided doses, taken with meals.

The treatment duration is varied depending on the parasitic infection being treated.

The data included in this NDA to support the efficacy and safety of ALB for the treatment of hydatid cyst disease and NCC is based primarily on data generated from published material augmented with actual data from patients' case histories and "compassionate use" data and not the conventional large, well controlled and multicentered clinical trials. There are data from one clinical trial conducted in Peru to support the treatment of NCC. No formal statistical analysis of the clinical data was conducted in the NDA. There are 5 "studies" (published data and compassionate use experience) for hydatid disease, 3 "studies" (published data, compassionate use experiences and clinical trial) for NCC. However, none of the studies for hydatid disease is considered as pivotal, and only one data set for NCC came from a clinical trial conducted in Peru which was a comparative dose range study. In addition, the clinical efficacy and safety sections of some studies may overlap to some extent. For the above mentioned reason, the pivotal publication data from the NDA submissions are decided by the Medical Officer as per hydatid disease and NCC.

# II. EVALUATION

# II.1. HYDATID CYST DISEASE

The data to support the safety and efficacy of ALB for the treatment of hydatid cyst disease are primarily based on the following studies:

- Published Data
- Compassionate Use Experience in the US
- Compassionate Use Experience in the UK
- Australia Compassionate Use Data
- France Pharmacovigilence

These investigations are described and evaluated in detailed below.

## II.1.A. PUBLISHED DATA

### II.1.A.1. STUDY DESIGN

This part of data was acquired from available 129 publications and/or manuscripts relating to the treatment of hydatid disease with ALB, which were obtained independently by physicians with personal interest in hydatid disease. Of these, 104 papers referred to E.G. infection, 23 papers referred to E.M. and 2 papers referred to E.V. There were 3060 patients totally exposed to ALB in these studies. Some duplication of patient data was likely to have occurred. The majority of patients received ALB treatment at a dose of 10~15 mg/kg/day for a common treatment duration 28~30 day cycles (with or without a 14~15 day treatment free interval). E.M. therapy noticeably differed from treatment of E.G., with courses usually lasting for years due to the progressive nature of the disease. Duration of follow-up varied considerably with widely varying periods of treatment, and ranged between 8 weeks to several years. Some comparative data were provided, which compared ALB with no treatment or MEB or FLUZ, principally MEB 30~75 mg/kg/day and FLUZ 50 mg/kg/day.

REVIEWER COMMENTS: Analysis of the published data is problematic since the pattern of disease varies widely in the number and site of cysts and in their clinical effects. There is also considerable variation in the methods used to evaluate the disease, both radiologically and clinically. It is therefore difficult to evaluate treatment responses, especially with most reported studies having small patient numbers. In evaluating this material, it should be recognized that although several distinct sources were used, individual patients might present in more than one data set.

### II.1.A.2. ANALYTICAL DEFINITIONS AND STATISTICAL METHODS

For E.G. infection, treatment efficacy was assessed with different means among these studies, some of them were assessed in terms of global clinical/radiological response, the others by individual cyst responses, some by both. Clinical outcomes were categorized as "cure", "improvement", "no change" and "worse". A treatment cure was defined as cysts disappear with respect to whole patients or to individual cysts in organs, and improvement was defined as reduction of cysts in size, increase of density and separation of membranes.

For E.M. infection, treatment efficacy was assessed in terms of global clinical/radiological response. Clinical outcomes were categorized as "cure", "improvement", "no change" and "worse". Because of the massive and invasive nature of its lesions, the criterion for "cure" and "improvement" of E.M. are different from those of E.G.

The cure rate and cure/improvement rate are computed for the global and cyst responses at follow-up.

Meta analysis is applied to compare ALB with MEB in the efficacy of treatments of E.G. infection. The DerSimonian-Laird method is adopted. The parameter of interest in each study is the difference of cure rates and cure/improvement rates between the ALB and MEB as per global and cyst responses. The presence of heterogeneity in the outcome efficacy variable was assessed by the chi-square statistics presented by the DerSimonian-Laird method. If the p-value from the test of homogeneity was not larger than 0.15, the studies are not considered to be combinable. It should be noted that this method treats each publication independently

REVIEWER COMMENTS: Due to the limited available information, it is impossible to assess the comparability of the treatment groups with respect to demographic characteristics, baseline disease characteristics, evaluability status, and medication compliance.

## II.A.3. RESULTS

The Medical Officer supplies a list of 16 papers out of 129 publications as "pivotal" to review. The purpose of reselecting of references as the primary references is to make endpoints of interest consistent and to avoid repetitive publication as much as possible.

Tables 1A and 1B show the treatment response details of the Medical Officer's pivotal publications, which have 15 papers regarding E.G. infection and 2 papers regarding E.M. infection. Totally, there are 931 patients (907 E.G. patients and 24 E.M. patients) included in the 16 papers. In these studies, ALB was compared with no treatment or MEB or FLUZ, and the rest were ALB open label studies. Among the studies, cure rates varied widely regarding global and cyst responses. It is noteworthy that different dosage and duration of treatment were used in these studies.

TABLE 1A: MEDICAL OFFICER'S PIVOTAL PUBLISHED STUDIES OF TREATMENT OF E.G. INFECTION

| Paper | Entry into Study | | Response at Follow-up | |
|---|---|---|---|---|
| | Patient | Cyst | Global (Cure/Improvement) | Cyst (Cure/Improvement) |
| 5. Brough (1989) Australia | | | | |
| ALB | 2 | N.A. | 2(0/2) 100.0% | N.A. |
| 9. Davis (1986) Various | | | | |
| ALB | 30 | N.A. | 23(5/18) 76.7% | N.A. |
| MEB | 85 | N.A. | 52(8/44) 61.2% | N.A. |
| | | | * 7.3% (-9.7%, 24.2%) | |
| FLUZ | 6 | N.A. | 1(1/0) 16.7% | N.A. |
| 10. Davis (1989) Various | | | | |
| ALB | 64 | N.A. | 49(18/31) 76.6% | N.A. |
| MEB | 45 | N.A. | 23(3/20) 51.1% | N.A. |
| | | | * 21.5% (6.4%, 36.6%) | |

| | | | | |
|---|---|---|---|---|
| 19. Gil-Grande (1993) Spain | | | | |
| ALB<br>None | 37<br>18 | N.A.<br>N.A. | 20(0/20) 54.1%<br>0 | N.A.<br>N.A. |
| 19a. Giorgio (1993) Italy | | | | |
| ALB<br>MEB | 13<br>7 | N.A.<br>N.A. | N.A.<br>N.A. | N.A.<br>N.A. |
| 20e. Horton (1989) Multicenter | | | | |
| ALB | 253 | N.A. | 201(72/129) 79.4% | N.A. |
| 21. Isaacs (1987) New Zealand | | | | |
| ALB<br>MEB | 2<br>7 | N.A.<br>N.A. | 2(1/1) 100.0%<br>3(1/2) 42.9% | N.A.<br>N.A. |
| 22b. Khuroo (1993) India | | | | |
| ALB<br>None | 20<br>10 | 23<br>11 | N.A.<br>N.A. | 14(0/14) 70.0%<br>10(0/10) 100.0% |
| 31. Morris (1987) UK | | | | |
| ALB | 16 | N.A. | 13(13/0) 81.3% | N.A. |
| 31c. Nahmais (1994) Israel | | | | |
| ALB | 68 | 168 | 39(28/11) 57.4% | 83(68/15) 49.4% |
| 42c. Teggi (1993) Italy | | | | |
| ALB<br>MEB | 46<br>22 | 411<br>243 | 33(8/25) 71.7%<br>15(4/11) 68.2%<br>* *-0.6% (-23.6%, 22.1%)* | 281(203/78) 68.4%<br>132(16/116) 54.3% |
| 42g Todorov (1990) Bulgaria | | | | |
| ALB<br>MEB | N.A.<br>N.A. | 160<br>157 | N.A.<br>N.A. | 120(76/44) 75.0%<br>104(89/15) 66.2% |
| 43 Todorov (1992) Bulgaria | | | | |
| ALB<br>MEB | 35<br>44 | 191<br>220 | 26(15/11) 74.3%<br>19(10/9) 43.2%<br>* *20.1% (-3.0%, 43.2%)* | 141(125/16) 73.8%<br>105(97/8) 47.7% |
| 45a. Wen (1994) China | | | | |
| ALB | 58 | 34 | 43(14/29) 74.1% | 32(0/32) 94.1% |
| 45b. Wen (1994) China | | | | |
| ALB | 19 | N.A. | 15(15/0) 78.9% | N.A. |

*: The cure rate difference between ALB and MEB and its 95% confidence interval

| TABLE 1B: MEDICAL OFFICER'S PIVOTAL PUBLISHED STUDIES OF TREATMENT OF E.M. INFECTION | | | | |
|---|---|---|---|---|
| Paper | Entry into Study | | Response at Follow up | |
| | Patient | Cyst | Global Cure (Cure/Improvement) | Cyst Cure (Cure/Improvement) |
| 45a. Wen (1994) China | | | | |
| ALB | 19 | N.A. | 8(0/8) 42.1% | N.A. |
| 46a. Wilson (1992) USA | | | | |
| ALB | 5 | N.A. | 4(1/3) 80.0% | N.A. |

Meta analysis is applied to compare ALB with MEB in the efficacy of treatments of E.G. infection for the pivotal publications. The DerSimonian-Laird method is adopted. Table 2 shows the results of meta analysis. With respect to global response, there are 5 papers of ALB-MEB studies available for meta analysis; with respect to cyst response, there are 3 papers. Heterogeneity is present among ALB-MEB studies regarding global response for cure/improvement rate and cyst response. With regard to global response, mean difference of ALB minus MEB in cure rate is 13.6%. Confidence interval results show that ALB is therapeutically superior to MEB in the treatment of E.G. infection regarding global response for cure rate.

| TABLE 2: PIVOTAL PUBLISHED PAPERS: COMBINED RESULTS BY META ANALYSIS OF TREATMENT OF E.G. INFECTION | | | | |
|---|---|---|---|---|
| Study | D.F. | P-value of Homogeneity Test | Standard Error | Mean Rate Difference and C.I. |
| Global Cure Rate | | | | |
| ALB - MEB | 4 | 0.298 | 0.051 | 13.6% (3.5%, 23.6%) |
| Global Cure/Improvement Rate | | | | |
| ALB - MEB | 4 | 0.122 | 0.065 | N.A. |
| Cyst Cure Rate | | | | |
| ALB - MEB | 2 | <0.001 | 0.149 | N.A. |
| Cyst Cure/Improvement Rate | | | | |
| ALB - MEB | 2 | 0.030 | 0.045 | N.A. |

REVIEWER COMMENTS: The safety data is not available for each of the 16 pivotal publications, therefore, no safety analysis is conducted.

## II.1.B. COMPASSIONATE USE EXPERIENCE IN THE US

### II.1.B.1. STUDY DESIGN

The compassionate use IND was first made in 1987 to supplement the European Data Files for ALB treatment of hydatid disease. This resulted in a total of 7 cases with data being received from more than 50 letters sent. All the data received consisted of brief summaries. During 1988~1990, the Agency collected and analyzed their returns which were published. An analysis of 68 patients treated under the emergency IND programme was thereafter provided. The paper described the pattern of hydatid disease experience over the period. Twenty-two of the patients were infected in the US, 66% among them in Alaska. No differentiation of hydatid species was made. Of the 35 patients who received chemotherapy, 11% were considered cured, 74% improved and 14% unchanged. Response to pre and post surgery treatment was good in most patients. No cyst outcome could be determined in these patients. Transient liver function abnormalities were seen in 11% of cases while a number of other adverse experiences were recorded. The Agency has requested that the Applicant provide the US experience as part of the NDA file. Only 7 case details were obtained by the Applicant up to 1987. This date was taken as the start year for the collection. The last entry data was September 1993. Data collection commenced in March 1994 and was completed in August 1994.

### II.1.B.2. RESULTS

The evaluable patient population was 55 totally, 32 males, 20 females, and 3 patients without data. The mean age of the population was 46.0±19.2 years with males being slightly younger (mean 43.1±19.5 years: range 13~83 years) compared to females (mean 50.9±18.2 years: range 11~74 years). Thirty of the cases were recorded as E.G. and 12 were E.M. Four of the E.M. cases were from Alaska. Patients came from 21 countries (no data for 3 patients). Seven cases of E.G. infection were listed as occurring in the US residents. Twenty-six patients had their origin in the Mediterranean Basin hydatid focus.

Fifty-four patients had evaluable data. Thirty-six patients had cysts at 1 site only, 14 had 2 sites affected, and 4 had cysts at 3 sites. Cysts were most common in the liver with 44 patients affected. Lung (13 patients) and abdomen (11 patients) were next most common and cysts in the pelvis, spleen, kidney and spine were recorded for only 2 patients each.

In 32 patients the cysts were newly diagnosed, with 25 in the liver, 4 in lung, 3 in abdomen and 3 in other sites. In 3 cases more than one organ was involved. Twenty-two cysts were single with 2 patients having 2 cysts and 3 having 3 cysts. There were 4 patients with large numbers of cysts (10, 20, 30 and 40 each). Nineteen patients were recorded as having recurrent cysts; 15 in liver, 8 in lung, 4 in abdomen and 3 other sites. In 10 cases more than 1 organ was involved. Nineteen patients had single cysts, 2 had 2 cysts and 1 had 3 cysts. Multiple cysts were more common, with 4, 6 (2 cases), 8, 12 and 21 cysts each. Overall 34 patients had measurable cysts recorded ranging from 3 to 20 cm diameter (mean 8.9 ± 4.1 cm).

Twenty-one patients had previous surgery for their new or recurrent cysts, while 32 had chemotherapy (ALB 10, MEB 7, PRZ 1, ALB+MEB 3). Twelve patients had both surgery and chemotherapy before the current data collection.

Data on treatment are available for 46 patients who underwent between 1 and 25 (mean 4.0) cycles of treatment with ALB. The majority (42; 87.5%) received cycles between 28 and 30 days long. The commonest dose used was 800 mg/day (34 patients: 72%). The follow up post treatment were available for 39 patients, with a mean of 26.3 ± 25.9 months and range from 2 weeks to 9 years.

Tables 3 and 4 summarize the ALB cyst response data for treatment of E.G. and E.M., respectively. Outcomes were evaluated using the standard criteria which were supplied to all respondents when the data

requests were initiated. There were 34 E.G. cysts and 10 E.M. cysts treated by ALB. The results show that 52.9% E.G. cysts and 40.0% E.M. cysts were cured/improved following treatment with ALB for cyst response, and 11.8% E.G. cysts and 30.0% E.M. cysts cured following treatment with ALB. Treatment cure/improvement rates with ALB are lower in the treatment of E.M. than that of E.G., but cure rate to the contrary.

| TABLE 3: THE US COMPASSIONATE USE: FOR TREATMENT OF E.G., CYST RESPONSES OF PATIENTS WITH ALB | | |
|---|---|---|
| Outcome | ALB (N=34) | |
| Cure or improvement | 18 | (52.9%) |
| Cure | 4 | (11.8%) |
| Improvement | 14 | (41.2%) |
| No Change or Worse | 16 | (47.1%) |

| TABLE 4: THE US COMPASSIONATE USE: FOR TREATMENT OF E.M., CYST RESPONSES OF PATIENTS WITH ALB | | |
|---|---|---|
| Outcome | ALB (N=10) | |
| Cure or improvement | 4 | (40.0%) |
| Cure | 3 | (30.0%) |
| Improvement | 1 | (10.0%) |
| No Change or Worse | 6 | (60.0%) |

Regarding safety and tolerability, 48 were reported as positive and only 1 petient was said to have not tolerated treatment and withdrawn. Five patients had recorded events, 3 of whom had moderate elevations in liver enzymes. One patient had mild epigastric pain and another suffered mild nausea, dizziness and hair loss during each cycle of treatment.

**REVIEWER COMMENTS**: No safety analysis can be conducted. Descriptive statistical analyses were only performed toward the efficacy due to the open label study.

## II.1.C. COMPASSIONATE USE EXPERIENCE IN THE UK

### II.1.C.1. STUDY DESIGN

The analysis of the compassionate use data which were obtained between 1982 and 1987 in Europe was used in the preparation of an application for approval of ALB to market in the UK. It represents the accumulation of all data available until that time. During this period, all supplies of ALB for the treatment of hydatid disease and other non-intestinal helminth diseases were sourced exclusively from the UK. It was therefore possible to trace the majority of physicians who had used ALB for hydatid disease and their patient case reports as well.

## 8.1.C.2. ANALYTICAL DEFINITIONS AND STATISTICAL METHODS

Patients with proven hydatid disease were treated with ALB according to a number of formal protocols, the aims of which were to standardize treatment regimens and accumulate data in 3 specific areas: a) treatment of inoperable disease at any site; b) pre-surgical treatment to prevent/reduce the risk of recurrence as a result of spillage or incomplete removal; c) post-surgical to prevent recurrence following cyst spillage. The duration of treatment was initially limited to 28 days using a dose of approximately 12 mg/kg/day (range 10~15 mg/kg/day). With the success of treatment in these early studies, longer durations of treatment were used although it was recommended that treatment be given for cycles of 28 days, with 14 days between cycles.

Because of the paucity of material at most centers, many patients were entered on a 'named patient' basis. Individual data were collected continuously since the first reports of the effect of ALB treatment in hydatid disease. Although attempts were made to obtain data on all patients receiving therapy, returns of data were disappointingly low.

Analysis for efficacy was undertaken on returned records where adequate data on the diagnosis and site of the cyst(s) were available, and where adequate duration of therapy (at least 28 days) and compliance was documented. Cysts were identified using standard techniques (X-ray, ultrasound or CT), together with immunological tests and biopsy data in some cases. Cyst sizes were recorded, and subsequently monitored during treatment and follow up with *detailed measurement of changes of size and appearance.*

The following scheme was considered as standard methodology for hydatid disease evaluation.

1. Cysts not operated (medical therapy)
a) Cure: If cyst size reported, cyst undetectable post-treatment. If cyst size not measurable but assessed clinically or by radiological techniques, cyst not detectable post-treatment.
b) Improvement: If cyst size reported >25% reduction in cyst size. If cyst not measurable, clinically assessed as improved. Cyst changes occurring during or post therapy on X-ray, ultrasound or CT associated with disturbance in cyst function.
c)No Change: Cyst not showing any change in appearance, and if measures <25% reduction in size.
d)Worse: Any increase in cyst size, or appearance of new cysts.

2. Biopsy specimens obtained at surgery were classified as viable or non viable.
a)On direct microscopy (flame cell activity observed directly or eosin exclusion indicated viability).
b)On inoculation into susceptible animals. Cysts present at sacrifice at 6 months showed viability.
Non viable cysts were considered chemotherapy cures while viable cysts were considered no change for the purpose of analysis of the bulk of the data.

3. Recurrence in both medically and surgically treated cases, recurrence was recorded if the duration of follow up post treatment exceeded six months.

4. Global Evaluation (cure, improved, no change, worse) by the above criteria were used if single cysts were present. Where multiple cysts in single or several organs were present, the following criteria were used.
Cure: all cysts cured or demonstrated non viable.
Improved: either some cysts cured and some improved, or some improved while others unchanged.
No change: all cysts apparently no change.
Worse: one or more cysts increasing in size. New cysts appearing.
This approach represented most closely the "in clinic" response and the behavior of the whole hydatid population to chemotherapy.

Safety assessments were based on review of data for the treatment with ALB. Because data was obtained from many centers with different normal range values, and samples were not taken at consistent times, no statistical analysis could be conducted. Abnormal values were identified and their behavior with time evaluated. Reports of adverse clinical experiences were recorded.

## II.2.C.3. RESULTS

### EFFICACY IN E.G. INFECTION

Data were obtained from 314 patients with E.G. infection treated with ALB. There were 163 males and 157 females with a mean age of 43.8±16.54 years and range of 6~83 years. Of these, 253 patients were evaluable for efficacy based on criteria.

Of the evaluable patients, 190 (75.1%) had involvement of a single organ: liver 130 (51.4%), lung 20 (11.1%), peritoneum 17 (6.7%) and other sites 15 (5.9%). The remainder had involvement of 2 organs in 52 cases (20.5%) and 3 organs in 1 case (4.3%). There were 269 simple or complex liver cysts, 86 lung cysts, 50 single or multiple peritoneum cysts, 28 single or multiple bony cysts, 16 spleen or pancreas cysts, and 7 in other sites (heart, kidney, brain), a total of 456 individual cysts being evaluated.

Medical treatment had been given to 65 patients (49 MEB, 6 FLUZ, 2 PRZ, 8 not stated) prior to inclusion. Treatment had been withdrawn normally at least 3 months prior to treatment with ALB (range 1 month to 5 years). Previous surgical removal of cysts had been undertaken in 191 patients (60.3%). In 76 a single operation had been performed, while 33 had two operations, 17 had 3 operations, 11 had 4 operations and 11 had five or more, the remaining 43 were not specified. The maximum number of operations was 35.

Evaluation of the data was made according to the stated criteria. The response of individual cysts to treatment is shown by site in Table 5. Improvement criteria are further subdivided to indicate whether the improvement is one of size (IS), of appearance(IA), or of clinical findings (IC) alone.

TABLE 5: THE UK STUDY: CYST RESPONSES ACCORDING TO SITE FOLLOWING ALB TREATMENT OF E.G.

| Site | No. of Cysts | Cure | Improvement | | | No Change | Worse |
|---|---|---|---|---|---|---|---|
| | | | IS | IC | IA | | |
| Liver | 269 | 88 (32.7%) | 62 (23.0%) | 9 (3.3%) | 48 (17.8%) | 58 (21.6%) | 4 (1.5%) |
| Lung | 86 | 34 (39.5%) | 30 (34.9%) | 1 (1.2%) | 1 (1.2%) | 19 (22.0%) | 1 (1.2%) |
| Peritoneum | 50 | 25 (50.0%) | 9 (18.0%) | 1 (2.0%) | 3 (6.0%) | 11 (22.0%) | 1 (2.0%) |
| Bone | 28 | 7 (25.0%) | 3 (10.7%) | 12 (42.8%) | 0 | 5 (17.8%) | 1 (3.6%) |
| Spleen/Pancreas | 16 | 6 (37.5%) | 2 (12.5%) | 2 (12.5) | 1 (6.3%) | 5 (31.2%) | 0 |
| Other | 7 | 0 | 1 (14.3%) | 0 | 2 (28.6%) | 4 (57.1%) | 0 |
| Total | 456 | 160(35.1%) | 107(23.5%) | 25 (5.5%) | 55 (12.1%) | 102(22.4%) | 7 (1.5%) |

Table 6 presents the overall cyst response following ALB treatment of E.G.

The majority of cysts were located in the liver. The responses of peritoneal cysts had a highest cure rate (50.0%), and a larger proportion of liver cysts (77.0%) were cured/improved. The overall cyst cure rate is 35.1% and the cyst cure/improvement rate is 76.1%.

Global response was assessed for the patients irrespective of whether lesions were in single or multiple organs. Global responses of patients are shown in Table 7, 28.5% patients were considered cured, while 79.4% patients showed cured/improved, 20.5% patients were no change or even worse.

**TABLE 6**: THE UK STUDY: CYST RESPONSE FOLLOWING ALB TREATMENT OF E.G.

| Total Cysts | Cure | Improvement | Cure or Improvement | No Change or Worse |
|---|---|---|---|---|
| 456 | 160 (35.1%) | 187 (41.1%) | 347 (76.1%) | 109 (23.9%) |

**TABLE 7**: THE UK STUDY: GLOBAL RESPONSE FOLLOWING ALB TREATMENT OF E.G.

| Total Patients | Cure | Improvement | Cure or Improvement | No Change or Worse |
|---|---|---|---|---|
| 253 | 72 (28.5%) | 129 (51.0%) | 201 (79.4%) | 52 (20.5%) |

## EFFICACY IN E. M. INFECTION

Only 35 patients with E.M. infection were treated at the time of the analysis. Twenty-eight cases were obtained from European and 7 from Alaska. In all there were 19 males and 16 females with mean age 47.8±17.8 years and range 12–81 years. In the European series 11 patients had been previously treated with FLUZ and 2 with MEB, and 10 had undergone surgery, principally for diagnostic purposes. None of the Alaskan series had received previous chemotherapy.

Of the 28 European patients and 7 Alaska patients, there were 36 cysts, which were involved in liver 32 (88.9%), lung 2 (5.6%) and other sites 2 (5.6%). The cyst responses to treatment are shown by site in Table 8. Table 9 presents the overall cyst response following ALB treatment of E.M.

The majority of cysts were located in the liver. The overall cyst cure rate is 13.9% and the cyst cure/improvement rate is 25.0%.

Global response was assessed for the whole patient irrespective of whether lesions were in single or multiple organs. Global responses of patients are shown in Table 10. 7.1% patients were considered cured, while 21.4% patients showed cured/improved. 78.4% patients were no change or even worse.

| TABLE 8: THE UK STUDY: CYST RESPONSE ACCORDING TO SITE FOLLOWING ALB TREATMENT OF E.M. | | | | | |
|---|---|---|---|---|---|
| Site | No. of Cyst | Cure | Improvement | No Change | Worse |
| Liver | 32 | 2 (6.1%) | 4 (12.2%) | 23 (71.9%) | 3 (9.4%) |
| Lung | 2 | 2 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 2 | 1 (50.0%) | 0 (0%) | 0 (0%) | 1 (50.0%) |
| Total | 36 | 5 (13.9%) | 4 (11.1%) | 23 (63.9%) | 4 (11.1%) |

| TABLE 9: THE UK STUDY: CYST RESPONSE OF FOLLOWING ALB TREATMENT OF E.M. | | | | |
|---|---|---|---|---|
| Total Cysts | Cure | Improvement | Cure or Improvement | No Change or Worse |
| 36 | 5 (13.9%) | 4 (11.1%) | 9 (25.0%) | 27 (75.0%) |

| TABLE 10: THE UK STUDY: GLOBAL RESPONSE OF FOLLOWING ALB TREATMENT OF E.M. | | | | |
|---|---|---|---|---|
| Total Patients | Cure | Improved | Cure or Improved | No Change or Worse |
| 28 | 2 (7.1%) | 4 (14.2%) | 6 (21.4%) | 22 (78.4%) |

REVIEWER COMMENTS: Explanation of E.M. data should be taken cautiously owing to very limited available data.

## SAFETY IN E.G. INFECTION

Thirty (9.6%) of the 314 patients with adequate documentation had clinical events recorded. Of these, 6 events were directly associated with hydatid lung disease. One patient was withdrawn with severe headaches after 2 weeks therapy. There was no valid record of laboratory changes.

Four deaths were recorded in the series of 314 patients with E.G. infection. One diabetic patient in the UK developed bacterial septicaemia and died, having received ALB for 5 days, 1 died as a result of a cyst rupture, 1 died while under anaesthetic, the other died of complications following surgery for hydatid. None could be attributed to ALB treatment.

REVIEWER COMMENTS: Some of the data presented in this evaluation were already contained in the published literature. There is no safety data in E.M. infection.

## II.1.D. AUSTRALIAN COMPASSIONATE USE DATA

### II.1.D.1. STUDY DESIGN

Unlike the majority of European countries, ALB was a compassionate use product for all indications in Australia until 1995 when the product was licensed. The Special Access Scheme (SAS) permitted the use of ALB following individual case approval, and the data resulting from the SAS were collected and analyzed prior to submission to the licensing authority. While this was only required for the period up to 1991, reports continued to be compiled up to the time of licensing. This set of reports provided an overview of efficacy and safety profiles of ALB. Endemic transmission in Australia was estimated 60~100 cases per annum. Six separate reports on the SAS data were available covering the period from 1984 when the first patient was enrolled until 1994.

The applicant noted that the returns in this programme rarely exceeded 50% of investigators supplied, and the data were inadequate to evaluate efficacy.

### II.1.D.2. RESULTS

#### EFFICACY

The method of evaluation of the hydatid cyst efficacy data was identical to that used for evaluation of the European material, and clinical symptoms were scored at baseline and at follow-up.

Of the total evaluable patients, there are 72 cysts. Table 11 presents the overall cyst response following ALB treatment of hydatid disease. The overall cyst cure rate is 13.9% and the cyst cure/improvement rate is 47.2%.

REVIEWER COMMENT: Global response is not evaluable due to discrepancy of data.

TABLE 11: AUSTRALIA STUDY: CYST RESPONSE FOLLOWING ALB TREATMENT OF HYDATID DISEASE.

| Report | Total Cysts | Cure | Improvement | Cure or Improvement | No Change or Worse |
|---|---|---|---|---|---|
| 1984 - 1990 | 34 | 10 (29.4%) | 11 (32.4%) | 21 (61.8%) | 13 (38.2%) |
| 1990 | 7 | 0 | 2 (28.6%) | 2 (28.6%) | 5 (71.4%) |
| 1991 | 9 | 0 | 6 (66.7%) | 6 (66.7%) | 3 (33.3%) |
| 1992 | 9 | 0 | 4 (44.4%) | 4 (44.4%) | 5 (55.6%) |
| 1993 - 1994 | 13 | 0 | 1 (7.7%) | 1 (7.7%) | 12 (92.3%) |
| Total | 72 | 10 (13.9%) | 24 (33.3%) | 34 (47.2%) | 38 (52.8%) |

**SAFETY**

Of the 236 patients with hydatid disease and 90 patients with other conditions, adverse events were reported by 40 hydatid patients and 14 non-hydatid patients. No deaths were reported in the hydatid patients.

Treatment withdrawal occurred in 4 hydatid patients. In contrast, six of the non-hydatid patients were withdrawn, the majority of these had AIDS.

Table 12 presents clinical adverse event rates following ALB treatment among hydatid patients and among non hydatid patients. Fisher's exact test shows that there is no significant difference with respect to at least one adverse event between hydatid and non-hydatid patients, but significantly fewer hydatid patients withdrew due to adverse events than non-hydatid patients.

**TABLE 12**: AUSTRALIA STUDY: ADVERSE EVENT RATES FOLLOWING ALB TREATMENT OF HYDATID DISEASE AND NON-HYDATID DISEASE PATIENTS

| outcome | Hydatid Patients (N=236) | Non-Hydatid Patients (N=90) | Fisher's P-value |
|---|---|---|---|
| At Least One AE | 40 (16.9%) | 14 (15.6%) | 0.868 |
| Withdrawal due to AE | 4 (1.7%) | 6 (6.7%) | 0.030 |

**REVIEWER COMMENTS**: The efficacy and safety data for ALB treatment of E.M. infections are not available for analysis.

## II.1.E. FRENCH PHARMACOVIGILENCE

During January 1989 to October 1993, 479 patients were treated on the programme and were examined by the Pharmacovigilence Department of SmithKline Beecham in Paris. The reports were submitted to the French Regulatory Authorities.

Among 479 patients, there were only 15 patients with hydatid disease (77.6% E.G., 22.6% E.M.). In general the patients with E.M. disease received longer treatment.

There were only 6 serious adverse events reported which led the patients withdrawal. Three of them were considered to be treatment unrelated, and the other 3 were considered drug related.

**REVIEWER COMMENTS**: No statistical analysis can be done toward French Pharmacovigilence Study.

# II.2. NEUROCYSTICERCOSIS

The data to support the safety and efficacy of ALB for the treatment of NCC are based on the following studies:

- Published Data
- Compassionate Use Experience in the US
- Clinical Study in Peru

These investigations are described and evaluated in detailed below.

## II.2.A. PUBLISHED DATA

### II.2.A.1. STUDY DESIGN

All data were obtained from available publications and/or unpublished manuscripts relating to the treatment of NCC with ALB. The majority of these papers were the results of unsponsored studies undertaken by physicians with a personal interest in NCC. There were 65 publications and/or manuscripts identified, which included totally 1044 patients. None of these studies was conducted in the US but principally in Latin America. Some duplication of patient data was likely to have occurred. The vast majority of patients received a single course of treatment, and all remaining patients received between two and three courses. All patients received ALB treatment within the dose range 10~25 mg/kg/day, and the majority received ALB 15 mg/kg/day. Duration of treatment varied to a great extent. The treatment duration historically recommended was 30 days, however, shorter courses of treatment were adopted and treatment durations of 15, 8, and 3 days were also reported, respectively. A number of papers compared ALB with no treatment or PRZ, and the others were ALB open label studies. The most common treatment regimen of PRZ was 50 mg/kg/day for 15 days. Thirty-one patients received treatment with ALB in combination with PRZ. The duration of follow-up to the time of data collection ranged between 2 weeks to 14 years.

The Medical Officer defines two "pivotal" analysis groups among 65 publications and/or manuscripts reports: List A, considered the best which is consisted of 7 papers; List B, considered fairly better which is consisted of the other 7 papers. The purpose of reselecting references is to make endpoints of interest more consistent and to avoid possible overlap as much as possible. The logics used to come up with the lists are as follows:

- all abstracts were disregarded
- all case reports were disregarded
- all manuscripts which had not yet been published were disregarded
- diagnostic criteria had to be stated clearly, and only studies of patients with parenchymal lesions that were nonenhancing and without surrounding edema were included

In collaboration with the Medical Officer, the Reviewer analyzes two sets of publications to evaluate the treatment of NCC with ALB. Set A is based on 7 papers of List A and Set B is based on 14 papers of List A and List B.

## II.2.A.2. ANALYTICAL DEFINITIONS AND STATISTICAL METHODS

Treatment outcomes were assessed in terms of changes to the numbers of cysts or their tomographic appearances (as detected by CT) at end-of-therapy, whilst some papers examined changes in clinical symptoms. Primary efficacy variable was the rate of clinical cure and cure/improvement evaluated either tomographic or clinical at end-of-therapy.

Equivalence of the two treatment groups with respect to the efficacy variable was assessed by computing the two-tailed 95% confidence interval of the difference in proportions. The confidence intervals are computed using a normal approximation to the binomial, and include a continuity correction. Confidence interval results are interpreted using the approach outlined on the draft of DAIDP "Points to Consider" document. The comparator was either no treatment or PRZ.

This reviewer performed analyses of the following safety variables: rates of some frequent adverse events: headache, nausea and dizziness. Comparisons were made by using Fisher's exact test.

It should be noted that all of the studies in Set A used the same CT criteria for brain lesions (i.e., nonenhancing, nonedematous, parenchymal lesions). Hence, meta analysis is conducted for the data in Set A, by which the results from the relevant trials are combined in order to evaluate the efficacy of treatments. The DerSimonian-Laird method is applied. The parameter of interest in each study is the difference of cure rates and cure/improvement between the ALB and no treatment or PRZ as per tomographic, clinical and cyst responses. There are 5 papers available for ALB-no treatment studies and 4 papers for ALB-PRZ studies in Set A. The presence of heterogeneity in the outcome efficacy variable was assessed by the chi-square statistics presented by the DerSimonian-Laird method.

Unless otherwise noted, all tests are two-sided and use a 5% level of significance.

REVIEWER COMMENTS: Subset analyses by demographic characteristics for the efficacy variable are impossible due to lack of the relevant information. There is no data available for the treatment related adverse event rates and the withdrawal rates, hence, statistical analysis is not performed.

## II.2.A.3. RESULTS

Table 13 summarizes details of treatment responses by treatment regimen and by study for data in Set A. There are 601 patients in Set A and 858 patients in Set B with tomographic response, and 577 patients in Set A and 807 patients in Set B with clinical response. Following ALB treatment, tomographic response data were derived from 255 patients in Set A and 410 patients in Set B; and clinical response data were derived from 223 patients in Set A and 336 patients in Set B.

Tables 14 and 15 summarize tomographic response data of treatments with ALB and no treatment for Set A and Set B, respectively, which were in terms of overall changes or more quantitatively changes to individual cysts. The results show that 66.7% and 75.4% of patients were cured/improved with ALB compared with 4.0% and 21.4% of patients with no treatment for Set A and Set B, respectively, and 39.2% and 39.5% of patients were cured with ALB compared with 2.4% and 6.4% of patients with no treatment for Set A and Set B, respectively. Confidence interval results from analyses of both sets of data show that ALB is therapeutically superior to no treatment with respect to tomographic response.

Tables 16 and 17 summarize tomographic response data of treatments with ALB and PRZ for Set A and Set B, respectively. The results show that 66.7% and 75.4% of patients were cured/improved with ALB compared with 78.2% and 79.6% of patients with PRZ for Set A and Set B, respectively, and 39.2% and 39.5% of patients were cured with ALB compared with 52.7% and 45.1% of patients with PRZ for Set A and Set B, respectively. Confidence interval results from analyses of Set B show that ALB is therapeutically

equivalent to PRZ with respect to tomographic response. However, confidence interval results from analyses of Set A do not show that ALB is therapeutically equivalent to PRZ with respect to tomographic response.

**TABLE 13: PUBLISHED DATA ON SET A: TREATMENT RESPONSE DETAILS**

| Paper | Entry into Study | | | Response at Three Months Follow-up | | |
|---|---|---|---|---|---|---|
| | Patient | | Cyst | Global (Cure/Improvement) | | Cyst |
| | Tomo | Clinical | | Tomographic | Clinical | |
| 3. Alarcon (1989) Ecuador | | | | | | |
| ALB | 18 | 18 | 27 | 13(11/2) 72.2% | N.A. | 17 63.0% |
| None | 5 | 5 | 10 | 1(0/1) 20.0% | N.A. | 1 10.0% |
| 3a. Alarcon (1990) Ecuador | | | | | | |
| ALB | 40 | 40 | 73 | 36(0/36) 90.0% | 29(29/0) 72.5% | 21 28.8% |
| 18. Cruz-Alcala (1990) Mexico | | | | | | |
| ALB | 30 | 30 | 69 | 27(22/5) 90.0% | 27(22/5) 90.0% | 56 81.2% |
| None | 18 | 18 | 104 | 0 | N.A. | 4 3.8% |
| PRZ | 76 | 76 | 375 | 59(42/17) 77.6% | 59(42/17) 77.6% | 313 83.5% |
| 22. Escobedo (1987) Mexico | | | | | | |
| ALB | 39 | 7 | 157 | 35(24/11) 89.7% | 7(7/0) 100.0% | 135 86.0% |
| None | 5 | 5 | NA | 0 | N.A. | N.A. |
| PRZ | 10 | 5 | NA | 9(7/2) 90.0% | N.A. | N.A. |
| 53. Sotelo (1990) Mexico | | | | | | |
| ALB | 49 | 49 | 568 | 45(32/13) 91.8% | 46(34/12) 93.9% | 482 84.9% |
| None | 33 | 33 | 314 | 0 | 0 | 0 |
| PRZ | 52 | 65 | 655 | 45(21/24) 86.5% | 54(24/30) 83.1% | 361 -55.1% |
| 56. Takayanaqui and Jardim (1992) Brazil | | | | | | |
| ALB | 21 | 21 | 101 | 14(11/3) 66.7% | 14(3/11) 66.7% | 89 88.1% |
| None | 16 | 16 | 113 | 2(1/1) 12.5% | N.A. | 7 6.2% |
| PRZ | 22 | 22 | 178 | 16(3/13) 72.7% | 12(5/7) 54.5% | 89 50.0% |
| 58. Vazquez and Sotelo (1992) Mexico | | | | | | |
| ALB | 58 | 58 | 591 | N.A. | N.A. | N.A. |
| None | 49 | 49 | 195 | 2(2/0) 4.1% | 0 | N.A. |
| PRZ | 60 | 60 | NA | 43(43/0) 71.7% | 33(33/0) 55.0% | N.A. |

| TABLE 14: PUBLISHED DATA ON SET A: TOMOGRAPHIC RESPONSES OF PATIENTS WITH ALB AND NO TREATMENT | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=255) | | None (N=126) | |
| Cure or Improvement | 170 | (66.7%) | 5 | (4.0%) |
| Cure | 100 | (39.2%) | 3 | (2.4%) |
| Improvement | 70 | (27.5%) | 2 | (1.6%) |
| No Change or Worse | 85 | (33.3%) | 121 | (96.0%) |
| 95% C.I.: Cure or Improvement | 62.7% (55.4%, 70.0%) | | | |
| Cure only | 36.8% (29.7%, 44.0%) | | | |

| TABLE 15: PUBLISHED DATA ON SET B: TOMOGRAPHIC RESPONSES OF PATIENTS WITH ALB AND NO TREATMENT | | | | |
|---|---|---|---|---|
| outcome | ALB (N=410) | | None (N=173) | |
| Cure or Improvement | 309 | (75.4%) | 37 | (21.4%) |
| Cure | 162 | (39.5%) | 11 | (6.4%) |
| Improvement | 147 | (35.9%) | 26 | (15.0%) |
| No Change or Worse | 101 | (24.6%) | 136 | (78.6%) |
| 95% C.I.: Cure or Improvement | 54.0% (46.2%, 61.8%) | | | |
| Cure only | 33.2% (26.8%, 39.5%) | | | |

| TABLE 16: PUBLISHED DATA ON SET A: TOMOGRAPHIC RESPONSES OF PATIENTS WITH ALB AND PRZ | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=255) | | PRZ (N=220) – | |
| Cure or Improvement | 170 | (66.7%) | 172 | (78.2%) |
| Cure | 100 | (39.2%) | 116 | (52.7%) |
| Improvement | 70 | (27.5%) | 56 | (25.5%) |
| No Change or Worse | 85 | (33.3%) | 48 | (21.8%) |
| 95% C.I.: Cure or Improvement | -11.5% (-19.9%, -3.1%) | | | |
| Cure only | -13.5% (-22.9%, -4.2%) | | | |

| TABLE 17: PUBLISHED DATA ON SET B: TOMOGRAPHIC RESPONSES OF PATIENTS WITH ALB AND PRZ | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=410) | | PRZ (N=275) | |
| Cure or Improvement | 309 | (75.4%) | 219 | (79.6%) |
| Cure | 162 | (39.5%) | 124 | (45.1%) |
| Improvement | 147 | (35.9%) | 95 | (34.5%) |
| No Change or Worse | 101 | (24.6%) | 56 | (20.4%) |
| 95% C.I.: Cure or Improvement | -4.3% (-10.9%, 2.4%) | | | |
| Cure only | -5.6% (-13.4%, 2.3%) | | | |

Tables 18 and 19 summarize clinical response data by treatments with ALB and no treatment for Set A and Set B, respectively. The results show that 55.2% and 66.1% of patients were cured/improved with ALB compared with 0% and 22.3% of patients with no treatment for Set A and Set B, respectively, and 42.6% and 47.0% of patients were cured with ALB compared with 0% and 3.7% of patients with no treatment for Set A and Set B, respectively. Confidence interval results from analyses of both sets of data show that ALB is therapeutically superior to no treatment with respect to clinical response.

| TABLE 18: PUBLISHED DATA ON SET A: CLINICAL RESPONSES OF PATIENTS WITH ALB AND NO TREATMENT | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=223) | | None (N=126) | |
| Cure or Improvement | 123 | (55.2%) | 0 | (0%) |
| Cure | 95 | (42.6%) | 0 | (0%) |
| Improvement | 28 | (12.6%) | 0 | (0%) |
| No Change or Worse | 100 | (44.8%) | 126 | (100.0%) |
| 95% C.I.: Cure or Improvement | 55.2% (48.0%, 62.3%) | | | |
| Cure only | 42.6% (35.5%, 49.7%) | | | |

| TABLE 19: PUBLISHED DATA ON SET B: CLINICAL RESPONSES OF PATIENTS WITH ALB AND NO TREATMENT | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=336) | | None (N=188) | |
| Cure or Improvement | 222 | (66.1%) | 42 | (22.3%) |
| Cure | 158 | (47.0%) | 7 | (3.7%) |
| Improvement | 64 | (19.0%) | 35 | (18.6%) |
| No Change or Worse | 114 | (33.9%) | 146 | (77.7%) |
| 95% C.I.: Cure or Improvement | 43.7% (35.5%, 52.0%) | | | |
| Cure only | 43.3% (36.9%, 49.7%) | | | |

Tables 20 and 21 summarize clinical response data by treatments with ALB and PRZ for Set A and Set B, respectively. The results show that 55.2% and 66.1% of patients were cured/improved with ALB compared with 69.3% and 72.4% of patients with PRZ for Set A and Set B, respectively, and 42.6% and 47.0% of patients were cured with ALB compared with 45.6% and 40.3% of patients with PRZ for Set A and Set B, respectively. Confidence interval results from analyses of Set B data show that ALB is therapeutically equivalent to PRZ with respect to clinical response. Confidence interval results for the cure rate from analyses of Set A data show that ALB is therapeutically equivalent to PRZ with respect to clinical response.

**TABLE 20**: PUBLISHED DATA ON SET A: CLINICAL RESPONSES OF PATIENTS WITH ALB AND PRZ

| Outcome | ALB (N=223) | | PRZ (N=228) | |
|---|---|---|---|---|
| Cure or Improvement | 123 | (55.2%) | 158 | (69.3%) |
| Cure | 95 | (42.6%) | 104 | (45.6%) |
| Improvement | 28 | (12.6%) | 54 | (23.7%) |
| No Change or Worse | 100 | (44.8%) | 70 | (30.7%) |
| 95% C.I.: Cure or Improvement | -14.1% (-23.4%, -4.8%) | | | |
| Cure only | -3.0% (-12.6%, 6.6%) | | | |

**TABLE 21**: PUBLISHED DATA ON SET B: CLINICAL RESPONSES OF PATIENTS WITH ALB AND PRZ

| Outcome | ALB (N=336) | | PRZ (N=283) | |
|---|---|---|---|---|
| Cure or Improvement | 222 | (66.1%) | 205 | (72.4%) |
| Cure | 158 | (47.0%) | 114 | (40.3%) |
| Improvement | 64 | (19.0%) | 91 | (32.2%) |
| No Change or Worse | 114 | (33.9%) | 78 | (27.6%) |
| 95% C.I.: Cure or Improvement | -6.4% (-14.0%, 1.2%) | | | |
| Cure only | 6.7% (-1.4%, 14.9%) | | | |

Tables 22 and 23 summarize cyst response data by treatments with ALB-no treatment and ALB-PRZ for Set A. The results show that 50.4% of cysts were cured with ALB compared with 1.6% and 63.2% of cysts with no treatment and PRZ, respectively. Confidence interval results show that ALB is therapeutically superior to no treatment and equivalent to PRZ with respect to cyst response. This analysis is not applicable for the data of Set B.

| TABLE 22: PUBLISHED DATA ON SET A: CYST RESPONSES OF PATIENTS WITH ALB AND NO TREATMENT | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=1586) | | None (N=736) | |
| Cure | 800 | (50.4%) | 12 | (1.6%) |
| 95% C.I.: Cure | 48.8% (46.1%, 51.5%) | | | |

| TABLE 23: PUBLISHED DATA ON SET A: CYST RESPONSES OF PATIENTS WITH ALB AND PRZ | | | | |
|---|---|---|---|---|
| Outcome | ALB (N=1586) | | PRZ (N=1208) | |
| Cure | 800 | (50.4%) | 763 | (63.2%) |
| 95% C.I.: Cure | -12.7% (-16.5%, -9.0%) | | | |

Tables 24 and 25 present adverse event rates of headache, and nausea and/or dizziness which are considered most commonly reported adverse experiences following the treatment of NCC. The rates with ALB are lower than the rates with PRZ, however, statistical significance is only detected in headache on Set B.

| TABLE 24: PUBLISHED DATA ON SET A: ADVERSE EVENT RATES FOLLOWING THE TREATMENT OF NCC | | | | | |
|---|---|---|---|---|---|
| outcome | ALB (N=78) | | PRZ (N=76) | | P-value Fisher's exact test |
| Headache | 43 | (55.1%) | 49 | (64.5%) | 0.254 |
| Nausea and/or Dizziness | 21 | (26.9%) | 26 | (34.2%) | 0.383 |

| TABLE 25: PUBLISHED DATA ON SET B: ADVERSE EVENT RATES FOLLOWING THE TREATMENT OF NCC | | | | | |
|---|---|---|---|---|---|
| outcome | ALB (N=120) | | PRZ (N=76) | | P-value Fisher's exact test |
| Headache | 52 | (43.3%) | 49 | (64.5%) | 0.005 |
| Nausea and/or Dizziness | 30 | (25.0%) | 26 | (34.2%) | 0.195 |

**REVIEWER COMMENT**: A number of papers did not provide safety data. In some cases safety data was only qualitative information. Treatment efficacy outcomes in these studies are evaluated in terms of changes of number or size of cysts (assessed by CT) and/or clinical response.

In order to obtain a more definitive conclusion regarding the efficacy of ALB, the reviewer performs meta analyses to the Medical Officer's pivotal publications with respect to tomographic, clinical and cyst

responses. The analyses were performed using the DerSimonian-Laird method, with study as the stratum of analysis. This approach incorporates the homogeneity test of treatment effect across studies. If the p-value from the test of homogeneity was not larger than 0.15, the studies are not considered to be combinable. It should be noted that this method treats each publication independently.

Table 26 shows the results of meta analysis of data in Set A by the DerSimonian-Laird method. Tests of the homogeneity demonstrate that ALB-no treatment studies regarding tomographic response for cure/improvement rate and cyst response for cure rate, and ALB-PRZ studies regarding clinical and cyst responses for cure rate are heterogeneous. Mean difference of ALB minus no treatment in cure rate regarding tomographic response is 63.6%. Mean difference of ALB minus PRZ in cure rate regarding tomographic response is 20.4%. Mean difference of ALB minus PRZ in cure/improvement rate regarding tomographic and clinical responses, respectively, are 5.8% and 11.5%.

With respect to both tomographic and clinical responses, meta analysis of the Medical Officer's pivotal publications demonstrates that ALB therapy is superior in efficacy to no treatment and equivalent to PRZ therapy in the treatment of NCC.

**TABLE 26**: PUBLISHED DATA ON SET A: COMBINED RESULTS BY META ANALYSIS OF RESPONSES FOLLOWING TREATMENTS OF NCC

| Studies | D.F. | P-value of Homogeneity Test | Standard Error | Mean Rate Difference and C.I. |
|---|---|---|---|---|
| Cure Rate of Tomographic Response | | | | |
| ALB - None | 4 | 0.464 | 0.042 | 63.6% (55.4%, 71.7%) |
| ALB - PRZ | 3 | 0.152 | 0.078 | 20.4% (5.1%, 35.8%) |
| Cure/Improvement Rate of Tomographic Response | | | | |
| ALB - None | 4 | 0.030 | 0.051 | N.A. |
| ALB - PRZ | 3 | 0.601 | 0.041 | 5.8% (-2.3%, 13.8%) |
| Cure Rate of Clinical Response | | | | |
| ALB - PRZ | 2 | 0.021 | 0.107 | N.A. |
| Cure/Improvement Rate of Clinical Response | | | | |
| ALB - PRZ | 2 | 0.985 | 0.043 | 11.5% (3.0%, 19.9%) |
| Cure Rate of Cyst Response | | | | |
| ALB - None | 3 | 0.052 | 0.034 | N.A. |
| ALB - PRZ | 2 | <0.001 | 0.103 | N.A. |

**REVIEWER COMMENTS**: Most of the studies in the pivotal publications were conducted by physicians with a personal interest in NCC. In some studies, ALB and PRZ were compared under similar treatment durations, some were not, some were ALB open label studies. Most of the studies did not apply the same dosage regimens, treatment comparators and different entry criteria. Interpretation of these data is

problematic and must be taken with care since NCC is a complex disease, varying widely in its presentation, the methods adopted to monitor disease progress vary (radiological and clinical) and most of these studies involved only a small number of patients. Therefore, statistical evaluation based on pooling of the data is not reliable. It is more appropriate to draw conclusions based on the results of meta analysis.

## II.2.B. COMPASSIONATE USE EXPERIENCE IN THE US

### II.2.B.1. STUDY DESIGN

Before this retrospective study, there had not been any previous attempt made to locate and follow up patients with NCC treated under the compassionate use IND process in the US. Almost all compassionate use data in the US were obtained retrospectively. The collection of date was conducted by physicians on patients issued with INDs during January 1991 to June 1994. The last date of entry for a patient of record was in September 1994, and patients were given adequate time for follow-up assessments.

The records of drug supplies dispatched under INDs from the Applicant in the UK to individual physicians in the US were obtained. Details of physicians who received drug for the treatment of patients with NCC were recorded. A case record form to collect relevant data for efficacy and safety evaluation was devised, but the number of responders was limited, as well as follow-up responders.

There were 158 physicians who had treated 169 patients under compassionate use of ALB were conducted. Forty-four (27.8%) physicians responded with data and 51 (30.2%) of their patients had data which were considered to be evaluable. There were 25 males and 26 females, whose mean age was 32.2±15.3 years, ranging 2~64 years. There was no apparent difference in age between the genders (male 32.0±11.7 years, female 32.3±18.4 years).

Cysts were located in the central nervous system in all cases. The majority of lesions were newly diagnosed (28; 54.9%), but 6 patients were recorded as having recurrent cysts (after either surgery or chemotherapy), 2 patients had new and recurrent cysts and 15 patients had no data.

Fourteen patients had previous surgery, but 33 patients no surgery and 4 not stated.

Twenty-one patients had previously received PRZ, 2 patients ALB and 2 patients both drugs. Only 9 patients had no previous drug therapy and 17 patients had no data.

The majority of patients (40; 78.4%) received a single course of treatment although 5 received 2 courses and one each, 3, 4, and 6 courses. No data was recorded for 3 patients.

Duration of treatment was ranged widely. The majority (22; 43.1%) received 28 to 30 days of treatment, while 7 received 7~8 days, 9 received 14~15 days, 5 received 21 days. One patient reportedly received 60 days continuous treatment and no data were recorded for 7 patients. Moreover, the dose used varied even more. Although the greatest number of patients received doses of 800 mg/day (27; 52.9%) while 2 patients received doses of 300 mg/day, 3 patients received 400 mg/day, 5 patients received 600 mg/day and 8 patients received more than 800 mg/day. No data was recorded for 6 patients.

The duration of follow-up to the time of data collection averaged 8.7±9.3 months with a range of 0.25~36 months.

The results of treatment were assessed by both radiological and clinical responses. The average time to outcome assessment was 4.9 ± 6.3 months. Thirty-nine patients had evaluable radiological responses and 46 patients had evaluable clinical responses.

### II.2.B.2. RESULTS

Tables 27 and 28 show radiologic and clinical responses of patients following treatment with ALB, respectively. The clinical response gives a better profile of ALB efficacy in the treatment of NCC.

**TABLE 27**: THE US COMPASSIONATE USE: RADIOLOGICAL RESPONSES OF NCC PATIENTS WITH ALB

| outcome | Patient (N=39) |
|---|---|
| cure or improvement | 29 (74.4%) |
| cure | 6 (15.4%) |
| improvement | 23 (59.0%) |
| no change or worse | 10 (25.6%) |

**TABLE 28**: THE US COMPASSIONATE USE: CLINICAL RESPONSES OF NCC PATIENTS WITH ALB

| outcome | Patient (N=46) |
|---|---|
| cure or improvement | 44 (95.6%) |
| no change or worse | 2 (4.3%) |

REVIEWER COMMENTS: This retrospective evaluation of radiological and clinical response to ALB treatment of NCC provides evidence of beneficial effect at both levels. However, the acquired data was so little compared to the potentially large and varied population available.

## II.2.C. CLINICAL STUDY IN PERU

### II.2.C.1. STUDY DESIGN

The objective of this prospective, randomized, double blind study was to compare the efficacy and safety of ALB 800 mg/day for 7 days with 800 mg/day for 14 days in the treatment of NCC. Peruvian patients were randomized to either 7 or 14 days of ALB therapy and followed by clinical EEG and CT criteria for at least three months (n=50), or one year (n=36) after treatment as overall determinants of treatment efficacy.

Fifty-five patients from different public and private clinics in Peru, diagnosed with NCC on the basis of a positive CT scan with active lesions and a positive serological test, were consecutively included in the study. Patients with inactive lesions were excluded as were pregnant or lactating women. Patients were dropped from the analysis if they refused to follow the study protocol, or if they did not return on three months follow-up visit. The Applicant mentions the nature of the heterogeneity of the patient population.

Informed consent was obtained from all patients. Patients were allocated to one of two treatment groups using a previously assigned randomized schedule. Group A received ALB 400 mg bid orally for 14 days, while Group B received ALB 400 mg bid orally for 7 days, followed by 7 days of a similar appearing placebo. Both groups received dexamethasone 1.5 mg tid given orally for 5 days, tapered to 0.5 mg tid in days 6 and 7 and then withdrawn. Patients receiving antiepileptic drug therapy were maintained on their current drug regimen. All patients were hospitalized during treatment and had clinical follow-up visits.

## II.2.C.2. RESULTS

Fifty (initially 55) patients who were originally randomized and treated completed three months evaluation, with 25 patients in each treatment. Table 29 displays the assessment of comparability of two ALB treatment groups with respect to demographic characteristics and baseline disease characteristics. Table 30 shows the main presenting symptoms in patients. All characteristics are comparable between two treatment groups except significant difference in baseline massive infection findings.

Table 31 shows adverse events and neurological symptoms during treatment of ALB in 50 Peruvian patients with NCC. Most patients 46 (92.0%) complained of headache during treatment. No patient died during the 15 days of therapy, but 2 patients died during the first year of follow-up.

Tables 32 and 33 display CT evaluation of the treatment effect at three months and one year follow-up, respectively. Group A and Group B are not significantly different in treatment efficacy with respect to cyst response at three months follow-up. For global response, due to the sample size in groups A and B, it is plausible that an underlying cure rate difference could exist and go undetected. However, there are significant differences in treatment efficacy with respect to cyst response at one year follow-up, and the treatment effect favors Group B.

TABLE 29: CLINICAL STUDY IN PERU: COMPARATIVE CHARACTERISTICS BETWEEN TWO ALB TREATMENT GROUPS (N=50)

| Characteristics | | Treatment Group | | Two Sided |
|---|---|---|---|---|
| | | A-14 days(n=25) | B-7days (n=25) | P-value |
| General | Male | 14 | 13 | NS |
| | Female | 11 | 12 | |
| | Age | 29.4±15.8 | 39.7±17.7 | NS |
| Antecedents | Pig raising | 17 | 16 | NS |
| | Teniasis | 11 | 10 | NS |
| Symptoms | History of seizure | 19 | 22 | NS |
| | Intracranial hypertension | 4 | 3 | NS |
| Baseline CT Findings | Cysts | 3.3±3.1 | 3.9±3.7 | NS |
| | Nodular enhancing lesions | 0.4±0.7 | 0.7±1.3 | NS |
| | Massive infections | 2.1±3.1 | 6.4±8.6 | <0.05 |

**TABLE 30**: CLINICAL STUDY IN PERU: MAIN PRESENTING SYMPTOMS AT STUDY ENTRY (N=50)

| Symptom | Patients |
|---|---|
| Headache | 45 (90%) |
| Seizures | 41 (82%) |
| Cranial nerve deficit | 19 (38%) |
| Memory loss | 14 (28%) |
| Sensitive | 12 (24%) |
| Motor deficit | 12 (24%) |
| Intracranial hypertension | 8 (16%) |
| Subcutaneous nodules | 2 (4%) |

Note: In some cases there was more than one presenting symptom.

**TABLE 31**: CLINICAL STUDY IN PERU: ADVERSE EFFECTS AND NEUROLOGICAL SYMPTOMS DURING TREATMENT (N=50)

| Symptom | Patients |
|---|---|
| Headache | 46 (92%) |
| Seizure | 12 (15%) |
| Nausea | 3 (6%) |
| Abdominal pain | 4 (8%) |
| Diarrhoea | 4 (8%) |
| Other symptoms | 5 (10%) |
| Death | 0 (0%) |

Note: There are 19 (38%) patients presented adverse effects except headache.

| TABLE 32: CLINICAL STUDY IN PERU: THREE MONTHS CT EVALUATION OF NCC FOLLOWING ALB THERAPY | | | | |
|---|---|---|---|---|
| Group | Cyst Evaluation | | Global Evaluation | |
| | Basal | Cure | Admission | Cure |
| Group A (14 days) | 66 | 51 (77.3%) | 20 | 8 (40.0%) |
| Group B (7 days) | 66 | 52 (78.8%) | 17 | 6 (35.3%) |
| Fisher's P-value<br>95% C.I. | 1.000<br>-1.5% (-17.2%, 14.1%) | | 1.000<br>4.7% (-32.0%, 41.4%) | |

| TABLE 33: CLINICAL STUDY IN PERU: ONE YEAR CT EVALUATION OF NCC FOLLOWING ALB THERAPY | | |
|---|---|---|
| Group | Cyst Evaluation | |
| | Basal | Cure |
| Group A (14 days) | 33 | 19 (57.6%) |
| Group B (7 days) | 40 | 33 (82.5%) |
| Fisher's P-value<br>95% C.I. | 0.036<br>24.9% (-48.3%, -1.6%) | |

# III. SUMMARY AND CONCLUSIONS
## (Which May be Conveyed to the Sponsor)

In this NDA submission, there are 5 "studies" (published data and compassionate use experiences) concerning hydatid cyst disease including E.G. and E.M. infections, and 3 "studies" (published data, compassionate use experiences and clinical trial) concerning NCC. The Applicant seeks approval of the therapy of ALB for the treatment of the diseases. The data to support the safety and efficacy of ALB for the treatment of hydatid cyst disease and NCC were based primarily on accumulated clinical reports from small numbers of patients and not on formal large, well controlled and multicentered clinical trials. The major flaws of this application are as follows:

1. The Applicant fails to provide independent, well controlled trials to support the Applicant's claim that ALB is of efficacy and safety in the treatment of hydatid disease and NCC.

2. The studies were not consistent in design; they interpreted the data in a different way based on distinct criteria of measuring efficacy endpoints; safety information was insufficient and adverse events were poorly recorded; subset analyses of demographic data were impossible due to lack of the data.

3. The comparators (MEB, FLUZ, and PRZ) used in the studies have not been approved for the treatments of hydatid disease and NCC in the US.

4. There were no formal statistical analyses of the clinical data included in the NDA, only descriptive statistics were used.

5. Most of the studies contained small numbers of evaluable patients or provided limited evaluable data which hinder to draw meaningful statistical conclusions.

6. For the treatment of hydatid cyst disease, the patients with single cysts are more amenable to treatment than those with multiple cysts. For the treatment of NCC, the patients with heavy infections behave differently from those with small numbers of cysts. However, these factors were not always considered in the analyses.

## III.1. HYDATID CYST DISEASE

*The following statements pertain to Published Data with particular focus on the 16 papers considered by the Medical Officer as pivotal publications, in which there are 15 papers concerning E.G. infection and 2 papers concerning E.M. infection:*

Treatment durations were different with the most common pattern of administration being 28~30 day cycles of treatment for E.G. therapy, and lasting longer for E.M. therapy. The majority of patients received ALB treatment at a dose ranged from 10 to 15 mg/kg/day for 30 days or more. The duration of follow-up varied widely and ranged between 8 weeks to years. The comparators used in these studies were no treatment or MEB or FLUZ. The principal treatment regimens of MEB and FLUZ were 30~75 mg/kg/day and 50 mg/kg/day, respectively.

The descriptive statistics of the 16 pivotal studies show that the cure rates varied widely among studies, regarding global and cyst responses.

Meta analysis is applied to compare ALB versus MEB in the treatment of E.G. infection. With respect to global response, there are 5 papers of ALB-MEB studies available for meta analysis; with respect to cyst response, there are 3 papers. The results of meta analysis demonstrate that ALB therapy is superior in efficacy to MEB therapy in the treatment of E.G. infection. The mean difference of ALB minus MEB in cure rate is 13.6% with a confidence interval of 3.5% and 23.6%.

*The following statements pertain to Compassionate Use Experience in the US*:

The dosage of 800 mg/day of ALB was commonly used and lasted for 28 to 30 days. The duration of follow-up ranged from 2 weeks to 9 years with an average 26.3 months.

1. The integrated results show that 52.9% of E.G. cysts were cured/improved and 11.8% of E.G. cysts were cured following ALB treatment.

2. The integrated results show that 40.0% of E.M. cysts were cured/improved and 30.0% of E.M. cysts were cured following ALB treatment.

*The following statements pertain to Compassionate Use Experience in the UK*:

The dosage of 800 mg/day of ALB was commonly used for cycles of 28 days and for 3 cycles.

1. The integrated results show that 76.1% of cysts and 79.4% of patients were cured/improved following the treatment of E.G. with ALB regarding cyst and global responses, respectively; 35.1% of cysts and 28.5% of patients were cured following the treatment of E.G. with ALB regarding cyst and global responses, respectively.

2. The integrated results show that 25.0% of cysts and 21.4% of patients were cured/improved following the treatment of E.M. with ALB regarding cyst and global responses, respectively; 13.9% of cysts and 7.1% of patients were cured following the treatment of E.M. with ALB regarding cyst and global responses, respectively.

*The following statements pertain to Australia Compassionate Use Data*:

The dosage of 800 mg/day of ALB was commonly used and lasted for 1 to 26 months.

1. The integrated results show that 47.2% of cysts were cured/improved and 13.9% of cysts were cured following the treatment of E.G. with ALB.

2. The rate of at least one adverse event is 16.9% following ALB treatment of hydatid disease. ALB treatment of hydatid patients has a significantly lower withdrawal rate due to adverse events than that of non-hydatid patients (1.7% versus 6.7%), supported by Fisher's exact test (p-value=0.030). However, most of the withdrawn non-hydatid patients had AIDS.

*Pertaining to French Pharmacovigilence, neither efficacy nor safety statements can be made due to the paucity of information.*

***REVIEWER CONCLUSIONS: Based on the analysis of the treatment of hydatid disease with E. G. infection, the results of meta analysis demonstrate that ALB therapy has an efficacy advantage over MEB therapy. However, the results do not sufficiently provide comprehensive evidence to confirm ALB as an effective and safe medicine in this indication due to the weakness of the nature of these studies. Upon considering the particularity of ALB for orphan drug status, the reviewer does not preclude to endorse this application before soliciting standpoints of clinicians.***

***Due to very limited data available relating to the treatment of hydatid disease with E. M. infection, the statistical conclusion toward the efficacy and safety profiles of ALB therapy for this indication cannot be reached.***

## III.B. NEUROCYSTICERCOSIS

*The following statements pertain to Published Data with particular focus on the Medical Officer's pivotal analysis groups*:

Most of the patients followed treatment with ALB 15 mg/kg/day for 30 days or more. Duration of treatment varied widely. The duration of follow-up ranged between 2 weeks to 14 years. The most common treatment regimen of PRZ was 50 mg/kg/day for 15 days.

1. The results of meta analysis demonstrate that mean difference of ALB minus no treatment in cure rate regarding tomographic response is 63.6% with confidence intervals of 55.4% and 71.7%. Mean difference of ALB minus PRZ in cure rate regarding tomographic response is 20.4% with confidence intervals of 5.1% and 35.8%. Mean difference of ALB minus PRZ in cure/improvement rate regarding tomographic and clinical responses, respectively, are 5.8% with confidence intervals of -2.3% and 13.8%, and 11.5% with confidence intervals of 3.0% and 19.9%, respectively. The above results demonstrate that ALB therapy is superior in efficacy to no treatment and equivalent to PRZ therapy in the treatment of NCC.

2. Headaches, nausea and/or dizziness are considered most commonly occurring adverse events affecting NCC patient. ALB is associated with a lower incidence rate than PRZ. In Set A, 55.1% of ALB versus 64.5% of PRZ experienced headaches, and 26.9% of ALB versus 34.2% of PRZ experienced nausea and/or dizziness. Fisher's exact test shows that there is no statistically significant difference in the adverse event rates for Set A. However, there is a statistically significant difference in headache for Set B.

*The following statements pertain to Compassionate Use Experience in the US*:

Treatment durations were variable. Most patients received treatment of ALB 15 mg/kg/day for 28 to 30 days. The duration of follow-up averaged 8.7 months.

The integrated summary shows that 74.4% and 95.6% patients are cured/improved following the treatment of NCC with ALB regarding radiological and clinical responses, respectively.

*The following statements pertain to Clinical Study in Peru*:

Patients were randomized to one of two treatment groups. Group A received ALB 400 mg bid for 14 days and Group B received ALB 400 mg bid for 7 days. Radiological scans were repeated at days 15, 90 and 360 after the initiation of treatment. Clinical follow-up visits were at the above dates as well as on days 30, 180, and 270.

No significant difference of ALB treatment efficacy between Group A and Group B was apparent in CT evaluation with respect to cyst response at three months follow-up. However, they are significantly different in treatment efficacy with respect to cyst response at one year follow-up, and the treatment effect favors Group B.

***REVIEWER CONCLUSIONS: Based on the analysis of the treatment of NCC, the results of meta analysis demonstrate that ALB therapy has an efficacy advantage over no treatment and is therapeutically equivalent to PRZ therapy. However, the results do not sufficiently provide***

***comprehensive evidence to confirm ALB as an effective and safe medicine in this indication due to the weakness of the nature of these studies. Upon considering the particularity of ALB for orphan drug status, the reviewer does not preclude to endorse this application and regulatory action will be adopted after soliciting for standpoints of clinicians.***

5/30/96

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cc:
Archival: NDA 20-666
HFD-520
HFD-520/Leissa
HFD-520/Coyne
HFD-520/Fogarty
HFD-520/Kataque
HFD-520/King
HFD-725/Harkins
HFD-725/Lin
HFD-725/Jiang
HFD-344/Thomas
Chron.
This review contains 31 pages and 33 tables.
WordPerfect 6.1/NDA20666.wpd/5-30-96

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Bio

MAY 22 1996

# CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

**NDA:** 20-666

**Submission Date:** December 8, 1995

**Product:** Albendazole CarbamateTablets 200 mg

**Sponsor:** SmithKline Beecham
Philadelphia, PA

**Type of Submission:** Original NDA **Priority Code:** 1P

**OCPB Reviewer:** Philip M. Colangelo, Pharm.D., Ph.D.

## I. SYNOPSIS

This NDA was submitted to support the use of albendazole (ABZ) 200 mg tablets for the treatment of hydatid cyst disease (HD) and neurocysticercosis (NCC), both of which are caused by larval infestations. The Human Pharmacokinetics and Bioavailibility Section was comprised solely of results from published literature studies that have been conducted primarily by investigators outside the U.S. These reports described the plasma pharmacokinetics of the pharmacologically active principle metabolite of albendazole, albendazole sulfoxide (ASOX), in both healthy volunteers and adult and pediatric patients with either HD or NCC after single and multiple doses ranging from 400 to 800 mg daily. Investigations of potential pharmacokinetic drug interactions with theophylline, cimetidine, dexamethasone, another anthelminthic drug, praziquantel, and a food effect study were included. In addition, the results from several studies of the *in vitro* hepatic metabolism of ABZ, distribution of ASOX into cyst and other tissues/fluids, and plasma concentration assay methods were also provided.

In general, the results from these studies were sufficient to gain an adequate understanding of ABZ/ASOX pharmacokinetics. However, none of the raw plasma concentration or pharmacokinetic data were available for inspection/verification from any of these literature papers. In nearly all studies, plasma ABZ concentrations were not quantifiable and the pharmacokinetic estimates for ASOX were comparable between subjects and patients. The sulfoxide metabolite attained maximal plasma concentrations within ~2 hours and has an average half-life in both subjects and patients of ~8 to 12 hours. The presence of a high fat meal increased the systemic exposure to ASOX by fold when compared to fasted conditions. The plasma protein binding of ASOX was ~70%, and plasma concentrations of ASOX were reported to be fold higher than those in cysts and fold higher than those in

cerebrospinal fluid. Bioconversion of ABZ to ASOX by the liver appeared to be rapid and extensive, as evidenced by the results of *in vitro* studies in both rat and human microsomal preparations. In rat intestinal preparations, the contribution of intestinal metabolism to ASOX was minimal (~2 to 3%) compared to that of the liver. A route of ASOX excretion appeared to be biliary, with urinary excretion of ASOX accounting for only ~1% of the administered albendazole dose over a 24-hour period and no ABZ detected in human urine. Fecal excretion of either ABZ or ASOX was not studied in any of the literature reports.

No significant alterations in ASOX pharmacokinetics were apparent with coadministration of albendazole and either intravenous aminophylline or oral cimetidine. However, coadministration with either oral praziquantel or oral dexamethasone substantially increased systemic exposure to ASOX, although no side effects or biochemical abnormalities were noted with the combination of albendazole and praziquantel.

The sponsor submitted results of *in vitro* multi-point dissolution testing between the tablet manufactured at the China facility, which was used for compassionate use for HD and NCC in the U.S., and the formulation to be manufactured and marketed in the U.S. The two formulations are identical in composition and dissolution for the to be marketed U.S. formulation was comparable to that of the China tablet (i.e., Q min for the to be marketed U.S. tablet vs 94% for China tablet). The sponsor also performed dissolution testing between the to be marketed U.S. formulation and the tablet manufactured at its French facility, which was used for compassionate use in the World Health Organization studies for HD and in the NCC clinical trial conducted in Peru. Dissolution at minutes for the French (i.e., Q %) and to be marketed U.S. formulations were acceptable.

## II. RECOMMENDATION

The literature studies submitted for the Human Pharmacokinetics and Bioavailability Section of this NDA and *in vitro* dissolution test results have been reviewed and were found to be acceptable to support the use of albendazole tablets in patients with hydatid cyst disease and neurocysticercosis. Comments 1 through 7 deal with the Proposed Labeling and should be conveyed to the sponsor and adequately addressed by the sponsor.

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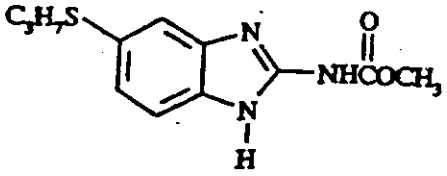
## III. BACKGROUND

Albendazole is a benzimidazole carbamate with broad spectrum anthelmintic activity. The sponsor has submitted this NDA for the use of albendazole 200 mg tablets in the treatment of (1) hydatid cyst disease (HD) caused by larvae of *Echinococcus granulosus* and *Echinococcus multilocularis* and (2) neurocysticercosis (NCC) caused by larval *Taenia solium*. Since the incidence of these diseases in the U.S. is .. considered to be rare, i.e., less than 1000 cases/year, the sponsor has requested Orphan Drug Designation for each of these indications. In order to qualify for Orphan Drug Status, *21 CFR 316* indicates that the drug is intended to treat a rare disease or condition, defined as affecting fewer than 200,000 people. The drug has been available in Europe and other international markets as a 200 mg tablet (Zentel®) for the treatment of intestinal parasites since 1982. A higher strength 400 mg tablet (Eskazole®) became available in Europe in 1992 for the treatment of HD. Albendazole tablets manufactured at the sponsor's facilities in France and China have been supplied to the U.S. for the treatment of HD and NCC on a compassionate use basis from 1984 up to the present time. The French made tablet was also used in the NCC clinical trial conducted in Peru. The sponsor currently does not have a U.S. tradename for the clinical use of albendazole tablets. In 1989, the suspension (Valbazen®) was approved for veterinary use in the U.S. for the treatment of animal helmintic infections.

## IV. DRUG CHARACTERISTICS AND DOSAGE FORMULATION

### 1. Physical and Chemical Characteristics

Albendazole Chemical Structure:




Molecular Weight: 265.33

Solubility: Albendazole is hydrophobic and practically insoluble in water (i.e, <1 mcg/ml at pH 7.4). It is slightly soluble in methanol, chloroform, ethylacetate, and acetonitrile.

$pKa_1 = 2.68\ Ka_1$; $pKa_2 = 11.83\ Ka_2$

## 2. Tablet Formulations and Dissolution

Albendazole tablets have been supplied to the U.S. for the treatment of HD and NCC on a compasionate use basis from the sponosr's manufacturing facilities in France and China. A comparison of the 200 mg tablet formulations manufactured at the sponsor's France and China facilities and the to be marketed formulation in the U.S., manufactured at the sponsor's Puerto Rico facility, are provided in the following table:

**FORMULATION COMPARISONS**

| *Component* | **SB-U.S. (mg/tablet)** | **SB-China (mg/tablet)** | **SB-France (mg/tablet)** |
|---|---|---|---|
| *Actives:* Albendazole, USP | 200.0 | 200.0 | 200.0 |
| *Inactives:* | | | |
| Lactose Monohydrate | | | |
| Starch | | | |
| Povidone | | | |
| Na Lauryl Sulfate | | | |
| Na Saccharin | | | |
| Microcrystalline Cellulose | | | |
| Na Starch Glycolate | | | |
| Mg Stearate | | | |
| Opadry Clear Film Coating | | | |
| Carnauba Wax | | | |
| | | | |
| **Total (Theoretical)** | | | |

*Removed after granulation process

The composition of all three fromulations are identical, with the exception of minor differences in the amounts of Mg stearate and film coating for the tablets manufactured at the France facility.

The sponsor conducted comparative multi-point dissolution testing between three qualification batches of the to be marketed U.S. tablets (X4-4AL, X1-5AL, X2-5AL) and the tablet manufactured at the China facility, identified as pivotal bioavailability batch

X94-115 (Lot #Z9312223), to support bioequivalence between the two formulations. This tablet was used in the U.S. for the treatment of HD and NCC on a compassionate use basis from March, 1994 to July, 1994. The sponsor also performed dissolution testing between the same to be marketed U.S. formulations and the tablet manufactured at its French facility. This tablet was used from October, 1984 to December, 1992 for compassionate use in the World Health Organization studies for HD and also in the NCC clinical trial conducted in Peru. The dissolution specification for the tablets is NLT % Q in minutes. The mean data are as follows:

**MEAN % DISSOLVED***

| *Tablet Batch/Lot* | 0 min | 10 min | 20 min | 30 min | 40 min |
|---|---|---|---|---|---|
| X94-115 (China) | 0 | 78 | 90 | 94 | 96 |
| Lot 640 (France) | 0 | 79 | 91 | 95 | 97 |
| X4-4AL (U.S. Qualification) | 0 | 90 | 95 | 97 | 98 |
| X1-5AL (U.S. Qualification) | 0 | 80 | 95 | 98 | 99 |
| X2-5AL (U.S. Qualification) | 0 | 72 | 89 | 93 | 94 |

*USP apparatus 2 (paddle) at 50 rpm in 900 ml 0.1M HCl at 37°C

The data showed comparable *in vitro* dissolution profiles for both clinical and the to be marketed formulations.

## V. LITERATURE REPORT SUMMARIES

The Human Pharmacokinetics and Bioavailability Section to support the use of albendazole for the treatment of hydatid cyst disease (HD) and neurocysticercosis (NCC) was comprised solely of published literature reports which covered five general areas of study. A complete bibliography of the references submitted by the sponsor under Section 6 is provided in **Appendix 2** (available upon request from OCPB). The pharmacokinetic parameters in healthy volunteers and patients are summarized in Tables I through IV of **Attachment 1, p 13**. Brief synopses of these reports are provided below for each of the five areas.

### 1. Analytical Methods

Five papers were submitted that focused on the separation and quantification of albendazole (ABZ) and its major metabolites: albendazole sulfoxide (ASOX) and albendazole sulfone (ASON) in plasma and cerebrospinal fluid (CSF) of humans and other animal species. The sulfoxide metabolite is the primary and pharmacologically active species of interest since it has been postulated that albendazole undergoes rapid and extensive biotransformation to ASOX before reaching the systemic circulation. Four additional papers,

which reported on the pharmacokinetics of ABZ and ASOX in healthy volunteers and patients, also provided analytical information under this section. An HPLC method with ultra-violet (UV) detection was employed in all studies, but the extent to which the method was validated varied between reports. Although an HPLC-UV method was validated by the sponsor, this method was apparently not used in any of the published reports included under Section 6. A total of 7 individual reports were used as analytical references among 9 clinical pharmacokinetic papers.

In most cases, the limit of detection (LOD) and/or lower limit of quantitation (LLOQ) for ABZ, ASOX and ASON were reported. The LLOQ ranged from ng/ml for ASOX in plasma across reports. The precision and accuracy of quality control samples, when reported, were within acceptable limits (i.e., less than ± 15%). Sample stability (i.e., freeze-thaw cycles and in-process) was generally not addressed by the reports.

**2. Pharmacokinetics in Normal Healthy Subjects**

Four reports of the pharmacokinetics of ABZ, ASOX, and ASON in young healthy subjects were submitted. All involved single dose tablet administration of 400 mg albendazole and one of these reports also included administration of 400 mg albendazole as a suspension. Following oral administration, plasma concentrations of albendazole were non-quantifiable in all studies, and thus, only the pharmacokinetics of the sulfoxide and sulfone metabolites have been described. In general, plasma concentrations of ASON were lower than those of ASOX (i.e., by %). The mean Cmax of ASOX following administration of albendazole tablets under fasted conditions was relatively low, at μg/ml. Maximum ASOX plasma concentrations were achieved within ~2 hours and the apparent elimination half-life ranged between 8 to 11 hours after single 400 mg ABZ doses. The total variability (%CV) for Cmax and AUC was high for both parameters, averaging ~40% (range %) and % (range %), respectively. One report of similar ASOX Cmax and AUC estimates between the 200 mg albendazole tablet and suspension, studied in crossover fashion, suggested (but did not definitively prove) that the poor oral availability was not formulation related, but was due to the low aqueous solubility of albendazole. Determination of ABZ/ASOX absolute bioavailability is not possible, appparently due to difficulties in formulating an intravenous solution.

One report examined dose proportionality in male patients with hydatid disease between single 800 mg and 1200 mg ABZ doses for 3 days. Only the mean AUC(0-72) was reported and the increase in this parameter for the respective doses (i.e., 14.3 mg.hr/l and 20.9 mg.hr/l) suggested dose proportionality over this dosage range.

The authors of one paper reported (as an unpublished observation) that the plasma protein binding of ASOX was ~70%. Besides plasma, the sulfoxide metabolite has been detected in bile, liver, and lung. Several reports of albendazole administration in patients with either HD or NCC have found detectable levels of ASOX in cyst walls, cyst fluid, and cerebrospinal fluid (see Section 4 below for details).

Albendazole appeared to be rapidly and extensively metabolized primarily by the liver following oral administration. Five metabolites have been identified in the urine of humans by thin layer chromatography in one paper, and of these five, the sulfoxide and sulfone metabolites predominate. The major pathways of albendazole metabolism appear to be oxidation of the sulfur atom, hydroxylation of the benzene ring, and hydrolysis of the carbamate group. These biotransformations appear to be catalyzed by the flavin-dependent monooxygenase (FMO) and CYP450 enzyme systems in the liver (see also Section 6 for details) A schematic of ABZ metabolism is provided as Attachment 2, p 14, where metabolites A (ASON), B, C (ASOX), I, and J are the 5 principal metabolites that have been postulated in human urine.

It appeared that urinary excretion was a minor route of ASOX elimination, with one paper reporting <1% of the administered ABZ dose excreted over a 24 hour period. Likewise, renal clearances of ASOX have been reported to be low in both healthy subjects ( ml/min) and patients ml/min). Albendazole has not been detected in human urine. The results from one report in patients with HD suggested that biliary elimination may be a route of ASOX elimination since plasma and biliary levels were comparable.

Determination of ABZ, ASOX, or ASON excretion in the feces was apparently not performed in any of the reports.

No formal pharmacokinetic gender analyses were reported. Although the results in healthy young adults primarily included males, the limited data available in female patients suggested that the pharmacokinetics of ASOX were comparable to those in males.

### 3. Food Effects

The effects of food on albendazole pharmacokinetics was described in three reports of healthy subjects and patients with either HD or NCC. It appeared that the presence of a high fat breakfast (estimated fat content 40 g) increased the systemic availability of ASOX, as evidenced by increases in Cmax and AUC by fold. The conclusion drawn from these papers was that albendazole should be administered with food if the goal of therapy is to treat systemic infections.

### 4. Pharmacokinetics in Patients with Hydatid Cyst Disease (HD) and Neurocysticercosis (NCC)

Nine pharmacokinetic reports in adult patients and one report in pediatric patients with hydatid cyst disease were provided. Three reports were provided for patients with neurocysticercosis. Of these 13 reports, 8 provided plasma pharmacokinetic parameters and concentrations of ASOX and/or ASON in various biological matrices collected from these patients. Following either single or multiple oral doses to either HD or NCC patients, the concentration of ABZ in plasma was non-quantifiable. Under fasting conditions, the plasma concentrations, Cmax, and AUC of ASOX in patients were, on average, comparable to those determined for healthy subjects. The apparent elimination half-life in patients was also similar to that determined in subjects, ranging from 8 to 12 hours. In one report, patients with biliary obstruction secondary to hydatid cyst disease had significantly higher ASOX Cmax fold increase), Tmax fold increase), and AUC fold increase) compared to those patients without obstruction. Elimination of ASOX was also prolonged in these patients with a mean apparent half-life of 31.7 hours. This provided further evidence for the biliary route as a pathway of ASOX elimination.

In general, plasma concentrations of ASOX in patients are higher than those attained in cyst fluid and CSF. Concentrations of ASOX in plasma have been reported to be fold higher than those in cysts and fold higher than those in CSF.

The potential for albendazole to induce its own metabolism and inhibit the metabolism of other compounds after repeated oral administration to HD patients was explored by the authors of one paper. Following a second 4-week treatment cycle with ABZ (200 mg tid), plasma concentrations of ASOX in HD patients were ~20% lower than observed during the first treatment cycle which suggested an induction phenomenum. In the same study of HD patients, a reduction (~30%) in aminopyrine N-demethylase activity was observed, using an aminopyrine breath test, during a 4-week ABZ treatment cycle as compared to a drug free interval. These latter results suggested moderate inhibition of aminopyrine metabolism (a CYP1A substrate), however, no pharmacokinetic interaction was observed with coadministration of ABZ and theophylline (see **Section 5** below for details). The *in vivo* results of induction appeared to be consistent with other *in vivo* animal and *in vitro* metabolism reports suggesting induction of CYP1A by albendazole (see Section 6 below for details). This induction phenomenum has, in part, prompted the recommendation of cyclical treatment with ABZ.

### 5. Pharmacokinetic Drug Interactions

Four reports were submitted investigating potential pharmacokinetic interactions when albendazole was coadministered with other drugs. In one paper, the pharmacokinetics of theophylline (given as intravenous aminophylline) was studied following a single 400 mg ABZ dose to 6 healthy subjects. No significant alterations were noted in theophylline systemic clearance, volume of distribution, or half-life by albendazole.

A second paper was a preliminary report on the effects of cimetidine on ASOX concentrations in plasma, cyst fluid, and bile following 4-week courses of either ABZ alone (20 mg/kg/day given bid) compared to ABZ (20 mg/kg/day given bid) given with cimetidine (10 mg/kg/day) in HD patients. No significant differences were detected between plasma ASOX levels either with or without cimetidine (sampled 4 hours after dose administration), however, significant increases were detected in ASOX concentrations in bile and cyst fluids upon coadministration with cimetidine. The mechanism for these increases was not apparent from this study.

The third paper investigated the pharmacokinetics of ASOX and a single 40 mg/kg dose of praziquantel (another cysticidal drug) when ABZ was coadministered (as a single 400mg dose) with this drug to healthy subjects since the combination may be beneficial in the treatment of mixed infections with helminths. The results indicated that the pharmacokinetics of praziquantel were not effected by coadministration with albendazole. However, Cmax and AUC of ASOX were substantially increased -fold, respectively) with praziquantel coadministration, but Tmax and half-life of ASOX remained unchanged. Despite the increase in systemic exposure to ASOX, no problems with side effects or any biochemical abnormalities were reported.

The fourth paper investigated the potential interaction between coadministration of albendazole (15 mg/kg/day tid) and dexamethasone (8 mg tid) to NCC patients. The mean steady-state plasma concentrations of ASOX were increased by a mean of 56% in the presence of dexamethasone as compared to ABZ given alone. In addition, plasma levels of parent ABZ were detectable in 4 of 8 patients receiving ABZ and dexamethasone in combination compared to no patients when ABZ was given alone. These results were in contrast to those reported for the combination of praziquantel and dexamethasone, where plasma concentrations of praziquantel were decreased by % in the presence of dexamethasone.

**6. *In Vitro* Metabolism**

A total of 7 literature reports were provided which studied the *in vitro* metabolism of albendazole: 4 papers investigated hepatic ABZ metabolism by rat liver microsomes, 2 papers investigated rat intestinal ABZ metabolism, and one paper investigated ABZ metabolism by human microsomes and human hepatoma cell lines. The results from both the human and rat hepatic microsome reports indicated that ABZ was extensively metabolized, first to the sulfoxide, and then subsequently to the sulfone metabolites. In both species, it appeared that the biotransformation to ASOX may involve both FMO and CYP450, whereas formation of ASON may be primarily catalyzed by CYP450, namely the CYP1A subfamily. In addition, the results from studies in rats suggested that albendazole induces its own metabolism via the sulfonation pathway rather than the sulfoxidation pathway. In rats, treatment with ABZ for 10 days (10.6 mg/kg) resulted in a reduction of ASOX AUC by % and an increase of ASON plasma concentrations as compared to single dose ABZ administration. There was also *in vitro* evidence of induction of CYP1A in rat hepatic microsomes following ABZ pretreatment. The results from the two preliminary rat intestinal papers suggested that the contribution of intestinal metabolism of ABZ to ASOX was quite small (2-3%) compared to that of the liver.

## VI. PROPOSED LABELING

See Appendix 1, p 15

## VII. COMMENTS TO BE SENT TO THE SPONSOR

**Labeling Comments:**

1. Under **PHARMACOKINETICS**, for all statements provided under the **Absoprtion, Distribution, Metabolism, Excretion,** and **Special Populations** sections that specifically reference the results from a particular literature paper(s), it is recommended that the sponsor include the number of subjects/patients that were studied in such papers (i.e., N = xx). This would be similar to what was done under the **Pharmacokinetic Drug Interactions** section. The **Special Populations** title should be added above the sections that outline results in **Renal Insuffiency, Biliary Effects, Pediatrics,** and **Elderly Patients**.

2. Under **Absorption and Metabolism**, the following changes are recommended:

   (i) *"Oral absorption appears to be enhanced when abendazole is coadministered with a fatty meal as evidence by higher (up to 8-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state."*

   Recommended Changes:
   Oral bioavailability appears to be enhanced when abendazole is coadministered with a fatty meal (estimated fat content 40 g) as evidenced by higher (up to 8-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state.

   (ii) *"Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range."*

   Recommended Change:
   Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range following ingestion of a fatty meal (fat content 43.1 g).

3. Under **Distribution**, clarification of the following statement is recommended:

   *"Mean (SD) plasma and cyst albendazole sulfoxide concentrations were 0.785±0.733 mcg/ml and 0.165±0.116 mcg/ml in patients treated for approximately for 1 month."*

   Please indicate how these mean values for abendazole sulfoxide (ASOX) plasma and cyst concentrations were determined and on what day and time following dose administration were these results obtained. From the references

paper was there evidence that the patient was treated for 1 month, with multiple samples collected over the 1 month period. In the Hurtado and Jung papers, it appeared that ASOX concentrations in plasma, cyst, and CSF were determined after 7 days of treatment, but no specific information was provided to indicate the total length of treatment, or the timing of the plasma, cyst, and CSF sample collections.

4. Under **Distribution**, the following change is recommended:

*"Limited data suggest that albendazole sulfoxide may be eliminated from cysts at a slower rate than observed in plasma."*

Recommended Change:
Limited *in vitro* and clinical data suggest that albendazole sulfoxide may be eliminated from cysts at a slower rate than observed in plasma.

5. Under **Metabolism and Excretion**, the following change is recommended:

*"Biliary elimination presumably accounts for the major portion of the elimination as evidenced by biliary concentrations of albendazole sulfoxide similar to those in achieved in plasma."*

Recommended Change:
Biliary elimination presumably accounts for a portion of the elimination as evidenced by biliary concentrations of albendazole sulfoxide similar to those in achieved in plasma.

6. Under **Pharmacokinetic Drug Interactions** with *Cimetidine*, the following change is recommended:

*"Albendazole plasma concentrations were unchanged 4 hours after dosing."*

Recommended Change:
Albendazole sulfoxide plasma concentrations were unchanged 4 hours after dosing.

7. Under **Biliary Effects**, the following change is recommended:

*"In patients with evidence of extrahepatic obstruction, both absorption of albendazole and elimination of albendazole sulfoxide were prolonged with mean values for albendazole sulfoxide Tmax and T½ of 10 hours and 31.7 hours, respectively."*

Recommended Changes:
In patients with evidence of extrahepatic obstruction (n = 5), the systemic availability of albendazole sulfoxide was increased, as indicated by a increase in Cmax and a increase in AUC. The rate of absorption/conversion and elimination of albendazole sulfoxide appeared to be prolonged with mean Tmax and T½ values of 10 and 31.7 hours, respectively. Plasma concentrations of parent albendazole were measurable in only one of the five patients.

Philip M. Colangelo 5/20/96
Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Frank Pelsor, Pharm.D., Team Leader

Biopharm Day Attendees (5/6/96): Jerry Collins, John Hunt, Hank Malinowski, Frank Pelsor

**cc:**
**Div. File - NDA 20-666**
**HFD-520 (Coyne)**
**HFD-520 (Fogarty)**
//
//
**HFD-340 (Viswanathan)**
**HFD-205 (FOI)**
**Drug file (Clarence Bott, HFD-870, PKLN RM 13B-31)**
**HFD-860 (DPE 1)**
**HFD-870 (DPE 2)**
**HFD-880 (Fleischer)**
**HFD-880 (Pelsor, Colangelo)**

# ATTACHMENT 1:

# PHARMACOKINETIC SUMMARY TABLES

## Table I

**Albendazole Sulfoxide Pharmacokinetic Parameters Following Single Dose Administration in Healthy Subjects (Data expressed as mean ± SD or range)**

| Investigator | No. Subjects | Age (years) | Dose (units) | Tmax (hours) | Cmax (ug/mL) | AUC(0-inf) (ug.h/mL) | T1/2 (hours) |
|---|---|---|---|---|---|---|---|
| Penicaut 1983 | | 21-28 | 400 mg fasted | 2.20 ± 0.09 | 0.22 ± 0.11 | 2.19 ± 1.25* | 9.04 |
| | | | 400 mg fasted | 2.40 ± 1.30 | 0.24 ± 0.13 | 1.99 ± 0.95* | 8.30 |
| | | | 400 mg SU fasted | 2.15 ± 0.74 | 0.25 ± 0.15 | 2.62 ± 1.51* | 8.22 |
| Marriner 1986 | | 18-37 | 400 mg fasted | 2.35 (1-4) | 0.20 ± 0.15 | 2.00 ± 2.77# | - |
| | | - | 400 mg fasted | - | (0.19-1.14) | 2.78 ± 2.54# | - |
| | | | 400 mg fed | - | - | 3.38 ± 2.44# | - |
| Guan 1990 | | - | 25 mg/kg fasted | 5.3 ± 1.1 | 0.40 ± 0.002 | - | 15 ± 5 |
| Homeida 1994 | | 25.7 ± SE 1.0 | 400 mg fasted | 2.6 ± 0.7 | 0.126 ± 0.015 | 1.68 ± 0.28 | 10.8 ± 2.0 |
| | | 16.4 ± SE 0.4 | 400 mg fed | 5.4 ± 0.9 | 0.698 ± 0.115 | 13.3 ± 3.3 | 11.6 ± 2.1 |

SU = Suspension; *AUC(0-24) data on file; #AUC(0-8)

## Table II

### Albendazole Sulfoxide Pharmacokinetic Parameters in Hydatid Patients
### (Data expressed as mean ± SD or range)

| Investigator | No. Patients | Age (years) | Dose/frequency (units) | Tmax (hours) | Cmax (ug/mL) | AUC(0-Inf) (ug.h/mL) | T1/2 (hours) |
|---|---|---|---|---|---|---|---|
| Lange 1988 | | 31-56 | 400 mg SD fasted | 2.25 (1-3)* | 0.22 (0.11-0.42)* | 1.09 (0.53-2.39)*# | - |
| | | | 400 mg SD fed | 3.75 (3.5-6)* | 1.31 (0.46-1.58)* | 5.46 (2.54-7.82)*# | - |
| Cotting 1990 | | 42 ± 13 | 200 mg SD fed | 2.9 ± 1.3 | 0.38 ± 0.18 | 4.51 ± 2.65 | 8.5 ± 6.0 |
| | | 51 ± 15 | 200 mg SD fed | 10 ± 4.9 | 0.83 ± 0.74 | 32.3 ± 19.9 | 31.7 ± 23 |
| | | 49 ± 15 | 200 mg SD fed | 3.8 ± 4.2 | 0.53 ± 0.30 | 6.89 ± 3.18 | 8.9 ± 2.3 |
| Morris 1985 | | 14-79 | 10 mg/kg/day MD fasted | - | (0.24-1.27) | - | (3-4) |

extrahepatic obstruction; restudied following complete or partial resolution of obstruction; *median; #AUC(0-8); SD = single dose; MD = multiple dose

## Table III

### Albendazole Sulfoxide Pharmacokinetic Parameters in Neurocysticercosis Patients
**(Data expressed as mean ± SD or range)**

| Investigator | No. Patients | Age (years) | Dose/frequency (units) | Tmax (hours) | Cmax (ug/mL) | AUC(0-inf) (ug.h/mL) | T1/2 (hours) |
|---|---|---|---|---|---|---|---|
| Jung 1992 | | 35-68 | 15 mg/kg SD fasted | 4.4 ± 1.5 | 1.34 ± 0.79 | 25.4 ± 22 | 11.3 ± 2.8 |
| Guan 1990 | | - | 25 mg/kg SD fasted | 7.7 ± 3.9 | 0.542 ± 0.195 | - | 16 ± 15 |
| Sánchez 1993 | | 18-58 | 5.0 mg/kg TID fed | 2.6 (2-6) | 0.79 ± 0.53 | 4.92 ± 3.10 | - |
| | | | 7.5 mg/kg BID fed | 2.8 (2-4) | 0.89 ± 0.43 | 8.06 ± 3.87 | - |

SD = single dose; BID = twice daily; TID = three times daily

## Table IV

### Albendazole Sulfoxide Pharmacokinetic Parameters in Pediatric Patients
### (Data expressed as mean (SD) or range)

| Investigator | No. Patients | Diagnosis | Age (years) | Dose/frequency (units) | Tmax (hours) | Cmax (ug/mL) | AUC(0-inf) (ug.h/mL) | T1/2 (hours) |
|---|---|---|---|---|---|---|---|---|
| Okelo 1993 | | HD | 6-13 | 10 mg/kg SD | 2.6 ± 0.48 | 0.38 ± 0.18 | 2.99 ± 1.60 | 7.68 ± 1.32 |

Pages 14+15
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Pharm/Tox

APR 23 1996

*REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA*
*DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, HFD-520*

**NDA#:** 20-666 (000)

**SPONSOR:** SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

**AUTHORIZED REPRESENTATIVE:**
Debra Hackett, (215) 751 - 3868

**DRUG NAME:** Albendazole Oral Tablets (200 mg)

**OTHER NAME(s):** Methyl 5-(propylthio)-2-benzimidazole carbamate

**CATEGORY:** Anti-parasitic Agent

**COMPOSITION:**

| Quantitative Composition of the Dosage Form. | |
|---|---|
| **Name of Components** | **Unit (mg/tablet)** |
| Active Components:<br>Albendazole, USP | 200.00 |
| Inactive Components:<br>Lactose Monohydrate, NF<br>Starch, NF<br>Povidone, USP<br>Sodium Lauryl Sulfate, NF<br>Sodium Saccharin, USP<br>Microcrystalline Cellulose, NF<br>Sodium Starch Glycolate, NF<br>Magnesium Stearate, NF<br>Opadry Clear YS-2-19071A<br>Carnauba Wax, NF | |
| TOTAL | |
| USP is used in the granulation and is removed in subsequent processing. | |

**RELATED SUBMISSIONS:** DMF #s

**NUMBER OF VOLUMES:** 95 Vols.

*INFORMATION CONVEYED TO THE SPONSOR:* YES (X), NO ( )

*DATE CDER RECEIVED:* December 11, 1995

*DATE ASSIGNED:* December 14, 1995

*DATE REVIEW STARTED:* February 9, 1996

*DATE 1st DRAFT COMPLETED:* April 16, 1996

*DATE REVIEW ACCEPTED BY SUPERVISOR:* April 23, 1996

*REVIEW OBJECTIVES:*
To review an original New Drug Application submitted in support of Albendazole Oral Tablets (200 mg) proposed to be used for the treatment of hydatid cyst diseases caused (by the larvae of Echinococcus granulosus), alveolar hydatid (by the larvae of Echinococcus multilocularis, and neurocysticercosis (by the larvae of Taenia solium.

*PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:*
Proposed treatment dosage is 400 mg, BID, po. Duration of treatment will be dependent on the parasitic infection being treated.

*PRECLINICAL DATA:*

*PHARMACOLOGY*

A. *Known Mechanism of Action:*
The mechanism of action of albendazole is believed to be primarily through the inhibition of intracellular microtubule formation. In addition, there is also evidence to support inhibition or uncoupling of certain parasite-specific pathways such as fumarate reductase, glucose metabolism, oxidative phosphorylation, transmembrane proton discharge, monoamine oxidase activity, or acetylcholine esterase activity.

B. *General Pharmacological Assessments:*
Albendazole is a benzimidazole carbamate related to thiabendazole and mebendazole compounds and shows activity as an anthelmintic in a similar manner. Albendazole, however, differs from the two classes of drugs in having a metabolite, albendazole sulphoxide, which is also active as an anthelmintic. This has been shown to be active against intestinal parasites through the parent molecule (action against human nematodes, some cestodes and trematodes) and through its metabolite against systemic parasites (larval nematodes and cestodes).

*REPORTED PHARMACODYNAMIC EFFECTS OF ALBENDAZOLE ARE SUMMARIZED BELOW:*

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**NEUROPHARMACOLOGY (CENTRAL AND PERIPHERAL NERVOUS SYSTEMS)**

ort/Title : November 1979/ 4-plate test (to study the anxiolytic activity of a substance)
ume/Page :
oratory :

| cies/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| use | 12M | 0, 100, 200<br><br>Meprobamate 100<br><br>Intraperitoneal<br><br>10% aqueous gum arabic | Each mouse, pretreated 30min before test, allowed to explore a box with a floor made up of four 8x11cm metal plates, 4mm apart, for 15sec. Then, when mouse passed from one plate to another, a 0.6mA current was passed through the floor for 5sec. The number of "punished passages" was measured for 12 separate one minute periods. | Meprobamate reduced the number of punished passages (i.e. was anxiolytic)<br>Albendazole slightly increased the number of punished passages.<br><br>Conclusion: Albendazole showed no anxiolytic activity |

B-24g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**INTERACTIONS WITH OTHER DRUGS**

**ıort/Title :** November 1979/ Apomorhpine-induced verticalisation
**ıme/Page :**
**ıoratory :**

| cies/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| ıse | 12M | 0, 100, 200<br><br>Intraperitoneal<br><br>10% aqueous gum arabic | Albendazole administered 1h before 0.3 or 0.75mg/kg apomorphine given sc. After 5min, verticalisation behaviour noted every 2min for the next 26min.<br>2 trials were conducted. | First trial: 200mg/kg albendazole led to reduction of apomorphine-induced verticalisation<br>Second trial: Neither 100 nor 200mg/kg albendazole had any effect<br><br>Conclusion: Albendazole has no effect on apomorphine-induced verticalisation in mice. |

B-24g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**INTERACTIONS WITH OTHER DRUGS**

ort/Title : November1979/ Harmaline-induced tremor in the mouse
ıme/Page :
oratory :

| cies/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| ıse | 10M | 0, 100, 200<br>Intraperitoneal<br>10% aqueous gum arabic | Albendazole was administered 30min before 30mg/kg harmaline given ip. Degree of tremor evaluated every 5min for the next 30 min | Albendazole at 100 or 200mg/kg was without significant effect on harmaline-induced tremor<br>Conclusion: Albendazole does not affect CNS GABAergic activity. |

3-24g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**INTERACTIONS WITH OTHER DRUGS**

**Report/Title :** November 1979/ Reserpine-induced ptosis
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 8M | 0, 100, 200<br><br>Imipramine 25mg/kg<br><br>Intraperitoneal<br><br>10% aqueous gum arabic | Albendazole or imipramine administered 1h before 2mg/kg reserpine was given ip.<br><br>Degree of ptosis noted every 30min for next 2h. | Albendazole 100 or 200mg/kg had no effect on reserpine-induced ptosis.<br><br>Imipramine was active at 30 and 60 min.<br><br>Conclusion: Albendazole does not affect reserpine-induced ptosis in the mouse. |

* 18-24g

ALBENDAZOLE

ITEM 5 (A) Pharmacology Studies - Secondary Effects

Tabular Summary

## NEUROPHARMACOLOGY (CENTRAL AND PERIPHERAL NERVOUS SYSTEMS)

Report/Title : November, 1979/ Escape (evasion) test
Volume/Page :
Laboratory :

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 8M | 0, 100, 200<br><br>Chlorpromazine 2.5, caffeine 10<br><br>Intraperitoneal<br><br>10% aqueous gum arabic | Mice, pretreated 20 min before testing, were restrained for 10sec in a lidless box which had an inclined mesh with a horizontal line 2cm from the rim of the box at the far end. Emergence was scored when mouse crossed the line. Time to first emergence, total emergences and behavioural modifications were measured. | Caffeine stimulated and chlorpromazine depressed emergent activity.<br>Albendazole very slightly depressed activity compared with negative controls. Albendazole-treated mice exhibited signs of abdominal cramps, assumed to be toxic effect.<br><br>*SB opinion:* Slight depression of activity with albendazole likely to be due to toxicity rather than effect on CNS |

* 18-24g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**NEUROPHARMACOLOGY (CENTRAL AND PERIPHERAL NERVOUS SYSTEMS)**

**Report/Title :** Test 0249/(AHP #3), July 1980/ Anticonvulsant - electroshock seizure test in mice
**Volume/Page :**
**Laboratory :**

*Part 1: Determination of mean convulsant current (CC50)*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 7M | None | Corneal electrodes used to apply 60Hz AC shock, 4msec duration at current intensities of 19, 23, 26, 28 and 33mA. Current causing seizure in 50% of untreated mice calculated | CC50 for control mice calculated as 25mA |
| Swiss ($OF_1$) | | | | |

* 18-20g

*Part 2: Effect of albendazole on mean convulsant current (CC50)*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 7M | 10 | CC50 (25mA) applied via corneal electrodes 0, 30, 60 90, 120 and 180min after dosing. | Albendazole increased number of seizures at 30, 60 and 90min after dosing, with largest increase (6/7 mice) at 30 min. |
| | | Oral gavage | | |
| | | Tween 80 | | |
| Swiss ($OF_1$) | | | | |

* 18-20g

*Part 3: Electroshock seizure threshold at various doses of albendazole*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 40M (0 and 1[illegible]g/kg) | 0, 1, 10, 100 | CC50 determined 30 min after dosing with albendazole | CC50 was lower than control value of 29 (23-36) mA at 1mg/kg -17 (15-20) mA, 10mg/kg - 25 (22-19) mA and 100mg/kg - 26 (23-29)mA. Deaths were only seen in albendazole-treated mice. |
| | | Oral gavage | | |
| Swiss ($OF_1$) | 30M (10 and 100mg/kg) | Tween 80 | | Overall conclusion to parts 2 and 3: Albendazole showed a slight but definite convulsant effect, most marked at the lowest dose of 1mg/kg. |

* 18-20g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**INTERACTIONS WITH OTHER DRUGS**

**Report/Title :** November 1979/ Pentetrazole-induced convulsions (to study the antagonism or synergy of the convulsant and toxic effects of pentetrazole)
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Mouse | 8M | 0, 100,200<br>Oral<br>Diazepam 1,<br>Reserpine 5<br>10% aqueous gum arabic | Mice were treated orally with vehicle, albendazole, diazepam (antagonist) or reserpine (synergist). After 30min, 160mg/kg pentetrazole (expected to produce death in about 15min in untreated mice) given sc. | Albendazole treatment resulted in a statistically significant reduction in the time to first tonic convulsion at 100 or 200mg/kg (by 8 and 18% respectively). Reserpine reduced the time by 35% and diazepam increased time by 31%.<br>All mice treated with albendazole or reserpine died, but later than did control mice.<br><br>Conclusion: Albendazole had slight convulsant activity which appeared to be dose related. |

* 18-24g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**CARDIOVASCULAR/RESPIRATORY SYSTEM**

**Report no./Title :** Test 0034/(AHP #7), 1980/ Cardiovascular Pharmacology in Dogs: Hemodynamics
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Dog<br><br>Mongrel | 2M + 2F | 0.5, 1.0<br><br>Intravenous<br><br>0.9% saline with Tween 80 0.2ml/30ml | Dogs anaesthetised with Na pentobarbital and chloralose. Effect of 10 min i.v. infusions of albendazole on range of indices of cardiovascular function measured. | 1 mg/kg: marked and prolonged hypotension with slight bradycardia in males. 40% decrease in aortic and coronary flow. Depression of ventricular contractility. Fall in systolic pressure. All effects maximal at 30 min from start of infusion, recovery at 1h.<br>0.5 mg/kg: no effect except slight bradycardia in males and some peripheral vasoconstriction. Slight cardiodepressant effect (less than at 1 mg/kg) |

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**CARDIOVASCULAR/RESPIRATORY SYSTEM**

**Report no./Title :** Test 0009/(AHP #9), 1980/ CardiovAscular Pharmacology in Dogs: Electrocardiographic Study
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Dog | 1M + 1F | 4, 10 | Albendazole administered once a day for 5 days. ECG | Albendazole had no effects on ECG |
| Beagle | | Oral | recorded pre-study and 1, 3 and 5h after each dose | |
| | | Capsule | | |

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**GENITOURINARY SYSTEM**

**Report/Title :** November 1979/ Diuretic activity in rats (method of Lipschitz)
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Rat<br><br>Wistar | 5M | 200<br><br>Chlorthiazide<br>50<br><br>Oral gavage<br><br>10% aqueous gum arabic | Rats fasted 18h, then fluid loaded with 25ml/kg 0.9% NaCl at time of albendazole administration.<br><br>Urine output measured hourly for 5h | Chlorthiazide increased urine output by 34%. Albendazole had no significant effect on urine output.<br><br>Conclusion: Albendazole had not diuretic nor antidiuretic effect in the rat |

* 200-250g

**ALBENDAZOLE**

**ITEM 5 (A) Pharmacology Studies - Secondary Effects**

**Tabular Summary**

**GENITOURINARY SYSTEM**

**Report/Title :** (AHP #5), July 1980/ Albendazole renal clearance in dogs
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Dog<br><br>Strain not known | 4F | 4<br><br>Oral<br><br>1% Tween 80 | Dogs fasted for approx 18h, then loaded po with 500ml water. They were restrained supine, the bladd and a front and hind leg vein were catheterised. 0.4 creatinine and 0.08% PAH in 4% mannitol-phosphat buffer (pH7.4) were infused iv at 3ml/min throughout the experiment. 1.5ml/kg of 1% creatinine was given iv 15min before start of first clearance period, which started 30min after water loading. Urine was then collected for 3 consecutive 10min clearance periods until dosing, then for 9 similar consecutive periods starting 20min after dosing. Excretion of electrolytes and water and PAH and creatinine clearances were measured. | There were no significant differences in excretion patterns between the pre-dose and post-dose clearance periods.<br><br>Conclusion: Albendazole did not affect renal clearance in dogs |

* 12-16kg

# ALBENDAZOLE

## ITEM 5 (A) Pharmacology Studies - Secondary Effects

## Tabular Summary

## HEPATIC SYSTEM

**Report/Title :** November 1979/ Bile Secretion in rats
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Method | Observations |
|---|---|---|---|---|
| Rat | 5 | 0, 200<br><br>Dehydrocholate<br>100<br><br>Intraduodenal<br><br>10% aqueous gum arabic | Rats fasted for 12-24h, then anaesthetized before introduction of catheter into the upper third of the bile duct. Dosed 1h later intraduodenally. Volume of bile measured every 30min from 1h before until 2h after dosing. | Dehydrocholate increased bile flow in the hour following treatment Albendazole caused no significant effect on bile flow.<br><br>Conclusion: The intraduodenal administration of 200mg/kg albendazole to the anaesthetized rat had no effect on bile flow |

* Mean weight 250g

*REVIEWER'S COMMENTS:*
*Neuropharmacologic studies on the nervous system functions of mice treatment with albendazole, 100 or 200 mg/kg/day, indicated that it had no anxiolytic effect and did not affect any activities in the apomorphine-induced verticalisation test, the harmaline-induced tremor test nor the reserpine-induced ptosis test. A slight reduction of response was observed in escape/evasion study performed in the mouse. Other study reports indicated that all mice showed signs of abdominal cramps, which may be albendazole-related toxicity.*

*Albendazole appeared to potentiate the convulsant effect of electroshock in mice, with the maximum effect seen at 1 mg/kg/day and not at higher dose levels (10 or 100 mg/kg/day). Pretreatment with 100 or 200 mg/kg/day albendazole, slightly reduced the time to first tonic convulsion induced by pentetrazole, but not that induced by strychnine or bicucillin. It is, therefore, concluded that orally-administered albendazole should be considered to be capable of potentiating convulsions induced by some, but not all, artificial stimuli.*

*Studies of the effects of albendazole on cardiovascular functions were carried out in dogs using the intravenous route. In one study, albendazole 1 mg/kg i.v., was shown to produce a marked and prolonged hypotension in male dogs. Sponsor reported that mortalities observed in dogs receiving 10 mg/kg intravenously in a separate study may be due to hemodynamic complication associated with albendazole. Similarly, in a study of the responses of dogs to a variety of autonomic stimuli. The oral administration of 4 or 10 mg/kg to dogs had no effects on the electrocardiogram (ECG), therefore, the cardiovascular response may not be dose limiting in humans.*

*Tests of renal function in rats (200 mg/kg/day orally) and dogs (4 mg/kg/day orally) and of bile secretion in rats (200 mg/kg/day intraduodenally) showed that albendazole was without effect on those functions at the doses studied.*

***TOXICOLOGY***

[redacted]

**A.** ***THE FOLLOWING TOXICOLOGICAL AND TOXICOKINETIC STUDIES WERE SUBMITTED, REVIEWED, AND SUMMARIZED BELOW:***

**ALBENDAZOLE**
**ITEM 5 (B) : Acute Toxicity Studies**
**Tabular Summary**

**Report no./Title:** A-1020-79/5900-79, November 1979/ Albendazole - Acute oral toxicity study in mice
**Volume/Page:** 1.10 / 000002
**Laboratory:**

| Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse | 5M + 5F* | 0, 5000 | Single dose, 14 day observation | Median lethal dose >5000mg/kg<br>No abnormalities seen in treated animals |
| CD-1 | | po | | |
| | | 1% Methocel | | |

* M 25-30, F 24-26 g at dosing.

# ALBENDAZOLE
## ITEM 5 (B) : Acute Toxicity Studies
## Tabular Summary

**Report no./Title:** (AHP #27)/2605-75, June 1975/ Acute oral toxicity in rats, compound no. SK&F 62979
**Volume/Page:** 1.10 / 000005
**Laboratory:**

| Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat | 5M + 5F* | 1000, 1410, 2000, 2820, 4000 | Single dose, 14 day observation | Median lethal dose: 2400 mg/kg |
| Wistar | | po | | Necropsy findings - urinary staining of abdomen, chromodacryorrhea, congestion of gut and red gut contents |
| | | 1% Methocel | | |

*186-297 g at dosing

# ALBENDAZOLE
## ITEM 5 (B) : Acute Toxicity Studies
## Tabular Summary

**Report no./Title:** B335A/(AHP #26), October 1976/ The acute oral toxicity of SK&F 62979 (Albendazole) in the rat
**Volume/Page:** 1.10 / 000013
**Laboratory:**

| Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>ICI Wistar-derived | 5M + 5F* | 500, 1000, 2500, 5000, 10000<br><br>po<br><br>2% tragacanth | Single dose, 14 day observation | Median lethal dose 1320 mg/kg<br>Deaths occurred 4-9 days after dosing, often preceded by prolonged anorexia. Some rats had mass of semi-solid drug occluding gut at necropsy but late-dying rats had empty guts. |

M 240-305 g, F 170-223 g at dosing

**ALBENDAZOLE**

**ITEM 5 (B) : Acute Toxicity Studies**

**Tabular Summary**

**Report no./Title:** B335C/(AHP #28), October 1976/ The acute oral toxicity of SK&F 62979 (Albendazole) in the hamster
**Volume/Page:** 1.10 / 000016
**Laboratory:** Smith Kline & French Laboratories Ltd., Welwyn, Herts, UK

| Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Syrian hamster | 5M + 5F* | 5000, 10000<br>po<br>2% tragacanth | Single dose, 14 day observation | Median lethal dose >10000 mg/kg<br>2 females at 5000 and 1 female at 10000 mg/kg died between days 4 and 8.<br>No abnormal necropsy findings. |

M 95-110 g, F 60 - 90 g at dosing

**ALBENDAZOLE**

**ITEM 5 (B) : Acute Toxicity Studies**

**Tabular Summary**

**Report no./Title:** B335D/(AHP #30), October 1976/ The acute oral toxicity of SK&F 62979 (Albendazole) in the rabbit

**Volume/Page:** 1.10 / 000019

**Laboratory:** Smith Kline & French Laboratories Ltd., Welwyn, Herts, UK

| Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rabbit | 2M + 1 or 2F | 250, 500, 1250, 2500 | Single dose, 14 day observation | Median lethal dose between 500 and 1250 mg/kg. Deaths, which occurred 1 to 7 days after dosing were preceded by diarrhoea. |
| New Zealand White | | po | | At necropsy, guts of rabbits which died contained fluid and were dilated by gas. |
| | | 2% tragacanth | | |

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report no./Title :** A-1015-79B/(AHP #32)/79-2423, March 1980/ A three month feeding study of albendazole in mice
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse<br><br>CD-1 | 10M + 10F | 0,200,400,800, 1600 nominal<br><br>Dietary, ground Purina lab Chow® | 90 days | Treatment-related deaths: 0, 200, 400 mg/kg - 0/20; 800 mg/kg - 0/10M, 1/10F; 1600 mg/kg - 5/10M, 10/10F.<br>Clinical condition: week 9 - lesions on pinna of 3M,2F at 800 and all surviving males at 1600 mg/kg.<br>Body weight and food intake: slight decrease in treated M, slight increase in F at doses up to 800 mg/kg; food intake increased in treated M.<br>Haematology: HCt, leukocytes slightly decreased in M at 800 and 1600 mg/kg; erythrocytes reduced in M at 800 and 1600 and F at 200, 400 and 800 mg/kg; Hb reduced in F at 800 mg/kg.<br>Organ weights: Liver increased in M, F at 200, 400 & 800 and M at 1600 mg/kg.<br>Post mortem: no treatment-related effects |

*39 days old, M 22-29, F 15-21 g at start of treatment,

**ALBENDAZOLE**
**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**
**Tabular Summary**

**Report/Title :** A-1019-79/79-2410, January 1980/ A one month feeding study of albendazole in mice
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose, Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse<br><br>CD-1 | 10M + 10F | 0, 1.25, 2.5, 5.0% of diet, resulting in intakes of approx. 0, 2, 4 and 6.5 (M) or 0, 2.5, 4.8 and 7.6g/kg/day (F) in week 1.<br><br>Dietary, ground Purina Lab Chow® | Nominally one month but treatment terminated on day 8 | Treatment-related deaths: Control - 0/20; 1.25% - 1M,1F; 2.5% - 2M,7F; 5.0% - 5M, 7F. All deaths occurred between days 4 and 8. All remaining animals killed on day 8.<br>Clinical condition: decedents showed decreased physical activity and, in some, staining of the perineal area. Survivors displayed no clinical symptoms.<br>Body weight and food intake: After 1 week, mean weight of surviving treated mice was 6-14% (M) and 18-24% (F) lower than controls. Food intake of survivors in week 1 was suppressed in all treated M groups (by up to 32%) and high dose females (by 18%).<br>Post mortem: no treatment-related findings |

* 38 days old, M 22-29g, F 17-27g at start of treatment

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report/Title :** A-1014-79/79-2375, June 1979/ A three week feeding study in rats with albendazole
**Volume/Page :** 1.11 / 000289
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague-Dawley | 5M + 5F | 0, 45, 60 (nominal)<br><br>dietary | 21 days | Treatment-related deaths: None (one high dose male died spontaneously on day 4).<br>Clinical condition: no treatment-related effects.<br>Body weight and food intake: body weight reduced by approx. 10% in M and F by week 3. Slight reduction in food intake (5-11%) in weeks 2 and 3 at 60 mg/kg.<br>Post mortem: no treatment-related effects. |

* 21 days of age, 31-41g (M), 29-39g (F) at start of treatment

# ALBENDAZOLE

## ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies

## Tabular Summary

**Report no./Title :** 2205 & 2206-TAR/(AHP #33), January 1980/ 4-week sub-acute oral toxicity study in rats
**Volume/Page :**
**Laboratory :**

*Preliminary study*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague-Dawley | 10M + 10F | 100, increasing to 600 (5M + 5F) or 200 (5M + 5F)<br><br>Oral gavage<br><br>Na CMC | 14 days (increasing doses) or 12 days (at 200 mg/kg) | All animals at increasing doses died between days 5 and 14 following piloerection, weight losses and diarrhoea.<br>At 200 mg/kg 7/10 died, with piloerection and diarrhoea in females from day 5. |

*Main study*

| | | | | |
|---|---|---|---|---|
| Rat<br>Sprague-Dawley | Main study:<br>15M + 15F<br>Additional 5M + 5F at 48 & 168 mg/kg for recovery | 0, 4, 16, 48, 168<br><br>Oral gavage<br><br>0.5% Tween 80 | 28 days + 28 days recovery at 48 and 168 mg/kg | Treatment-related deaths by day 24: 0, 4 and 16 mg/kg - 0/30, 48 mg/kg - 7/40, 168 mg/kg - 39/40.<br>Clinical condition: no effects at 4 and 16 mg/kg. At 48 mg/kg, nasal swelling and colored nasal secretion from day 9, piloerection, marked weight loss; no effects in recovery period. At 168 mg/kg, from day 5 a deterioration in general health, diarrhoea, piloerection, nasal swelling with bloody nasal discharge and marked weight loss.<br>Body weight and food intake: no effects at 4 and 16 mg/kg. At 48 mg/kg weight loss in F in week 2 and reduced gain in M & F; no effect in recovery period; no effect on food intake. At 168 mg/kg marked loss from start; marked reduction in food intake.<br>Haematology: (F at 168 mg/kg not bled due to clinical condition): slight anaemia in M at all doses and in F at 48 mg/kg. Marked leukopaenia in M at 48 and 168 mg/kg only in week 1 but in F at 16 and 48 mg/kg only in week 4.<br>Blood chemistry and urinalysis: no effects<br>Organ weights: At 48 mg/kg reduced testis and ovary weight and increased liver weight (F). Testis weight recovered in off-dose period.<br>Microscopic appearance: no effects at 4 and 16 mg/kg. At 48 and 168 mg/kg hypoplasia of seminiferous epithelium and medullary hypoplasia of bone marrow, especially granulocytic series. Reversibility of these changes seen after recovery. |

164-222g, F 132-178g at start of dosing

# ALBENDAZOLE

## ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies

## Tabular Summary

**Report no./Title :** 75-1109/(AHP #34), October 1979/ A three month oral toxicity study of SK&F 62979 in rats
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat | 20M + 20F | 0, 2, 10, 30 | 91-96 days | No treatment-related effects. |
| Long-Evans | | dietary, ground Standard Laboratory Diet | | |

* 5-7 weeks old, M 100-143g, F 89-134g at start of treatment

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report no./Title :** 2203- & 2204-TSC/(AHP #35), January 1980/ Sub-acute toxicity study in dogs Albendazole (4-week)
**Volume/Page :** 1.12 / 000002
**Laboratory :**

*Preliminary study*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Dog | 2M + 2F | In one M, 100 increasing to 400 over 10 days | 10 day total in preliminary study | First M (increasing doses) died day 11. |
| Beagle | | In 1M + 2F, day 1 - 400, days 2 - 12, 200 | | One female died day 1 at 400 mg/kg |
| | | Oral gavage | | In surviving M + F, diarrhoea was the only symptom. |
| | | 1% CMC or 2% Tween 80 | | |

Report no./Title : 2203- & 2204-TSC/(AHP #35), January 1980/ Sub-acute toxicity study in dogs Albendazole (4-week)
(continued)

*Main study*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| | 4M + 4F. Additional 1M + 1F at 48 & 168 mg/kg for recovery | 0, 4, 16, 48, 168<br>Oral gavage<br>2% Tween 80 | 28 days + 4 weeks recovery at 48 and 168 mg/kg | Treatment-related deaths: 5M, 5F at 168 mg/kg between days 2 and 11; 1F at 48 mg/kg on day 12. Most deaths occurred at night - no symptoms observed.<br>Clinical observations: no effect at 4 and 16 mg/kg. Diarrhoea (1/10) and vomiting (1/10) at 48 mg/kg. 1/5F at 168 mg/kg showed polypnea, tachycardia and respiratory distress on day 2 and was killed.<br>Body weight: no significant effect at 4 and 16 mg/kg. 48 mg/kg - weight loss, especially in week 1. 168 mg/kg - 3/4 survivors lost weight.<br>Haematology: leukopaenia, marked in 1M at 168 mg/kg in week 1 and slight in 1F at 48 mg/kg in week 4, with recovery during off-dose period.<br>Blood chemistry: trend to increased ALP at 16, 48 and 168 mg/kg.<br>Organ weight: trend to decreased testis at 168 mg/kg.<br>Microscopic pathology: no treatment-related changes. |

* Approx 8 months old at start of both phases.

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report no./Title :** 75-1110/(AHP #36), October 1975/ A three month oral toxicity study of SK&F 62979 in dogs.
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Dog | 4M + 4F | 0, 2, 10, 30 | 91 - 94 days | Haematology: erythrocyte cholinesterase lower in males at 30 mg/kg |
| Beagle | | Oral | | No other treatment-related effects. |
| | | Gelatin capsule | | |

* 5 months old at start of treatment

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report no./Title :** A-1018-79/79-2371/(AHP #43), September 1980/ A six month oral toxicity study with albendazole in dogs.
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Dog | 6M + 6F | 0, 5, 30, 60 | 186-190 or 194 days | One female at 60 mg/kg died (NOT treatment-related) day 159. |
| Beagle | | Oral | | Body weight: no effect at 5 or 30 mg/kg. At 60 mg/kg, slight reduction in gain (terminal body weight less than control by 10% in M, 7% in F). |
| | | Gelatin capsule | | Haematology: no effects at 5 mg/kg. Hb, HCt & RBC reduced in months 3 - 6 at 60 mg/kg, especially in males. Treatment-related reduction inWCC at 30 (-12 to -18%) and 60 mg/kg (-47 to -48%), mostly due to neutropaenia. Blood chemistry: ALP higher than control at all doses at most sampling times, but of no toxicologic significance due to lack of other LFT increases or pathology. Organ weights: testis reduced at 60 mg/kg. Microscopic pathology: at 60 mg/kg, marrow in 3/6 F was hypocellular (granulocytic and erythrocytic) and in 1/6 F moderately severe decrease in erythrocytic and granulocytic series. |

* 5 - 7 months at start of treatment

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

**Report no./Title :** A-1024-80/80-2480/(AHP #40), September 1983 (revised following PWG reviewJuly 1987)/ A long term oral (dietary) carcinogenicity study of albendazole in mice. **

**Volume/Page :** Report is located in Volume 1.14 up to and including Volume 1.32, starting at page 000002 in each volume.

**Laboratory :**

Report no./Title : A-1024-80/80-2480/(AHP #40), September 1983 (revised following PWG reviewJuly 1987)/ A long term oral (dietary) carcinogenicity study of albendazole in mice. **
(continued)

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse<br><br>CD-1® (ICR derived) | 100M + 100F + 25M/25F at HD and control for monthly haematology from month 3 | 0, 25, 100, 400<br><br>Dietary<br><br>Ground Purina Lab Chow® #5001 | 760 days | Food intake: Slightly increased in treated M in first 6 weeks.<br>Haematology: No effects at 25 and 100 mg/kg. RCC slightly decreased in F at 400 mg/kg, with lesser effect in M. WCC slightly decreased in M at 400 mg/kg months 3 to 18 but trend reversed during final 6 months. Platelets increased throughout study in M and F at 400 mg/kg.<br>Macroscopic pathology: Opacity of the eyes was more frequent at 400 mg/kg. Flaccid or small testes were more frequent at 400 mg/kg.<br>Microscopic pathology: Cytoplasmic vacuolation of hepatocytes was increased in albendazole-treated groups but this finding is reversible and of little toxicologic significance. Bilateral degeneration of the seminal epithelium was increased at 400 mg/kg. Unilateral cataract was more frequent in males at 400 mg/kg.<br>There was no effect on the incidence of neoplasia. The incidence of endometrial polyps was higher at 400 mg/kg but the incidence was within the expected range.<br><br>CONCLUSION<br>Albendazole was not carcinogenic in this study |

**Report no./Title :** A-1024-80/80-2480/(AHP #40), September 1983 (revised following PWG reviewJuly 1987)/ A long term oral (dietary) carcinogenicity study of albendazole in mice. **
(continued)

*40 days old, M 20-31g, F 17-24g at start of treatment,

** The results and the histological material from this study were the subject of a review by an FDA-constituted Pathology Working Group, the conclusions of which, published in 1985 and 1987, were that albendazole was non-carcinogenic under the conditions of this study

**ALBENDAZOLE**

**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**

**Tabular Summary**

Report no./Title : A-1022-80/80-2448/(AHP #42), October, 1983 (Revised following PWG review August 1987)/ A long term oral toxicity/carcinogenicity study of albendazole in rats**

Volume/Page : Report is located in Volume 1.33 up to and including Volume 1.57 starting on page 000002 in each volume.

Laboratory :

*$F_0$ Generation*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague-Dawley CD® | $F_0$: 100M/100F | $F_0$: 0, 0, 1.0, 2.5, 5.0<br><br>Dietary<br><br>Ground Purina lab Chow® | $F_0$: 60 days prior to mating and until $F_1$ weaned. $F_1$ exposed to same doses until 28 days old | No treatment-related effects |

*$F_0$ 6 weeks old, M150-234g, F 119-180g at start of treatment

Report no./Title : A-1022-80/80-2448/(AHP #42) **(continued)**

*$F_1$ Generation*

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| | $F_1$: 100M/100F + 25M/25F at HD and control groups for monthly haematology | $F_1$: 0, 0, 3.5, 7.0, 20.0<br><br>Dietary<br><br>Ground Purina lab Chow® #5001 | $F_1$ from 28 days of age for 845-855 days | Mortality: No effect at 3.5 or 7.0 mg/kg. Males at 20 mg/kg showed slightly increased death rate for last 8 months.<br>Haematology: No effect at 3.5 or 7.0 mg/kg. Slightly reduced total WCC and neutrophil count at 20 mg/kg in males (months 22 and 24) and females (months 24 and 28).<br>Blood chemistry: No effect at 3.5 or 7.0 mg/kg. ALP slightly increased in males at 20 mg/kg at 3 and 6 months. CHOL slightly increased in females at 20 mg/kg at most sampling times.<br>Macroscopic pathology: Flaccid testes slightly more frequent at 20 mg/kg.<br>Microscopic pathology: Bilateral degeneration/atrophy/maturation arrest of germinal epithelium of the testis increased at 20 mg/kg.<br>Fatty metamorphosis of the liver was slightly increased at 20 mg/kg, but this reversible change was within the expected range.<br>Endometrial polyps of the uterus/cervix were more frequent in treated than in control females, especially at 20 mg/kg, but the incidence was within the expected range.<br>Follicular adenoma of the thyroid gland was seen most frequently at 20 mg/kg, but the incidence was within the expected range.<br><br>CONCLUSION<br>Albendazole was not carcinogenic in this study |

* $F_1$ 28 days old at start of treatment

** The results and the histological material from this study were the subject of a review by an FDA-constituted Pathology Working Group, the conclusions of which, published in 1985 and 1987, were that albendazole was non-carcinogenic under the conditions of this study

**ALBENDAZOLE**
**ITEM 5(C): Subchronic/Chronic/Carcinogenicity Studies**
**Tabular Summary**

**Report/Title :** Assessment of the potential oncogenicity of albendazole
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse, CD-1 | 100M/100F | see AHP #40 | see AHP #40 | *This report draws together the findings of pathology working group reviews conducted by Pathco Inc. following questions raised by the FDA Centre for Veterinary Medicine regarding neoplastic and non-neoplastic endpoints in the two oncogenicity studies, particularly with regard to histiocytic sarcoma, endometrial stromal polyp and thyroid follicular cell adenoma in rats. Evidence for genotoxicity was also reviewed.* |
| Rat, Sprague-Dawley CD® | $F_0$: 100M/100F<br>$F_1$: 100M/100F | see AHP #42 | see AHP #42 | |

Report/Title : Assessment of the potential oncogenicity of albendazole (continued)

| Species/Strain | No/Group* | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|

Following weight-of-evidence analysis, it was concluded:

1. There is no evidence of a tumorigenic effect of albendazole in mice fed the chemical at up to the MTD.
2. The incidence of histiocytic sarcoma in male rats fed albendazole is within the historical control range.
3. The incidence of endometrial stromal tumours in rats fed albendazole is within the historical control range; and this slight increase in benign polyps is not biologically meaningful.
4. The incidence of thyroid follicular cell tumours in the high-dose group (rats) is not significantly greater than in the control group, and is not accompanied by an increase in preneoplastic and malignant lesions as would be expected with a thyroid carcinogen. The incidence in the intermediate dose groups cannot be directly compared with those in the control and high-dose groups because of differences in histologic technique used in preparing the slides of the thyroid.
5. There is no evidence that albendazole has any genotoxic potential.

**ITEM 5 (D) : Special Toxicity Studies**
**Tabular Summary**

**Report no./Title : A-1031-90/5890-90, May 1991/ A closed-patch repeated insult dermal sensitization study of albendazole in guinea pigs (Buehler method)**
**Volume/Page: 1.97 / 000002**
**Laboratory :**

*Dose-range study*

| Species/Strain | No/Group* | Dose/ Route/Vehicle | Procedure | Observations |
|---|---|---|---|---|
| Guinea pig | 3M + 3F | 100, 50, 25, 10%. | 0.2ml of each test material applied once to shaved dorsal skin beneath a Hilltop Chamber®, occluded for 6h. Observed for irritation at 24 and 48h | Irritation: None |
| Hartley albino | | Dermal | | |
| | | 100% moistened with saline; 50, 25 and 10% in acetone | | |

* see main study for ages and weights of animals

**ITEM 5 (D) : Special Toxicity Studies**

**Tabular Summary**

**Report no./Title :** A-1031-90/5890-90, May 1991/ A closed-patch repeated insult dermal sensitization study of albendazole in guinea pigs (Buehler method)

**Volume/Page:**

**Laboratory :**

*Main study*

| Species/Strain | No/Group* | Dose/ Route/Vehicle | Procedure | Observations |
|---|---|---|---|---|
| Guinea pig<br><br>Hartley albino | 10M + 10F in sensitization group, 5M +5F in irritation control | 100% albendazole,<br><br>Dermal<br><br>0.2cc moistened with 0.2ml saline | Induction: (sensitization group only) - material applied beneath Hilltop Chamber® to right, shaved dorsal skin, occluded, for 6h once weekly for 3 weeks. Dermal response scored 24 and 48h after first application.<br>Challenge: (both groups) - above treatment applied to left dorsal skin. Dermal responses scored 24 and 48h later. | Dermal responses: none<br><br>Conclusion: Albendazole exhibited no potential to produce dermal sensitization. |

* 5-6 weeks old, M 337-383g, F 309-356g at start of treatment

## ALBENDAZOLE

### ITEM 5 (D) : Special Toxicity Studies

### Tabular Summary

**Report no./Title :** (AHP #25), November 1975/ Local irritation, skin sensitivity and acute toxicity studies using SK&F 62979.
**Volume/Page : 1.97 / 000057**
**Laboratory :** Smith Kline & French Laboratories, Philadelphia, Pa, USA

| Species/Strain | No/Group* | Dose/ Route/Vehicle | Procedure | Day | Observations |
|---|---|---|---|---|---|
| Rabbit | 3M | 100mg | Group I & II -powder instilled into left | 1 | No irritation in either irrigated or non-irrigated eyes. |
| *Pel Freez* | | Eye | *conjunctival sac, Grou* II - powder removed by irrigation after 4 min. Rabbits observed periodically for 72h | | |
| | | 500mg/site | Powder applied to gauze pads and | 1 | No irritation on either abraded or non-abraded skin |
| | | Abraded and non-abraded skin | applied to abraded or non-abraded skin, occluded for 23h. Observation at 24, 48 and 72 h. | | |
| | | dry powder on gauze pads | | | |

* 2.5 to 3 kg

Tabular Summary of Acute Oral Toxicity in Mice is not included here.

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** (AHP #53), June 1980/Expert study of the action of the compoound albendazole on the fertility of the male rat, per os
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Rat<br><br>Sprague Dawley CD | 20 M (treated)<br>20F (untreated) | 0, 1, 10, 30<br><br>Oral gavage<br><br>0.5% GT | M treated for minimum of 60 days | TREATED MALES<br>Treatment-related deaths: none at 0, 1 or 10 mg/kg. At 30 mg/kg, 3/20 males died between day 14 and day 33, following clinical symptoms and weight loss. Death of one other male on day 56 could not be definitely attributed to treatment.<br>Clinical condition: No symptoms at 0 or 1 mg/kg. At 10 mg/kg, one male had dried blood around nose on one day. At 30 mg/kg all animals showed piloerection and few animals had nasal lumps.<br>Body weight: At 30 mg/kg group mean weight gain was slightly reduced<br>Food consumption.: slightly reduced at 10 and 30 mg/kg.<br>Male fertility: all surviving males in each group sired offspring.<br>Macroscopic appearance of males: At 30 mg/kg, testes smaller than in controls.<br>Microscopic appearance of males: (not all rats examined) At 10 mg/kg, a few hypoplastic seminiferous tubules seen in 4/5 rats: at 30 mg/kg, focal hypoplasia of seminiferous epithelium in 8/10 rats.<br>UNTREATED FEMALES<br>No intergroup differences in body weight gain or clinical condition in animals autopsied on day 13 of pregnancy or allowed to deliver young. One pregnant female previously mated with a 30 mg/kg male died during parturition (not considered treatment-related)<br>NEONATES<br>No intergroup differences in litter size, litter weight, survival nor physical and behavioural development. |

*5-6 weeks old, M 204-264 at start of dosing, F224-287 on first day of pregnancy

**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-2011/75/74-1096/AHP #44, July 1975/ A segment II mouse teratology study of SK&F 62979
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Mouse | 21- 26F | 0, 2, 5, 10, 30 | Days 6-15 PC (Proof of | No effects on dams and no evidence of embryotoxicity or teratogenesis. |
| CD-1 (ICR derived) | | Oral gavage | mating = day 0) | |
| | | 0.5% MC | | |

* group mean weights 26.0 - 28.8g at mating

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-2008-75/74-1047/(AHP #45), June 1975/ A segment II rat teratology study of SK&F 62979**
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat | 20F | 0, 2, 5, 10, 30 | Days 6-15 PC (Proof of | Maternal Body weight: No effects at 2 to 10 mg/kg. Weight gain at 30 mg/kg 36% less than control days 6-15 and 59% less days 15-20. |
| Long-Evans | | Oral gavage | mating = day 0) | Embryotoxicity: No effects at 2 to 10 mg/kg. At 30 mg/kg, number of viable fetuses reduced (0.8/dam vs 11.2 control), resorptions increased (10.1/dam vs 0.4). Only 2/16 dams at 30 mg/kg had live fetuses on day 20 of gestation. |
| | | 0.5% MC | | Teratogenesis: albendazole was teratogenic at 30 mg/kg, all 7 live fetuses having malformations of the axial or appendicular skeleton. The incidence of malformed fetuses at the lower doses was similar to controls, but the nature of the malformations indicated a possible treatment-related effect. |

CONCLUSION
Albendazole was teratogenic at 30 mg/kg and the results at 10 mg/kg and below were equivocal.

* group mean weights 234 - 239g at mating
** high dose range

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-2010-76/75-1274/(AHP #46), January 1976/ A segment II rat teratology study of SK&F 62979 **
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat | 19 -21F | 0, 0.5, 2, 5, 10 | Days 6-15 PC (Proof of | Maternal toxicity: no effects. |
| Long-Evans | | Oral gavage | mating = day 0) | Embryotoxicity: no effects at 0.5, 2 or 5 mg/kg. At 10 mg/kg fetal weight and size and degree of skeletal ossification were reduced. |
| | | 0.5% MC | | Teratogenicity: no effect at 0.5, 2 or 5 mg/kg. At 10 mg/kg 5/19 litters contained fetuses with malformations vs. 1/20 in control. |
| | | | | CONCLUSION<br>Albendazole was teratogenic at 10 mg/kg but not at 5 mg/kg or below |

* group mean weight 235 - 238 g at mating
** low dose range

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** 78-6-0628/(AHP #47), June 1980/ Embryotoxicity of ten metabolites**
**Volume/Page :** 1.98 / 000238
**Laboratory :**

| Species/Strain | No/Group* | Dose Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague Dawley (OFA strain) | Control - 36F. Other groups 3 - 23 F, depending on the metabolite under test. | 0, 0.2, 0.25, 0.3, 0.4 or 0.5 mmol/kg<br><br>Oral<br><br>Aqueous suspension | Days 8-15 PC (Proof of mating = day 1) | Only albendazole and its principal metabolite, albendazole sulphoxide, were embryotoxic or teratogenic. The no effect level for each was 0.2 mmol/kg which is approximately 6 mg/kg in each case. **For the remaining metabolites no teratogenicity was observed at any dose.** |

* 210-220 g at mating
** Thesis for the degree of Veterinary Doctor

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-2009-75/75-1134/(AHP # 51), August, 1975/ A teratology study of SK&F 62979 in rabbits.
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rabbit<br><br>New Zealand White | 15F | 0, 2, 5, 10, 30<br><br>Oral gavage<br><br>Methocel 90® HG premium 1500 | Days 7-19 PC (proof of mating = day 0) | Treatment-related deaths: 5/15 dams at 30 mg/kg vs. 0/15 controls.<br>Maternal body weight: At 10 and 30 mg/kg, lower than control during the dosing period, but variations in all groups at other times made interpretation doubtful.<br>Reproductive performance: 2/15 dams at 30 mg/kg had corpora lutea but no implantations, suggesting early embryo losses.<br>Embryotoxicity: No effect at 2 to 10 mg/kg. At 30 mg/kg, reduced number of viable fetuses (1.7/dam vs. 8.4 control) and increased number of resorptions (7.2/dam vs. 1.0). The % live fetuses was lower (18.9 vs. 89.3) and weight and size of fetuses were slightly lower.<br>Teratogenicity: No effect at 2 to 10 mg/kg. At 30 mg/kg all fetuses were malformed, with ectrodactyly.<br><br>CONCLUSION<br>Albendazole was maternally toxic, embryotoxic and teratogenic at 30 mg/kg. |

* group mean weights 4.8 - 5.1 kg at mating

# ALBENDAZOLE

## ITEM 5 (E) Reproduction Studies

### Tabular Summary

**Report/Title :** A-2004-77/ Swine embryotoxicity and teratogenicity studies with albendazole
**Volume/Page :**
**Laboratory :** SmithKline Animal Health Products, Applebrook Research Center

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Pig | C - 22F | C - 0 | C and II - days | Control - 21/22 F farrowed and all piglets were normal |
| | I - 22F | I, II, III - 30 | 7,14,21,28 & | I - 7/22 F farrowed, 3/7 litters contained abnormal piglets |
| | II - 24F | | 35 PC | II - 5/24 F farrowed, 2/5 litters contained abnormal piglets |
| Willow Glen | III - 22F | Oral drench | I - days 5,12, | III - 9/22 F farrowed, 3/9 litters contained abnormal piglets |
| Farm | | | 19,26 & 33 PC | Deformities were similar in each group. Skeletal deformities included fusion of |
| | | † | III - days 9,16, | vertebrae and of ribs, supernumary ribs, skull deformities, extra or reduced |
| | | | 23,30 & 37 PC | numbers of digits, shortened limbs, absence of limb bones (especially radius). S |
| | | | | tissue deformities included renal aplasia or hypoplasia and ectopic kidney. |

Conclusion: Albendazole 30mg/kg is highly embryotoxic and teratogenic in swi

* Division into groups does not feature in report, but is made here for the better understanding of this summary
† Vehicle not stated

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-1026-80/483-001/(AHP # 54), April 1981/ Albendazole perinatal and postnatal study in rats
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose (mg/kg/day Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague Dawley CD | 25F | 0, 5, 20, 40<br><br>Oral gavage<br><br>0.5% Methocel® | Days 16-20 PC (19/group) or 16 PC-20 PP (6/group)<br><br>(Proof of mating or parturition = day 0) | There were no treatment-related effects at 5 or 20 mg/kg and there was no effect of treatment on neuropharmacological evaluations at the end of lactation at any dose.<br><br>At 40 mg/kg weight gain of dams was reduced on days 16-20 PC and 0-4 PP. Pup survival measured on days 4, 12 and 21 PP was severely reduced and pup body weight was severely reduced from day 0 to day 21 PP. Of the 55 pups which died, 33 had soft tissue malformations.<br><br>CONCLUSION<br>When administered to pregnant rats from days 16-20 of pregnancy Albendazole at 40 mg/kg caused fetal malformations, as well as impaired survival, in their offspring. The maternal doses of 5 or 20 mg/kg were without effect. |

* 15 weeks old, 224 - 319 g at start

**ALBENDAZOLE**
**ITEM 5 (E) Reproduction Studies**
**Tabular Summary**

**Report no./Title :** A-1077-77/A-1077-77-1/A-1077-77-2/(AHP #55), August 1980/ A three-generation reproduction study with albendazole in rats
**Volume/Page :**
**Laboratory :**

| Species/Strain | No/Group* | Dose/ Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|
| Rat<br><br>Long-Evans | 12M, 24F per parental generation ($F_0$, $F_1$ and $F_2$)<br><br>2 matings per generation | 0, 30, 75, 150ppm**<br><br>Oral<br><br>Dietary, ground Purina lab Chow® | For 64 days prior to mating of $F_0$ and continuous for $F_0$, $F_1$ and $F_2$ generations. Each generation produced 2 litters. | No effect on mortality or clinical observations in any generation.<br>Body weight: $F_0$ - at 75 and 150ppm reduced weight gain in M during latter part of growth period. $F_1$ and $F_2$ - increased weight gain at 30 and 75 ppm in M, no effect at 150ppm. No effect in F of any generation.<br>Mating, pregnancy, fertility, offspring viability, litter survival to weaning, pup sex ratio: No effects.<br>Gestation length/pup survival: $F_0$ - slight decrease in gestation length only in first pregnancy at 150ppm and slight decrease in pup survival i the ensuing lactation interval. No effect in second $F_0$ pregnancy or litter at 150ppm nor in other generations nor at other doses.<br>Pup body weight: No effects at 30 or 75ppm. At 150ppm pup weight tended to be lower than in control except in $F_{2a}$ litter, when it was higher. |

* $F_0$ 50 days old at start

** Mean achieved doses:

| | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | 30ppm | 75ppm | 150ppm | 30ppm | 75ppm | 150ppm |
| Rest phase | 1.5 | 3.8 | 7.8 | 2.0 | 5.1 | 10.3 |
| Growth phase | 2.7 | 7.0 | 14.2 | 3.0 | 7.5 | 14.8 |

**ALBENDAZOLE**

**ITEM 5 (F) : Mutagenicity**

**Tabular Summary**

***In vitro*, non-mammalian cell system**

**Report no./Title :** A-1025-80/(AHP#57), November, 1980/ Mutagenicity evaluation of albendazole (SK&F 62979) in the Ames Salmonella/microsome plate test

**Volume/Page :** **1.100/000002**

**Laboratory :**

***In vitro*, non-mammalian cell system :**

| Objective | Test system/Strain | Replicates /Group | Dose per plate /Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To evaluate mutagenic activity of albendazole in a *Salmonella typhimurium* assay with and without metabolic activation | *Salmonella typhimurium*. TA-1535, TA-1537, TA-1538, TA-98, TA-100 | Two | 1, 10, 100, 500, 1000, 2500, 5000, 10000 ug in DMSO<br><br>and appropriate positive and negative controls<br><br>with or without S9 (rat) or S9 (calf) | 2 days | Albendazole was not toxic to any *Salmonella* strain<br><br>Albendazole exhibited no genetic activity and was considered non-genotoxic under the test conditions |

**ALBENDAZOLE**

**ITEM 5 (F) : Mutagenicity**

**Tabular Summary**

***In vitro*, non-mammalian cell system**

**Report no./Title :** LB No. 20998, December 1980/ Mutagenicity evaluation of albendazole (SK&F 62979) in the Ames salmonella/ microsome preincubation plate test

**Volume/Page :** **1.100/000018**

**Laboratory :**

| Objective | Test system/Strain | Replicates /Group | Dose per plate /Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To evaluate mutagenic activity of albendazole in a *Salmonella typhimurium* assay with and without metabolic activation in a preincubation protocol | *Salmonella typhimurium* TA-1535, TA-1537, TA-1538, TA-98, TA-100 | One | 1, 10, 100, 500, 1000, 2500, 5000, 10000 ug in DMSO<br><br>and appropriate positive and negative controls<br><br>with or without S9 (rat) | 2 days, following incubation of the bacteria with test substance for 20 min before plating out | Albendazole was not toxic to any *Salmonella* strain<br><br>Albendazole exhibited no genetic activity and was considered non-genotoxic under the test conditions |

**ALBENDAZOLE**
**ITEM 5 (F) : Mutagenicity**
**Tabular Summary**
***In vitro*, non-mammalian cell system**

**Report no./Title :** A-1027-81/(AHP#58), March, 1981/ Mutagenicity evaluation of SK&F 81038 in the Ames salmonella/microsome plate test
**Volume/Page :** **1.100/000033**
**Laboratory :**

***In vitro*, non-mammalian cell system**

| Objective | Test system/Strain | Replicates /Group | Dose per plate /Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To evaluate mutagenic activity of SK&F 81038, a metabolite of albendazole, in a *Salmonella typhimurium* assay with and without metabolic activation | *Salmonella typhimurium* TA-1535, TA-1537, TA-1538, TA-98, TA-100 | Two | 1, 10, 100, 500, 1000, 2500, 5000, 10000 ug in DMSO<br><br>and appropriate positive and negative controls<br><br>with or without S9 (rat) or S9 (calf) | Two days | SK&F 81038 was not toxic to any *Salmonella* strain<br><br>SK&F 81038 exhibited no genetic activity and was considered non-genotoxic under the test conditions |

**ALBENDAZOLE**

**ITEM 5 (F) : Mutagenicity**

**Tabular Summary**

***In vitro*, mammalian cell system**

**Report no./Title :** LB No. 21000, January 1981/ Mutagenicity evaluation of albendazole (SK&F 62979) in an *in vitro* cytogenetic assay measuring chromosome aberration frequencies in chinese hamster ovary (CHO) cells

**Volume/Page :** **1.100/000049**

**Laboratory :**

| Objective | Test system/Strain | Replicates /Group | Concentrations /Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To evaluate the ability of albendazole to induce chromosome aberrations in CHO cells, with and without metabolic activation | CHO (CHO-WBI) cells | One (100 cells per group scored for chromosome aberrations) | 0.047, 0.094, 0.188, 0.375, 0.75, 1.5 ug/ml* in DMSO<br><br>and appropriate positive and negative controls<br><br>with or without S9 (rat) | Without S9, 10 -12h<br><br>With S9, 2h** | There was no significant increase in chromosom aberrations in CHO cells exposed to albendazole<br><br>Conclusion: Albendazole was non-genotoxic under the conditions of the study |

* Maximum concentration selected on the basis of toxicity in culture to BALB/3T3 cells, which are considered to provide a good estimate of toxicity to CHO cells

** Because S9 (rat) is toxic to CHO cells

**ALBENDAZOLE**

**ITEM 5 (F) : Mutagenicity**

**Tabular Summary**

***In vitro*, mammalian cell system**

**Report/Title :** A-1030-82/T1709.109, April 1982/ Activity of T1709 (albendazole) in the *In vitro* mammalian cell transformation assay in the presence of exogenous metabolic activation

**Volume/Page :** 1.100/000065

**Laboratory :**

*In vitro*, **mammalian cell system:**

| Objective | Test system/Strain | Replicates /Group | Concentrations Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To investigate the *in vitro* morphological transforming potential of albendazole in the presence of metabolic activation. | BALB/3T3 clone A31 mouse cell line | 15 | 10, 30 100ug/ml in DMSO<br><br>and appropriate positive and negative controls, ALL in the presence of S9 | 2h (Evaluation 4-6 weeks later) | Cytotoxicity: albendazole was non-toxic<br>Cell transformation: Transformant foci were seen in solvent controls (1/15 cultures) and 10ug/ml albendazole (2/15) but not at 30 or 100ug/ml albendazole. Therefore, albendazole caused no statistically significant increase relative to controls in the number of transformant foci.<br><br>Conclusion: albendazole was non-genotoxic under the conditions of the experiment. |

**ALBENDAZOLE**
**ITEM 5 (F) : Mutagenicity**
**Tabular Summary**
***In vitro*, mammalian cell system**

**Report/Title : LBI 21002, December, 1980/*In vitro* transformation of mouse BALB/3T3 cells assay with activation by primary rat hepatocytes**
**Volume/Page : Full report not included; summary report is provided in Item 5, Toxicology Narrative, Volume 1.8**
**Laboratory :**

*Preliminary study*

| Objective | Test system/Strain | Replicates /Group | Dose per culture /Vehicle | Exposure Duration | Observations |
|---|---|---|---|---|---|
| To investigate effect of albendazole on colony-forming ability of BALB/3T3 cells in the presence and absence of metabolic activation | Mouse BALB/3T3 cells | 3 | 1mg to 0.061ug/m (15 doses in 2-fold dilution steps)<br><br>DMSO<br><br>Primary rat hepatocytes used for metabolic activation | 2 days exposure, 4-5 days growth | Survival relative to control<br>With metabolic activation: from 5.4% at 0.244ug/ml to 62.4% at 0.061ug/ml<br>Without metabolic activation: from 14.6% at 0.244ug/ml to 77.6% at 0.061ug/ml |

**Report/Title : LBI 21002, December, 1980/*In vitro* transformation of mouse BALB/3T3 cells assay with activation by primary rat hepatocytes**

| | | | | | |
|---|---|---|---|---|---|
| *Main study*<br>To investigate the *in vitro* morphological transforming potential of albendazole in the presence and absence of metabolic activation. | Mouse BALB/3T3 cells | 15 | 0, 0.009375, 0.01875, 0.0375, 0.075 and 0.15ug/ml, with appropriate positive and negative controls<br><br>DMSO<br><br>Primary rat hepatocytes for metabolic activation | 2 days exposure, 4 weeks growth | With metabolic activation, increases in transformed foci were seen at 0.1875ug/ml (1.3x control) to 0.15ug/ml (2.4x control), but statistical significance was only seen at 0.0375ug/ml (2.1x control)<br>Without metabolic activation, NO increase in transformed foci at any concentration of albendazole<br><br>Conclusion Albendazole was considered to be weakly active in the BALB/3T3 cell transformation assay only in the presence of metabolic activation provided by primary rat hepatocytes. |

**ALBENDAZOLE**
**ITEM 5 (F) : Mutagenicity**
**Tabular Summary**
***In vivo***

**Report no./Title :** 61/212, November 1990/Albendazole: Micronucleus Test in the Mouse
**Volume/Page :** **1.100/000086**
**Laboratory :**

| Objective | Species/Strain | No/Group | Dose (mg/kg) Route/Vehicle | Treatment Duration | Observations |
|---|---|---|---|---|---|
| To detect chromosomal damage and/or aneuploidy in mouse bone marrow after oral administration | Mouse<br><br>BKW | Rangefinding - 2M + 2F | 500, 1000, 2000, 5000<br><br>0.5% CMC | Single dose with 3 day observation | No clinical signs or deaths. Dose for main study set at 5000 mg/kg |
| | | Main test - 5M + 5F | 5000<br>0.5% CMC<br><br>+ve control 50mg/kg cylcophosphamide | Single dose, with kills at 24, 48 and 72h<br><br>only 24h kill for cyclophos-phamide | At 24 and 48h, a small, but non-toxicologically significant, increase in micronucleated PCE's No change in NCE/PCE ratio.<br><br>Conclusion: Albendazole was considered to be non-genotoxic under the test conditions |

# ALBENDAZOLE
## ITEM 5: ADME Studies
## Tabular Summary of Reported Studies

**Report/Title:** A-4006-78/ (AHP#13), August 1979/ The Isolation and Quantitation of Metabolites from Urine of Charles River Mice Treated Orally with $^{14}$C-Labeled SK&F 62979 (Albendazole)
**Volume/Page:**
**Laboratory:** SmithKline Animal Health Products, Applebrook Research Center

| Species/Strain | Dose / Route of Administration | No. of animals per sex | Method | Observations |
|---|---|---|---|---|
| Mouse/Charles River CD | 13.25 mg/kg (p.o.) | 12 Males (2 groups of 6 treated identically) | Urine was collected at 24 h intervals for 72 hours. The principle metabolites were identified in urine extracts using thin layer chromatography techniques. | Following single dose administration of [$^{14}$C]albendazole in the mouse, approximately 20.5% of the dose was excreted in the urine within 72 hours. Most of the recovered radioactivity (19.5% of the dose) was excreted within the first 24 hours. [$^{14}$C]Albendazole was extensively metabolized by the mouse. Albendazole was not visible after autoradiography, but the zone corresponding to that in which albendazole would have been located c. mprised only 0.5% of the total recovered radioactivity. Metabolism of albendazole in the mouse involved oxidation at the sulfur atom to the corresponding sulfoxide and sulfone and was similar that reported for the rat. The zone corresponding to metabolite C (albendazole sulfoxide) accounted for 24.2% of the total recovered radioactivity; metabolite O (propyl group hydroxylation) had 29.9% of the total recovered radioactivity and metabolite E (propyl group hydroxylation), 21.6%. Metabolite I, formed from hydrolytic cleavage of the carbamate to the corresponding 2-amino derivative, important in the steer, sheep and, to a lesser extent in the rat, comprised only 3.7% of total extractable radioactivity. |

# ALBENDAZOLE
## ITEM 5: ADME Studies
## Tabular Summary of Reported Studies

**Report/Title:** A-4003-78 (AHP#14), May 1978/ The Isolation and Identification of the Albendazole Metabolites E & G from the Urine of Sprague-Dawley Rats Orally Dosed with Methyl [5-(propylsulfonyl)-1H benzimidazol-2-yl]carbamate $^{14}C$ ring.
**Volume/Page:**
**Laboratory:** SmithKline Animal Health Products, Applebrook Research Center

| Species/Strain | Dose / Route of Administration | No. of animals per sex | Methods | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague-Dawley | 10 mg/kg (p.o.) | 2/F | Rats were dosed three times at weekly intervals. Urine was collected for 24 hours after each dose. Metabolites were identified in urine extracts on the basis of NMR (in the case of E), FDMS and thin-layer mixed spot comparison of disparate systems. | Metabolites E and G were identified as methyl [5-[(2-hydroxypropyl) sulfonyl]-1H-benzimidazol-2-yl] carbamate and methyl [5-[(3-hydroxypropyl) sulfonyl]-1H-benzimidazol-2-yl] carbamate, respectively. |

# ALBENDAZOLE
## ITEM 5: ADME Studies
## Tabular Summary of Reported Studies

**Report/Title:** A-4003-78/(AHP#15), May 1979/ Urinary Excretion and Identification of Metabolites from Urine of Sprague-Dawley Rats Orally Dosed with Albendazole-$^{14}$C, Albendazole Sulfoxide-$^{14}$C and Albendazole Sulfone-$^{14}$C
**Volume/Page:**
**Laboratory:** SmithKline Animal Health Products, Applebrook Research Center

| Species/Strain | Dose / Route of Administration | No. of animals per sex | Methods | Observations |
|---|---|---|---|---|
| Rat<br><br>Sprague-Dawley | [$^{14}$C]albendazole<br>13.25 mg/kg;<br><br>[$^{14}$C]albendazole sulfoxide<br>14.05 mg/kg;<br><br>[$^{14}$C ]albendazole sulfone<br>14.85 mg/kg<br><br>(p.o.) | 18F<br>(6 per group) | Urine was collected at 24 h intervals for 72 hours. The principle metabolites were identified from urine extracts using thin layer chromatography techniques. | [$^{14}$C]Albendazole was extensively metabolized by the rat. Albendazole was not visible after autoradiography, but the zone corresponding to that in which albendazole would have been located comprised 1.9% of the total recovered radioactivity. Metabolism of albendazole in the rat involved oxidation at the sulfur atom to the respective sulfoxide (C) and sulfone. The zone corresponding to metabolite C (albendazole sulfoxide) accounted for 26.6% of the total recovered radioactivity. Hydroxylation of the propyl group to β- and γ-hydroxysulfone metabolites E and G, respectively, accounted for 14% and 24.2% of the total recovered radioactivity. Hydrolytic cleavage of the carbamate to the corresponding 2-amino derivative (I) accounted for 14.8% of the radioactivity.<br><br>[$^{14}$C]Albendazole sulfoxide when administered, was not as extensively metabolized as albendazole. However, the composition of the urine extract was similar to the that from rats dosed with albendazole. $^{14}$C-Albendazole sulfone was extensively metabolized when administered. Metabolites E and I accounted for 81% of total extractable radioactivity. No lower oxidation state of sulfur was detected. |

# ALBENDAZOLE
## ITEM 5: ADME Studies
## Tabular Summary of Reported Studies

**Report/Title:** A-4015-80(Report #16), March 1981/ Pharmacokinetic Study of the Effect of Albendazole $C^{14}$ in Rats [*translated from* "Expertise pharmacocinetique de l'albendazole $C^{14}$ chez le rat"]
**Volume/Page:**
**Laboratory:**

| Species/Strain | Dose / Route of Administration | No. of animals per sex | Methods | Observations |
|---|---|---|---|---|
| Rat<br><br>Wistar | 10 mg/kg (p.o.) | 12M/12F | For tissue distribution studies, rats were sacrificed 15 and 30 min and 1, 2, 3,5,7,12,18,24,48 and 72 h after dosing. Radioactivity in blood and tissues was determined by liquid scintillation counting. | Radioactivity in blood reached a maximum approximately 3 hours after single dose administration of [$^{14}$C]albendazole in the rat. Thereafter, radioactivity declined rapidly to negligible concentrations 18-24 hours after dosing. The maximum tissue radioactivity was generally observed in tissues obtained 2-3 hours after dosing. The highest concentrations of radioactivity were found in the liver and kidney. After 24 hours radioactivity was low in all organs, the liver showing the greatest retention. |
| | | 3M/3F | Urine and feces were collected daily for 5 days. Radioactivity was determined by liquid scintillation counting. | Approximately 80% of the dose was recovered in urine and feces up to 5 days after oral administration of [$^{14}$C]albendazole in the rat. An average total of about 11% of the radioactivity was eliminated in the feces and 69% in the urine. Almost all (85%) of the radioactivity excreted over 5 days was recovered in the urine during the first 24 hours. It is probable that a greater percentage of the dose was eliminated as there was some evidence that fecal collection was incomplete. |

# ALBENDAZOLE
## ITEM 5: ADME Studies
## Tabular Summary of Reported Studies

**Report/Title:** October 1986 (Report #17), Bioavailability Study of Albendazole in Rabbits
**Volume/Page:**
**Laboratory:**

| Species/Strain | Dose / Route of Administration | No. of animals per sex | Methods | Observations |
|---|---|---|---|---|
| Rabbit<br><br>New Zealand White | 10 mg/kg and 30 mg/kg<br><br>(p.o.) | 7F | Blood samples were obtained at 0.5, 1,2,4,8,12 abd 24 hours after dosing. Plasma concentrations of albendazole, albendazole sulfoxide and albendazole sulfone were determined by HPLC. Pharmacokinetic parameters were calculated using noncompartmental methods. | Albendazole was rapidly absorbed and metabolized following oral administration in rabbits. Plasma concentrations of albendazole were low (<0.25 ug/mL) or undetectable following both the 10 and 30 mg/kg doses. Mean AUC(0-t) for albendazole sulfoxide increased in an approximate dose proportional manner between 10 and 30 mg/kg. Maximal plasma concentrations of albendazole sulfoxide occurred between 2 and 4 hours after dosing with mean values of 3.43 ug/mL and 8.48 ug/mL following the 10 and 30 mg/kg doses, respectively. Plasma concentrations of albendazole sulfone were about 1/3 those of albendazole sulfoxide with concentrations still rising at 24 hours in some animals. |

*RESULTS:*

*ACUTE TOXICITY STUDIES:*

*[i]. CD-1 Mouse (po)*
*$LD_{50}$ > 5 g/kg; No abnormalities were observed in treated animals.*

*[ii]. Wistar Rat (po)*
*$LD_{50}$ = 2.4 g/kg;*
*Necropsy findings: urinary staining of abdomen, chromodacryorrhea, congestion of gut, and red gut contents.*

*[iii]. ICI-derived Wistar Rat (po)*
*$LD_{50}$ = 1.32 g/kg;*
*Necropsy findings: Deaths occurred 4 to 9 days after dosing, report showed prolonged anorexia. Some rats had mass of semi-solid drug occluding gut, however, late dying rats had empty guts.*

*[iv]. Syrian hamster (po)*
*$LD_{50}$ > 10 g/kg;*
*Necropsy findings: No abnormal findings observed.*

*[v]. New Zealand White Rabbit (po)*
*$LD_{50}$ between 500 and 1250 mg/kg;*
*Necropsy findings: dead animals showed dilated gut and fluid-filled gut.*

*SUBCHRONIC/CHRONIC TOXICITY STUDIES:*

*[i]. 3-Month feeding study of albendazole in CD-1 Mouse*
*Dose: 0, 200, 400, 800, 1600 mg/kg/day for 90 days.*
*Results - no significant treatment-related effects observed.*

*[ii]. 3-Week feeding study of albendazole in S.D. Rats.*
*Dose: 0, 45, 60 mg/kg/day for 21 days.*
*Results - no significant treatment-related effects observed.*

*[iii]. 4-Week sub-acute oral toxicity study of albendazole in S.D. Rats.*
*Dose: 100 mg/kg, increasing to 200 and to 600 mg/kg for 14 days.*
*Results - all animals at increasing doses died between days 5 and 14 following piloerection, weight losses, and diarrhea.*

*[iv]. 3-Month oral toxicity study of albendazole in Long-Evans Rats.*
*Dose: 0, 2, 10, 30 mg/kg for 91 to 96 days.*
*Results - No treatment-related effects reported.*

*[v]. 4-Week sub-acute toxicity study of albendazole in dogs.*
*Dose: 0, 4, 16, 48, & 168 mg/kg, po; for 28 days plus 4 weeks of recovery period at 48 and 168 mg/kg.*
*Results - At 48 and 168 mg/kg, diarrhea, vomiting, polypnea, tachycardia, and respiratory distress were observed. Leukopenia was observed at 48 and 168 mg/kg dose groups, which disappear during the recovery period. Blood chemistry showed increases in alkaline phosphatase at 16, 48, & 168*

*mg/kg groups. Testis decreased at 168 mg/kg. Tissue histopathology was unremarkable.*

*[vi]. **A 6-Month oral toxicity study of albendazole in dogs.***
***Dose:** 0, 5, 30, & 60 mg/kg, po; for 186 to 194 days.*
***Results** - At high dose, a slight reduction in weight was observed. Hemoglobin, hematocrit, and red blood cells were reduced in 3 to 6 months at 60 mg/kg, especially in male dogs. Neutropenia was observed at 30 mg/kg. Blood chemistry showed significant increases in alkaline phosphatase (ALP) at all dose levels. Testis reduced at 60 mg/kg. Microscopic pathology data showed high incidences of hypocellular marrow (granulocytic and erythrocytic) at 60 mg/kg in both sexes.*

*[vii]. **REPRODUCTION TOXICITY:***
***Segment I:***
*In the rat study, there was evidence of testicular atrophy noted in the rats which received 10 or 30 mg/kg/day for at least 60 days before mating, however, all surviving males produced offsprings without any treatment-related effect on litter size.*
***Segment II:***
*In common with other benzimidazole compounds, albendazole has been shown to be teratogenic.*
*[a]. In the mouse teratology study, no effects were seen at up to 30 mg/kg/day.*
*[b]. In the first teratology study in rats albendazole was teratogenic at 30 mg/kg/day causing skeletal malformations. At 2, 5, and 10 mg/kg/day, the nature and frequency of the malformations indicated a possible treatment-related effect. However, a second study demonstrated that albendazole was teratogenic in rats at 10 mg/kg/day but not at 5 mg/kg/day. The teratogenicity after oral administration of albendazole and equimolar doses of ten of its metabolites was also examined in the rats. Only albendazole and its principal metabolite, albendazole sulfoxide, were embryotoxic or teratogenic, the NOEL for each being approximately 6 mg/kg/day, in each case.*
*[c]. In rabbits no malformations were seen at 2 or 10 mg/kg/day, but at the maternally toxic and embryotoxic dose of 30 mg/kg/day, all offspring were malformed.*
*[d]. When mated pigs were treated weekly with 30 mg/kg/day between days 5 and 37 after mating, only 30% of the females bore live young, compared with 95% controls, and in 38% of the litters, skeletal and soft tissue deformities were present in the treatment group, compared with 0% in the control litters.*
***Segment III***
*When pregnant female rats were treated with 40 mg/kg/day from day 16 of pregnancy to the end of lactation in a peri and post natal study, weight gain was retarded and survival and weight gain of their offspring were severely affected. Of 55 pups which died, 33 had soft tissue malformations. No adverse effects were seen at 10 or 20 mg/kg/day and there was no effect on the performance of the offsprings in neuropharmacological evaluations, including survivors in the high dose group.*
*Although female rats in the three generation study received a*

*dose during pregnancy which has been shown to be within the teratogenic range (mean of 14.8 mg/kg/day) during the growth phase, no adverse effects were seen in the offspring, including the ability to reproduce.*

*[viii]. **SPECIAL TOXICITY STUDIES:***
*Albendazole was shown to be non irritant to the skin and eye in rabbits and to have no potential to produce dermal sensitization in guinea pigs.*

*[ix]. **MUTAGENICITY:***
*The mutagenicity of albendazole has been examined in-vitro in non-mammalian and mammalian test systems and in-vivo in the mouse micronucleus test. No mutagenic activity was seen in bacterial mutation (Ames) assays with or without metabolic activation, with or without preincubation nor in the Chinese Hamster Ovary test of chromosomal aberration. Two in-vitro transformation assays in BALB/3T3 cells were performed. In one assay, weak transforming ability was seen, in the presence of metabolic activation provided by primary hepatocytes, at 0.01875 to 0.15 µg/ml. In the second study, metabolic activation by rat liver (S9), albendazole had no effect in this assay at concentrations up to 100 µg/ml and was not cytotoxic at that level. In the mouse micronucleus test, no mutagenic activity was seen in mice given a single dose of 5 gm/kg/day and where the bone marrow was examined after 24, 48 and 72 hr.*
*Albendazole is, therefore, not considered mutagenic.*

*[x]. **ONCOGENIC POTENTIAL OF ALBENDAZOLE:***
*Carcinogenicity studies were conducted in the mouse and rat. The results and histological material of each study were subjected to a review by an FDA-constituted Pathology Working Group (PWG).*
*Study 1: Mice were treated via the diet with 0, 25, 100 or 400 mg/kg/day for 108 weeks. There was no effect on the incidence of neoplasia. The incidence of endometrial polyps was higher than in controls at 400 mg/kg/day, but within the range of historical control data.*
*Study 2: The rat carcinogenicity study was conducted under more stringent conditions as the $F_0$ generation was treated with 0, 1, 2.5 or 5 mg/kg/day via the diet for 60 days before mating and till their $F_1$ offspring were weaned. The weanlings were then entered into the main study at 28 days old when the doses of treated groups increased to 3.5, 7 or 20 mg/kg/day. Treatment continued at these levels for another 116-117 weeks. Although endometrial polyps and follicular adenoma of the thyroid gland were seen most frequently at 20 mg/kg/day, the incidence was considered within the historical data range. Therefore, albendazole was considered not carcinogenic in rodents.*
*A satellite group of animals from the carcinogenicity studies was evaluated for toxicological response. This group of animals showed no toxicities which had not been already described in the shorter term studies.*

*[xi].*

*[a]. **PHARMACOKINETIC STUDIES: ADME OF ALBENDAZOLE IN ANIMAL MODELS:***

*The pharmacokinetics of albendazole have been studied in the rat, dog, and rabbit while the biotransformation has been studied in the rat and mouse. Following oral dosing in all species examined, albendazole was rapidly converted to albendazole sulfoxide, such that albendazole concentrations in plasma were negligible or below detectable limits. The systemic anthelmintic activity of albendazole was attributed to the primary metabolite, albendazole sulfoxide. Studies with oral [$^{14}$C]albendazole in the rat and mouse indicated that albendazole was moderately well absorbed. In the mouse, approximately 20% of the administered dose was recovered in the urine following administration of [$^{14}$C]albendazole. In studies in the rat, radioactivity excreted in the urine ranged from 30 to 70% of the administered dose following single oral doses of [$^{14}$C]albendazole (10-13.25 mg/kg).*

*The absorption of albendazole followed First-Order-Kinetics in the rat probably due to passive diffusion with no evidence for a saturable mechanism. Maximal plasma concentrations of albendazole sulfoxide occurred between 2 and 6 hours following oral dosing in the rat, rabbit and dog. The extent of albendazole sulfoxide bioavailability appeared to be lower in the dog compared with the rat and rabbit. Albendazole sulfoxide mean $AUC_{(0-t)}$ in the dog was 10.6 µg.h/ml compared to 32.9 and 31.9 in the rat and rabbit, respectively, following single oral doses of albendazole at 10 mg/kg. However, in all species, albendazole sulfoxide was the primary circulating metabolite with plasma concentrations consistently higher (3 to 7-fold) than those of the sequential metabolite, albendazole sulfone. The pharmacokinetics of albendazole sulfoxide appeared to increase in a dose-dependent manner between 10 and 30 mg/kg following single oral doses in the rabbit.*

*Albendazole-related metabolite was rapidly eliminated from tissues and blood following a single oral dose of [$^{14}$C]albendazole at 10 mg/kg to male and female Wistar rats. Maximal radioactivity was observed in organs and blood 2-3 hours after dosing. The highest amount of drug-related metabolite was observed in the liver and kidneys. Radioactivity in the blood declined with a half-life of about 3 hours. After 10 days of treatment with albendazole at 10.6 mg/kg/day in rats, albendazole sulfoxide $AUC_{(0-18)}$ decreased by about 52%, while plasma concentrations of albendazole sulfone were increased (92%) compared with single dose administration. These data seem to suggest auto-induction of metabolism following repeated administration of albendazole to rats. Other studies showed that increases in cytochrome $P_{450}$ enzyme activity in vitro (30-fold increase in 7-ethoxyresorufin O-deethylase) and results of immunoblotting assays suggest that the increased sulfonation observed in vivo can be attributed to*

*the induction of rat liver cytochrome $P_{450}$IA. Another important metabolic route reported in both the rat and mouse was hydroxylation of the propyl group to hydroxysulfone metabolites. In the rat, an additional pathway of importance was hydrolytic cleavage of the carbamate to the 2-amino derivative. The cleaved intermediate comprised about 14.8% of the total extractable radioactivity. However, the formation of the 2-amino derivative was less important in the mouse, and comprised only 3.7% of the total extractable radioactivity.*

*[b].*
***COMPARISON OF ADME DATA IN ANIMAL AND MAN:***

*Albendazole has been shown to be poorly absorbed following oral administration in healthy volunteers and hydatid and neurocysticercosis patients, probably due to low water solubility. It has been determined that albendazole oral absorption is enhanced following administration with fatty meals as evidenced by increased (up to 8X) plasma concentrations of albendazole sulfoxide compared to the fasted state. Systemic availability of albendazole sulfoxide appears to be greater in rats, rabbits and dogs compared to man. Plasma concentrations of albendazole sulfoxide were approx. 10X higher in rats and rabbits and 3X higher in dogs compared to healthy subjects following single oral doses administered to humans in yogurt at 10 mg/kg.*

*Therefore, based on the difference in systemic availability, albendazole sulfoxide concentrations in humans following the recommended clinical doses of 400 mg, BID (ca. 8 mg/kg) would be lower than the exposure achieved at the NOEL of 30 mg/kg in the 3-month oral toxicity study in rats and of the 5 to 10 mg/kg in the 3- and 6-month oral toxicity studies in dogs.*
*Reported data showed that albendazole sulfoxide induced the metabolism of 7-ethoxyresorufin in human hepatoma cells by as much as 100X, which is consistent with induction of cytochrome $P_{450}$ IA; a phenomenon that was similar to what has been reported for the rat following repeat administration.*
*Furthermore, no quantitative albendazole metabolism study has been conducted in humans, 4 of the 5 major metabolites identified in human urine were also reported in the rat and mouse. One metabolite identified in human urine, formed by hydroxylation of the benzene ring of albendazole sulfone, was not quantifiable in urine extracts of mice and rats but was found in urine of cattle and sheep. It was, therefore, speculated that sulfoxidation of albendazole in man may involve both the flavin-dependent microsomal monooxygenases and the cytrochrome $P_{450}$ monooxygenases, as previously shown in the rat. In addition, following oral dosing, albendazole (parent compound) has not been detected in human urine which is comparable to what has been reported in the rodents.*

***SUMMARY AND EVALUATION***

*1. All of the preclinical studies referenced in this submission NDA 20-666 (000) have been reviewed previously in connection with NADA 110-048 (Albendazole - VALBAZEN®).*

*2. This submission proposed to use oral albendazole tablets for the treatment of hydatid cyst diseases caused (by the larvae of Echinococcus granulosus), alveolar hydatid (by the larvae of Echinococcus multilocularis, and neurocysticercosis (by the lavae of Taenia solium. The proposed dosage form is 400 mg, BID, p.o., and duration of treatment will be dependent on the parasitic infection being treated.*

*3. The acute toxicity of albendazole in the mouse, rat, and dog appeared to be low and the sponsor speculated that acute poisoning in man may be remote. Subacute studies in the mouse, rat, and dog showed that the testis, kidneys, liver, and the hematopoietic systems are targets of toxicity. Recovery Studies showed that albendazole-associated effects significantly reversed following cessation of treatment. In the presence of testicular toxicity, fertility in males and females appeared not to be affected by treatment with albendazole. Benzimidazole compounds, e.g. albendazole, are known to be teratogenic but there may be a NOEL level for this effect for albendazole.*
*Pharmacokinetic and metabolic studies indicated that albendazole was well absorbed after oral administration to rodents and rabbits. It was rapidly converted to its sulfoxide, which also had anthelminthic properties, and the sulfoxide intermediate was then subjected to further metabolism. Albendazole was evaluated for its mutagenicity potential in several in-vitro and in-vivo systems, but considered not mutagenic. Also, carcinogenicity studies in mice and rats showed albendazole not to be carcinogenic in animal models.*

***RECOMMENDATION:***
*I.*
*Albendazole is a broad spectrum anthelmintic and antiprotozoal agent. It has been approved for use in humans for the treatment of intestinal helminths and hydatid disease in several countries of the world, including most European countries for over 15 years. Albendazole has been shown to be effective in the treatment of Echinococcus granulosus, Echinococcus multilocularis and Taenia solium.*
*II.*
*Based on the preclinical data reviewed in this document, albendazole was shown to be teratogenic in several animal species. Therefore, it is recommended that albendazole be classified as "Pregnancy Category C". Furthermore, albendazole produced significant increases in liver enzyme levels during treatment in dog indicating liver as a potential target organ of toxicity. It has also been reported to cause liver toxicity in*

hydatid disease as a result of drug damage to the hepatic cysts. It is, therefore, recommended that appropriate monitoring of hepatic enzyme activities should be done and albendazole use be stopped if significant increases in liver enzyme levels are observed.

III.

From the standpoint of pharmacology and toxicocology data submitted in support of albendazole, I have no objections to the approval of this NDA.

Oluwadare M. Adeyemo 4/23/96

Oluwadare M. Adeyemo, Ph.D.
Pharmacologist, HFD-520

cc: NDA 20-666 (000)
HFD-340
HFD-520/Pharm/MAdeyemo
HFD-520/MO/PCoyne
HFD-520/Chem/DKatague
HFD-520/CSO/PFogarty
HFD-520/Micro/JKing
HFD-520/Biopharm/PColangelo
HFD-520/Statist/JJiang

Concurrence Only:
HFD-520/Dep.DD/LGavrilovich
HFD-520/Team-Leader/REOsterberg

4/24/96

4/24/96

Clin. micro

**Division of Anti-Infective Drug Products (HFD-520)**
Clinical Microbiology Review Notes #1

**NDA # 20-666** **DATE COMPLETED: 30 April, 1996**

**APPLICANT(NDA):**

SmithKline Beacham
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

**CHEM/THER. TYPE:**
benzimidazole

**SUBMISSION REVIEWED: Original NDA**
**PROVIDING FOR: Antiparasitic indications**

**PRODUCT NAMES(S):**
Proprietary: None designated

Non-Proprietary/USAN: Albendazole

**CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.**

Carbamic acid, [5-(propylthio)-1-*H*-benzimidazol-2-yl]-methyl ester

Molecular formula: $C_{12}H_{15}N_3O_2S$

Molecular Weight: 265.33

**DOSAGE FORMS(S)**
**Tablet**

**STRENGTHS:**
200 mg per tablet

**ROUTE(S) OF ADMINISTRATION:**

Oral

**PHARMACOLOGICAL CATEGORY:**
Antihelminthic

**DISPENSED:** __X__ Rx ___ OTC

**INITIAL SUBMISSION:**
Received by CDER: 11 December, 1995
Received by Reviewer: 15 December, 1995
Review Completed: 30 April, 1996

**AMENDMENT(S)**
Received by CDER: N/A
Received by Reviewer:
Review Completed:

**RELATED DOCUMENTS:** N/A

**REMARK(S):**
Significant portions of the text of this review were supplied by the applicant as an electronic submission of summary text and data to the NDA. However, the full data format consisted of publications and references. Appropriate references were evaluated for the purposes of NDA review. Where applicable, the summations of the full data format were edited into the FDA perspective and included in this review.

This application contains microbiological data beyond the scope of the proposed Indications for this drug. Much of the microbiological data pertains to organisms such as *Entamoeba histolytica.* In time, such organisms may become significant for this drug, but the Review Team has chosen to restrict considerations to those parasites which will be covered under the medical Indications. From the microbiological perspective, only *Echinococcus* species and *Taenia solium* will be considered along with issues related to benzimidazole resistance.

**CONCLUSIONS and/or RECOMMENDATIONS:**

This NDA is approvable with the following proposed draft labeling for the Clinical Pharmacology section.

**Clinical Pharmacology**

The principal mode of action for albendazole is by its inhibitory effect on tubulin polymerization, which results in the loss of cytoplasmic microtubules. Albendazole appears to be active against the following organisms.

*Echinococcus granulosus*

*Echinococcus multilocularis*

*Taenia solium*

**Pharmacokinetics ...**

**Microbiological Review Notes:**

**TABLE OF CONTENTS**

## INTRODUCTION

Benzimidazoles were originally developed as plant fungicides and later as veterinary anthelmintics. The first benzimidazole to be developed for human use was thiabendazole in 1961. Since then three other benzimidazoles (mebendazole, flubendazole, albendazole) have been approved in various parts of the world for human use. All these are benzimidazole carbamates and show a broad spectrum of activity against helminth parasites. More recently albendazole has been shown to be active against some protozoa and possibly, some fungal infections. This review only pertains to those species of parasites requested for full clinical indications.

## PRECLINICAL EFFICACY

*In vitro*

Mechanism(s) of Action.

Albendazole is a benzimidazole carbamate known to be active against a number of different human and veterinary parasites, but for a long time the mechanism of action was obscure. The mode of action against lower eukaryotes is similar for most benzimidazole carbamates. The first approach to finding a mechanism was published in 1973 by Prichard et al who suggested that the benzimidazoles inhibited fumarate reductase. Since then numerous mechanisms have been proposed. Some of these mechanisms, along with their dates of publication, are listed below in Table A.

**Table A: Listing of formerly proposed modes of action for the benzimidazole anthelmintics**

| Function |
|---|
| Inhibition of fumarate reductase |
| Inhibition of glucose uptake |
| Inhibition of microtubule formation |
| Uncoupling of oxidative phosphorylation |
| Altered metabolic pathways |
| Inhibition of transmembrane proton discharge |
| Inhibition of monoamine oxidase activity |
| Inhibition of acetylcholine esterase |

However, it is now clear that the primary mode of action is to bind to the cytoskeletal protein matrix, inhibiting the polymerization of tubulin to form the microtubulin matrix of the eukaryotic cell.

The molecular and biochemical mechanisms have been extensively studied over the last 20 years. Tubulin and microtubules are universally present in eukaryotic cells, and the lower toxicity to mammalian cells is related to the reversibility of tubulin binding of the benzimidazole; the reversibility is not exhibited in the parasite. Thus, the mammalian cell behaves in a similar manner to a benzimidazole resistant parasite cell.

## Antimicrobial Spectrum of Activity.

### Activity of Antihelmintics

The assessment of activity of antiparasitic drugs is complicated since many parasites are not capable of being cultured or maintained *in vitro* in the laboratory, while in others the relationship between *in vitro* effects and those *in vivo* are unclear. Much of the available data on the sensitivity of specific species is based on *in vivo* experience over many years.

### General spectrum of activity

Albendazole has been shown to have activity *in vitro* or *in vivo* in animal models or in man principally against helminth species, but more recently some data have emerged which provide evidence for antiprotozoal and antifungal activity.

### Helminths

In general, although animals may be intermediate hosts for human parasites, it is only as larval stages. Conversely, some species of helminths may have adult stages in animals with man as an accidental host for a larval stage. Most helminth species do not survive in culture and do not transfer well to animals in their adult stages. Data for human species of helminth parasites is essentially only available for man as the animal model.

## Mechanism(s) of Resistance Studies (Panel).

Resistance to albendazole and other benzimidazole anthelminthics is well described for nematode parasites of domestic animals. However, no clinically significant resistance has been described for human helminth parasites. The applicant suggests that there are three probable reasons for this. First, there are no generally accepted *in vitro* methods for susceptibility testing of helminths, thus making assessment of any drug failures very difficult. The evidence for resistance in animals is generally based on evidence of falling efficacy in monitored animal populations rather than laboratory data. Secondly, the conditions required for resistance are heavy infestation pressure on the host combined with frequent drug therapy. While these conditions occur in domestic animals, particularly farm animals, these conditions do not currently occur in human populations. Finally, while resistance has been seen in ruminants (sheep/cattle), the pharmacokinetics of albendazole in sheep/cattle is markedly different from man. In animals, the drug recycles through the rumen to extend the half life of albendazole to 48 hours or more (compared to 7-8 hours in man); in animals the helminths are exposed to prolonged high concentrations of drug. While this prolonged high concentration increases efficacy against certain species of animal helminths, e.g. *Fasciola hepatica*, it also increases drug

pressure substantially.

Epidemological Studies (Published Literature).

N/A

*In vivo*

Pharmacokinetics/Bioavailability
(Human and animal).

N/A

Animal Prophylactic and Therapeutic Studies.

*Echinococcus granulosus* and *Echinococcus multilocularis*

The first drug with any significant activity in hydatid disease was mebendazole. Several workers independently reported the effect of mebendazole against *Echinococcus* in small laboratory animals with peritoneal cysts. The thin walled cysts of rodents, however, are

not considered an ideal model for hydatid disease in man. Cysts in man tend to be large, often solitary hepatic or pulmonary cysts, usually with a thick fibrous ectocyst layer. Cysts seen in infected sheep are very similar in macroscopic appearance to those seen in man; the sheep model is considered valid for hydatid disease in man.

Penetration of albendazole sulphoxide (the active metabolite) into hydatid cysts *in vitro* has been studied in an ovine model and in man (human daughter cysts, cyst masses comprising small cysts from gerbil intraperitoneal infestations and single larger gerbil cysts). While penetration in the *in vitro* model was very rapid, entry was much slower *in vivo*. In man a significant difference was seen between cyst concentration in patients treated for 24 hours and those treated for one month; in the latter group mean cyst fluid concentration of 165 µg/l was measured. *In vivo*, concentrations of albendazole sulphoxide are similar or exceed those shown to be active *in vitro*, while only the highest mebendazole levels achieved *in vivo* have been shown to have *in vitro* activity .

The significance of *in vitro* activity is questionable based on observations with a prophylaxis model using gerbils. The gerbil model is important because the model provides an opportunity to study post-operative albendazole prophylaxis. Prophylaxis is important for *E. granulosus* because recurrence is an important problem following operations for hydatid disease in man. In the gerbil model, significant protection against an intraperitoneal injection of 5,000 protoscolices was achieved by a one month course of albendazole (10mg/kg/day). However, when prophylaxis was delayed for 15 days after peritoneal inoculation, albendazole had no protective effect. These observations suggest that protoscolices are most easily killed by initiating therapy immediately following spillage.

*Taenia solium*

Neurocysticercosis (NCC) may follow normal human gut infestation with the parasite, *Taenia solium*. Neurocysticercosis is characterized by cysts in the brain containing larvae of *Taenia solium*. These cysts are the target for treatment of NCC by albendazole in a manner similar to hydatid cysts. However, NCC in humans is a blind alley in its life cycle from the parasite's perspective because human brain tissue is not normally ingested. Similarly, cysts from living human brain tissue is not generally available for *in vitro* studies. Overall, the activity of albendazole for *Taenia solium* can only be determined through clinical efficacy studies; the Microbiology portion of the final albendazole labeling will by necessity be based on the FDA approved clinical success for treating NCC due to *Taenia solium*.

CLINICAL EFFICACY

Clinical Microbiology N/A

Isolates/relevance to approved indications. N/A

Inoculum density studies N/A

Disk content Studies. N/A

MIC broth/agar dilution comparisons. N/A

MIC/Disk diffusion Correlation Studies. N/A

Quality Control Studies (MIC and Disk diffusion). N/A

Cross Resistance/Cross Susceptibility Studies. N/A

Anaerobic Studies. N/A

*Haemophilus* and *Neisseria* Studies. N/A

Bacteriological Efficacy N/A

Correlation of Test Results with Outcome Statistics. N/A

Package Insert.

Isolates Approved

*Echinococcus granulosus*

*Echinococcus multilocularis*

*Taenia solium*

Interpretative Criteria Established. N/A

James R King 5/3/96
James R. King

Microbiologist, HFD-520

SMicro/ASheldon
RD initd 5/3/96 ABS 5/3/96

DepDir/LGavrilovich 5/3/96

cc: Orig. NDA # 20-666
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon
HFD-502
HFD-520
HFD-520/Micro/King
HFD-520/MO/Coyne/Leissa
HFD-520/Pharm/Adeyemo
HFD-520/Chem/Katague
HFD-520/CSO/Fogarty

Printed for signatures on 3 May, 1996

Chem

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS**
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-666 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 23-APR-96

| SUBMISSION/TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| ORIGINAL | 08-DEC-95 | 11-DEC-95 | 14-DEC-95 |
| AMENDMENT(MINOR) | 05-APR-96 | 09-APR-96 | 09-APR-96 |

**NAME & ADDRESS OF APPLICANT:** SMITHKLINE BEECHAM PHARM
One Franklin Plaza
P.O Box 7929
Philadelphia, PA 19101

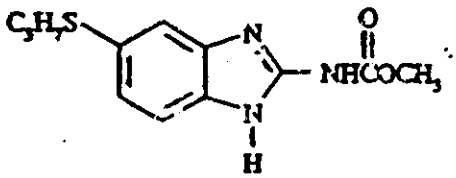
**DRUG PRODUCT NAME**
Proprietary: Albendazole( Zentel) Tablets
Nonproprietary/USAN: Albendazole, USP
Code Names/#'s:
Chemical Type/
Therapeutic Class: 1 P

**ANDA Suitability Petition/DESI/Patent Status:**
N/A [if applicable]

**PHARMACOLOGICAL CATEGORY/INDICATION:** Treatment of hydatid cyst disease and neurocysticercosis

**DOSAGE FORM:** tablets
**STRENGTHS:** 200 mg, MDD=800 mg
**ROUTE OF ADMINISTRATION:** oral
**DISPENSED:** ___X___ Rx _____ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:** Methyl 5-(propylthio)-2-benzimidazolecarbamate




*Molecular Formula:* $C_{12}H_{15}N_3O_2S$

*Molecular Weight:* 265.33

**SUPPORTING DOCUMENTS:**

DMF
DMF

**RELATED DOCUMENTS (if applicable):**

Albendazole is a broad spectrum antihelmentic and antiprotozoal agent. It is available for patient use in about 100 countries for treatment of intestinal helminths and in several countries ( including UK and Germany) for the treatment of hydatid disease. It is available as ESKAZOLE, a 400 mg tablet, and as ZENTEL, a 200 mg tablet. In 1989, the applicant albendazole suspension, VALBAZEN, was approved in the United States for the treatment of animal helmintic infections. Albendazole has also been available for treatment in the US on a 'compassionate use" IND basis since 1986 for hydatid cyst disease and later for neurocysticercosis. The applicant does not hold an IND for human use of Albendazole for the above two infections, but maintain Drug Master Files for cross-referencing purposes to support investigator-sponsored INDs.

**CONSULTS:**

Biopharmaceutics- IN PROGRESS

**REMARKS/COMMENTS:**

The applicant has requested Orphan drug designation for each indication on November 13, 1995. The expected combined incidence of both hydatid disease and neurocystecircosis in the US is less than 1000 cases annually. This is well below the 200,000 cases defined for a "rare disease or condition".

The data to support safety and efficacy of albendazole in this NDA is based primarily on data generated from published material augmented with actual data from patient's case histories and "compassionate use" data and not from the conventional large, well-controlled multicentered clinical trials. In addition, there are data from one clinical trial conducted in Peru to support the treatment of neurocysticercosis.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is approvable for manufacturing and controls under section 505 of the Act. All manufacturing facilities are currently in acceptable GMP compliance. Attached is an acceptable EER dated 3/22/96, which should be valid up to 365 days.

As post approval commitments, the applicant is requested to provide specification limits for impurities and or degradation products at or above 0.1% in the drug substance and drug product. The applicant is also requested to submit a trademark for the drug product as soon as available.

Daniel B. Katague 4/23/96
D.B.KATAGUE, Review Chemist

cc: Orig. NDA 20-666
HFD-520/Division File
HFD-520/KATAGUE/
HFD-520/MO/Coyne
HFD-520/Pharm/Osterberg
HFD-520/Micro/King
HFD-520/CSO/Fogarty
HFD-520/SUPERVISOR 5/1/96

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20666-1

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# ENVIRONMENTAL ASSESSMENT

# AND

# FINDING OF NO SIGNIFICANT IMPACT

# FOR

## Albendazole Tablets

## NDA 20-666

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

**FINDING OF NO SIGNIFICANT IMPACT**

**NDA 20-666**

**Albendazole Tablets**

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Albendazole Tablets**, **SmithKline Beecham Pharmaceuticals** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Albendazole is a synthetic drug which will be administered orally in the treatment of hydatid disease. The active moiety is used in the U.S. in an approved veterinary product. The Center for Veterinary Medicine reviewed an environmental assessment and issued a finding of no significant impact on March 23, 1989.

The drug substance will be manufactured by SmithKline Beecham Quimica, S.A. de C.V., Cuernavaca, Mexico. The drug product will be manufactured by SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Albendazole may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Test data indicate that albendazole will partition significantly to sludge and thus there is potential that it may be transported to the terrestrial environment where it will be moderately immobile. However, albendazole is expected to be degraded or metabolized to some extent to compounds that are much more likely to enter the aquatic environment. Albendazole is expected to be eliminated from the environment by photodegradation and

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be sent to licensed disposal companies. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The incremental increase in the use of this drug that will result from this approval does not change the Agency's previous conclusion that a finding of no significant impact is appropriate. The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/18/96 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

4/18/96
DATE CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-666/PFogarty copy to NDA/HFD-520
HFD-357/EA File NDA #20-666
HFD-357/Docket File
HFD-205/FOI COPY

# ENVIRONMENTAL ASSESSMENT
## Albendazole Tablets

1. **DATE:** July 24, 1995

2. **NAME OF APPLICANT:** SmithKline Beecham Pharmaceuticals

3. **ADDRESS:** Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

## 4. DESCRIPTION OF THE PROPOSED ACTION:

### 4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for the manufacture, marketing and distribution of Albendazole Tablets for the treatment of hydatid disease in humans. Albendazole is a benzimidazole carbamate that has broad spectrum anthelmintic activity, and is effective against most nematodes and some cestodes. A 200 mg tablet has been commercially available in Europe and other international markets for the treatment of intestinal parasites since 1982 under the trade Zentel® Eskazole®, a 400 mg dosage form, became available in Europe in March 1992 for the treatment of *Echinococcus* infection or hydatid disease. In June 1989, SB Animal Health's albendazole suspension (Valbazen®) was approved in the U.S. to treat animal helmintic infections.

### 4.2 Need for the Proposed Action

Albendazole is a synthetic benzimidazole carbamate substance which is effective against parasitic diseases. Albendazole has been used in the treatment of hydatid cyst disease, neurocysticercosis, and microsporidiosis. The manufacture of albendazole tablets is significantly important in the treatment of hydatid disease. Because of the wide spectrum of albendazole activity, the need of combination therapy is minimized. The mode of action of albendazole, as an anthelmintic substance, is presumed to be similar to other 2-amino substituted benzimidazole anthelmintics which eliminate helminths via interfering with the polymerization of microtubulin.

This Environmental Assessment reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste

product production. It also includes references to pertinent fate and effects data and evaluations that are available to date for albendazole.

The manufacture of albendazole drug substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Drug Substance will be Produced

Albendazole, the drug substance in the product which is the subject of the proposed action, is manufactured in five process stages at the site below.

4.3.1 Cuernavaca, Mexico

SmithKline Beecham Quimica, S.A. de C.V.
Calle 37-Este 126, Civac
Jiutepec, Morelos
Mexico

4.4 Location where Drug Product will be Produced

4.4.1 Cidra, Puerto Rico

Albendazole drug product (200 mg Tablets) will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Road 172, km 9.1
P.O. Box 11975
Cidra, Puerto Rico

The SmithKline Beecham Pharmaceuticals Co. facility is equipped for manufacturing, packaging, warehousing, and performing Quality Assurance operations for pharmaceuticals. The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. Details on the environmental characteristics of the Cidra community are given in Appendix III. Stability testing of commercial batches will also be carried out at

4.5 Locations where Product will be Used

Albendazole Tablets that are the subject of this New Drug Application (NDA) will be used in the United States of America with predominant use coinciding with areas of greatest population density.

4.6 Locations where Product will be Disposed of

Albendazole drug product returned goods will be collected at the following site:

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Documentation for the Bristol disposal facilities is provided in Appendix I.

## 5. DESCRIPTION OF CHEMICAL SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION:

Albendazole drug substance is described below. The environmental fate and effects of albendazole are described in Items 7 and 8 of this assessment, respectively. Albendazole is a very stable compound at room temperature and in neutral aqueous solution. No degradation products have been reported from albendazole stability studies. Stability data

albendazole was 100.3% on April 1, 1987; on January 7, 1992 the same albendazole sample was reanalyzed and results showed a potency of 99.8%. Therefore, the compound is stable, and no degradation is likely to arise under normal storage conditions.

5.1 Complete Nomenclature for Albendazole:

**British Approved Name (BAN):** Albendazole

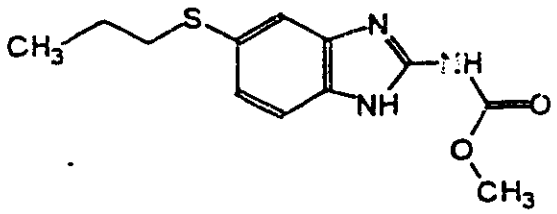
**United States Adopted Name (USAN):** Albendazole

**Uninverted USAN Name:**
Methyl 5-(propylthio)-2-benzimidazolecarbamate

**Other Names Used Within This Application:**
1.) Carbamic acid, [5-(propylthio)-1*H*-benzimidazol-2-yl]-methyl ester
2.) [(5-n-propylthio)-1*H*-benzimidazol-2-yl] carbamic acid, methyl ester

**Chemical Abstracts Name:**
Carbamic acid, [5-(propylthio)-1-*H*-benzimidazol-2-yl]-methyl ester

| | | |
|---|---|---|
| 5.1.1 | CAS Number: | 54965-21-8 |
| 5.1.2 | Laboratory Code: | SK&F-62979 |
| 5.1.3 | Molecular Formula: | $C_{12}H_{15}N_3O_2S$ |
| 5.1.4 | Molecular Weight: | 265.33 |
| 5.1.5 | Structural Formula: | SK&F 62979 (albendazole) |




| | | |
|---|---|---|
| 5.1.6 | Description: | Albendazole is a white to off-white powder |
| 5.1.7 | Melting Point Range: | Melting occurs at 214-215°C with decomposition |

5.1.9 Impurities:

Five impurities have been identified in albendazole prepared by the current route of synthesis. The structural formula and description of impurities from the synthesis process are presented in Item 3.A/Drug Substance of the Chemical, Manufacturing, and Controls section of the Albendazole Tablets NDA.

The assay for albendazole is performed by a reversed phase HPLC analysis, or by a titrimetric method with 0.1 N perchloric acid. The HPLC analysis is run isocratically at room temperature. The flow rate is 0.7 mL/min and the detector wavelength is set at 254 nm. Under these conditions the retention time of albendazole is 12 minutes (the HPLC method is described in Item 3.A of the Chemical, Manufacturing, and Controls section of the Albendazole Tablets NDA).

The residual solvents are identified by gas chromatography. Impurities are identified by TLC and/or HPLC. Identification of albendazole is carried out by infra-red analysis and thin layer chromatography.

## 6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

### 6.1 Introduction from Production of Albendazole

The production of albendazole drug substance and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. For this assessment, engineering estimation are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology that may be implemented before actual approval of the albendazole application.

#### 6.1.1 Drug Substance Production at Cuernavaca

Albendazole drug substance will be made in five process stages (regarding the environmental fate of the process compounds) at Cuernavaca, at the SmithKline Beecham Pharmaceuticals' facility in Cuernavaca, Mexico. The chemicals and the quantities expected to be used at Cuernavaca are presented in Tables 1, 2A and 2B in Confidential Attachment 1. The projected fifth year number of lots made per process stage is presented in Table 15

Cuernavaca are presented in Confidential Attachment 1. Environmental evaluations of the impacts from drug substance production follow.

#### 6.1.1.1 Waste Stream Summary and Disposition

The wastes generated at Cuernavaca will be either recovered or disposed of using appropriate procedures (see Destination of Waste Streams in Confidential Attachment 1, Table 4) such that their disposal will not violate applicable regulations. The waste stream chemicals, their description and quantities expected to be produced at Cuernavaca during the five stages of albendazole production are presented in Tables 3, 4, 5A and 5B in Confidential Attachment 1.

#### 6.1.1.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for the five stages, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay sample solutions, and floor and equipment washings.

#### 6.1.1.3 Controls Exercised on Wastes

The following specific permits have been issued to the Cuernavaca plant in Mexico.

- Discharge Registry - Authorized by the Secretaria the Recursos Hidraulicos, SARH (Hydraulic Resources Department). November 28, 1973.

- A treatment plant contract with ECCACIV to collect, transport and treat wastewater in accordance with the Secretaria de Desarrollo Urbano y Ecologia (SEDUE) (Secretariat of Urban and Ecological Development) Regulations, signed in April, 1992. There is no expiration for the contract between the Cuernavaca site and ECCACIV.

- Solid wastes are confined in the Residuos Industriales Multiquim, S.A. de C.V. (RIMSA). Register No. 5081 form SEDUE.

### 6.1.1.3.1 Air and Fugitive Emissions

The gas/vapor emissions and particulates produced during the process stages are controlled by the following systems:

- Scrubber system
- HAVEG absorption system
- Odex system
- Dust extractor

Air emissions generated during the production process, consisting of volatile organic compounds, will be controlled by condensers. In additio.., there is an odex system with a caustic scrubbing solution connected to each reactor and centrifuge to further treat condenser and reactor emissions prior to discharge to the atmosphere. Air emissions are in compliance with the Reglamento para la Prevencion y Control de la Contaminacion Atmosferica Originada por la Emision de Humos y Polvos (Regulation for the Prevention and Control of the Atmospheric Contamination Originated by the Emission of Vapors and Dusts), Chapter 2, Articles 20 and 21.

Dust emissions are controlled by a dust extraction system in the powder handling areas to comply with the above mentioned dust regulations.

### 6.1.1.3.2 Incinerated Wastes

The incinerator at Cuernavaca was sized to destroy the waste volumes expected from th. SmithKline Beecham plant at Cuernavaca operating at a total maximum capacity of 368 tonnes of chemical production per year.

The MKI-25-RC Incinerator System, Serial No. 192, is designed for the destruction of the liquid waste streams identified below on a sustained 24 hour per day, 7 days per week basis:

| Quantity | Description | Nominal Average Composition (% by weight) |
|---|---|---|
| 592 gph | Aqueous wastes | 69.6% water; 20.0% organic; 6.0% NaCl; 4.0% $Na_2SO_4$; 0.4% NaBr |
| 25 gph | Solvents with dissolved tars | < 10.0% water; > 86.0% hydrocarbons; |

After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before being discharged to the environment through a stack. This scrubber unit consists of a caustic solution circulating through a packed bed. The solution, typically NaOH and water, is continuously recirculated through the two scrubbers and it is treated, after being disposed, in the wastewater treatment facility in Cuernavaca (ECCACIV). The maximum capacity of the incinerator is 30,000,000 Btu/hr, and the maximum feed is 20,000 tonnes (solid, liquid, gaseous waste)/year. Table 9, in Confidential Attachment 1, lists the quantities and the chemical waste stream sent for on-site incineration regarding albendazole production at Cuernavaca.

6.1.1.3.3 Aqueous Waste Recovery and Disposal

Several organic solvents are recovered from the aqueous waste streams (see Table 4 in Confidential Attachment 1). The solvent waste streams recovered either on or off-site and recycled back to the process represent 38% of the total wastes (by weight) produced during albendazole substance production. The non-recovered organic solvent is discharged into the wastewater treatment facility in Cuernavaca (ECCACIV). Table 6, in Confidential Attachment 1, lists the quantities and the chemicals (organic and inorganic) discharged into the ECCACIV wastewater treatment plant based on an albendazole production of one lot per day (maximum production and "worst case" scenario). The total process contribution of total suspended solids (TSS) and chemical oxygen demand (COD) are presented in Confidential Attachment 1, Table 6. Aqueous wastes not suitable for solvent recovery or discharge are either disposed in a landfill or sent off-site for contract disposal (see Table 7 and 8 in Confidential Attachment 1).

6.1.1.3.4 Solid Waste Disposal

Waste streams consisting primarily of solids produced during the albendazole five process stages are listed in Confidential Attachment 1, Tables 7 and 8. Waste disposal companies currently employed have been audited by SmithKline Beecham personnel for competence. There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.1.3.5 Regulated Aqueous Effluent Components

The total suspended solids (TSS) and the theoretical oxygen demand (ThOD) (it was

Confidential Attachment 1. The contributions from the albendazole process in terms of TSS and COD are calculated from data presented in Tables 5A and 5B in Confidential Attachment 1. The effluent from the site, prior to be discharged into the ECCACIV, is routinely monitored by the SmithKline Beecham Cuernavaca Quality Assurance department to ensure effluent adherence to consent levels.

Review of the measured (current level) and calculated (process contribution) concentrations of affected aqueous effluent components and a comparison with their limits (see Table 6 in Confidential Attachment 1) resulted in the determination that the Cuernavaca facility is expected to be in compliance with their aqueous effluent limits, regarding TSS and COD concentrations, during production of albendazole at 5th year production levels.

#### 6.1.1.4 Environmental Legislation

General environmental control criteria were established under the New Ecological Law (Ley general de Equilibrio Ecologico y Protection al Medio Ambiente) - date January 28, 1988.

The environmental requirements of the ecological law regulations include waste treatment, disposal of storm water, chemical storage, drum storage, air emission, odor emission control, sludge and solids waste disposal, noise control, and air monitoring.

Since the initial plant start-up, environmental legislation has been updated and at the present the following basic laws apply:

- Water Pollution: March 29, 1973
  Regulation for the prevention and control of water pollution.

- Air Pollution: November 25, 1988
  Regulation of the general law of ecological equilibrium and environmental protection regarding "the prevention and control of atmospheric pollution matter".

- Toxic and Dangerous Waste: November 25, 1988
  Regulation of the general law of ecological equilibrium and environmental protection regarding dangerous residue matter.

### 6.1.1.5 Personnel Safety

Personnel working in the plant are provided with safety helmets, safety glasses/goggles, uniforms, safety shoes and gloves as their normal protective equipment. If conditions warrant, the operators have at their disposal an air breathing system, air suits, aprons, and boots. The working directions are written, advising the operators which safety equipment must be used to handle each operation. In addition, the plant has Material Safety Data Sheets for chemicals handled in the plant.

### 6.1.1.6 Emergency Response Plan

The SmithKline Beecham Cuernavaca site maintains an updated Emergency Response Plan that covers the employees general procedure in case of an emergency, the emergency brigade program, evaluation of the emergency exits, and the return of activities after an emergency call. Training courses for the employees are offered periodically, and a list of the courses and attendees are documented and filed in the Cuernavaca site.

The site also has a chemical spill control plan. All storage vessels are contained within spillage bunds (dikes). Furthermore, each tank has a discharge valve and the site is provided with spill control kits.

### 6.1.1.7 Certification of Compliance

SmithKline Beecham Pharmaceuticals, Cuernavaca, Mexico, will operate within its permits during the production of albendazole drug substance. A citation of and statement of compliance is provided in Appendix II.

### 6.1.2 Introduction from Production of Drug Product at Cidra

Albendazole drug product (Albendazole Tablets) will be produced in a continuous process that consists of granulation, drying and blending, compression and coating, and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of albendazole 200 mg tablets will employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products. The chemicals and the quantities expected to be used at Cidra during product production are presented in Tables 10 and 11 in Confidential Attachment 2. The projected fifth year production estimates are presented in Table 15 in Confidential Attachment 2. All data tables for drug

product production at Cidra are presented in Confidential Attachment 2. Environmental evaluations of the impacts from drug product production follow.

#### 6.1.2.1 Waste Stream Summary and Disposition

The waste stream summary and product description (per lot) expected to be produced at Cidra are presented in Tables 12 and 13 in Confidential Attachment 2.

Effluent chemicals consist of an minimum estimated loss of 1.5 % of the input chemicals, and a maximum estimated loss of 5%. Waste generated at the Cidra facility will be disposed of using appropriate procedures (see Destination of Waste Stream in Confidential Attachment 2, Table 12), such that release into the environment will not exceed Cidra permit levels (Appendix III).

#### 6.1.2.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay solutions, end floor and equipment washings.

For the purpose of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on the projected fifth year of Albendazole Tablets production for the United States.

#### 6.1.2.3 Controls Exercised on Wastes

##### 6.1.2.3.1 Dryer Water Vapor

Dryer water vapor consists of water evaporated during drying processes. This stream is filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment.

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the

Commonwealth of Puerto Rico. The facility is operating under the following permits: PFE-21-0692-0772-I-II-III-O (2/1/94) and PFE-21-1094-1272-II-C (2/27/95).

6.1.2.3.2 Aqueous Wastes Disposed Of Through Biotreatment

The aqueous waste streams (production and floor and equipment washing) are sent to the on-site wastewater treatment facility. The streams are first pumped through a series of sand filters and an activated carbon adsorption system. The waste streams are then discharged into an equalization holding tank for aeration. Sanitary waste bypasses sand and carbon columns and goes directly to the equalization basin. The pH of the influent stream is adjusted with sodium hydroxide or carbon dioxide prior to entering the activated sludge system. The residence time of the effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a safety factor of 127,000 gallons per day. The biotreated waste stream then goes to a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent as supernatant.

The pH of the aqueous effluent (supernatant) is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. Filtered effluent is collected in a filter effluent sump. This filtered effluent then passes through a Reverse Osmosis (RO) module for total solids and organic removal. RO permeate is collected in a 100,000 gallon storage tank and RO reject is further treated in the Puerto Nuevo Regional Wastewater Treatment Plant. The effluent from the RO is then chlorinated, aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). Approximately 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged into the Las Quebradillas Creek. Rainwater runoff from the grounds of the Cidra facility are also discharged to the same creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan).

The activated carbon (granular Calgon AC, 8 X 30 mesh) from the biotreatment facility is replaced approximately every three months, and the spent carbon is returned to the manufacturer for regeneration. Settled sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting

the water. More water is then removed from the concentrated sludge slurry by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Dried sludge removed from the beds is disposed of at a municipal landfill after testing using the Toxicity Characteristic Leaching Procedure (TCLP).

For the purpose of this environmental assessment, the total quantity of drug product components estimated to be emitted into the on-site biotreatment facility is 1.5% (minimum) to 5% (maximum) of the total batch.

Final effluent levels from biotreatment facility were calculated using the following equation:

$$(A \times 10^6 \text{ (mg/kg)} / B)C = D$$

where:
A = total quantity of component to waste per day (kg/day);
B = site effluent discharge rate (L/day);
C = removal efficiency;
D = concentration of component in effluent (mg/L).

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of compounds occurs during treatment, and that biodegradation and filtration are the only removal mechanisms. Effected components and their calculated contributions to the effluent, based on a maximum daily production, are presented in Table 14 in Confidential Attachment 2. Review of the calculated concentrations of affected aqueous effluent components, and a comparison with their permitted effluent levels (Table 16 in Confidential Attachment 2) resulted in the determination that the Cidra facility is expected to be in compliance with their aqueous effluent permits.

Therefore, the contributions of the compounds used in the 200 mg tablet formulation of albendazole to the total quantity of regulated components in the effluent are not expected to cause effluent concentrations to exceed the permit levels, since nearly complete removal of the compounds by the wastewater treatment facility is expected. The quality of the effluent discharge meets Puerto Rico's water quality standards. The on-site treatment facility operates under a National Pollutant Discharge Elimination System (NPDES) Permit. In Puerto Rico, the NPDES Permit Program is administered by the Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations include the Puerto Rico Harmful Spills Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the on-site wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix III.

6.1.2.3.3 Solid Wastes

Solid wastes containing drug product (rejects, protective clothing, drums, filters, pharmaceutical processing collected dust) are disposed of off-site to Ogden Martin Systems of Lake, Inc., Okahumpka, Florida, US. There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.2.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

Federal Water Pollution Control Act, as amended
Clean Water Act, as amended
Resource Conservation and Recovery Act
Safe Drinking Water Act
Toxic Substances Control Act
National Environmental Policy Act

6.1.2.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.1.2.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico, will operate within its permits during the production of Albendazole Tablets. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III. A Material Safety Data Sheet for albendazole is given in Appendix IV.

## 6.2 Introduction from Use of Drug Product

Human pharmacokinetic studies (using radiolabeled albendazole) referenced herein indicate that <1% of the total applied dose is excreted via urine as several albendazole metabolites, whereas the compound(s) excreted via feces have not been identified. For the purposes of this assessment, then, it is assumed that 100% of the applied albendazole dosage will be excreted into the environment (primarily via feces) as unchanged albendazole. This scenario may be taken as the "worst case", since the more polar albendazole sulfoxide (and other metabolites) have been identified in human bile (reference [6], in Confidential Attachment 4) and in urine, indicating that the drug material excreted is most likely not just the parent drug albendazole.

The fraction of albendazole that is absorbed into the bloodstream undergoes extensive first-pass metabolism, as determined during pharmacokinetics studies in patients being treated for hydatid disease, during which albendazole was not detected in the plasma and thus appeared to be metabolized extremely rapidly. Estimates of the Maximum Expected Emitted Concentrations (MEEC) and the Predicted Environmental Concentrations (PEC) of albendazole and albendazole sulfoxide from use of Albendazole Tablets is given in Confidential Attachment 3. Analyses of the fate and effects of albendazole (and its metabolites) are presented in Item 7 and Item 8, respectively, of this assessment.

## 6.3 Introduction from Disposal of Drug Product

Albendazole drug product returned goods will be collected at the following site:

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Documentation for the Bristol disposal facilities is provided in Appendix I. Based on the controlled and highly efficient thermal destruction of unused albendazole drug substance and product, no material should be introduced into the environment from disposal.

## 7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Results of environmental fate studies of albendazole and its metabolites are presented below. These study summaries were obtained from an earlier comprehensive environmental assessment by SmithKline Beecham for the New Animal Drug Application for the use of albendazole in cattle, entitled *Environmental Assessment of Albendazole: A Broad-Spectrum Anthelmintic*, dated March 7, 1989 [1]. The Freedom of Information Act summary of that assessment is thus used as a reference herein.

### 7.1 Metabolism

#### 7.1.1 Pharmacokinetics in Animals

Albendazole has been used for about 30 years in the treatment of helminthiasis in animals, and is now used around the world for veterinary applications. Metabolism studies using several species have been performed. From studies performed in cattle and sheep, albendazole is rapidly metabolized via sulfur oxidation and/or carbamate hydrolysis. The primary albendazole metabolites detected in cattle and sheep excreta were albendazole sulfoxide, albendazole sulfone, and albendazole 2-aminosulfone; several other minor metabolites have also been identified. The excretion pattern for cattle is summarized below.

**Percentage of Albendazole and Primary Metabolites Excreted by Cattle**

| | Albendazole | Albendazole sulfone | Albendazole sulfoxide | Albendazole 2-aminosulfone | Others | Total |
|---|---|---|---|---|---|---|
| Urine | 0.4 | 5.2 | 20.1 | 19.9 | 30.4 | 76.0 |
| Feces | 0.4 | 3.4 | 4.5 | 3.1 | 12.6 | 24.0 |
| Total | 0.8 | 8.6 | 24.6 | 23.0 | 43.0 | 100 |

7.1.2 Pharmacokinetics in Humans

Although now widely available in many countries for the treatment of intestinal helminthiasis in man (reference[2], in Confidential Attachment 4), there is little data on the pharmacokinetics and excretion of albendazole in humans. Available data on human excretion are limited to urine only. The primary metabolite identified in urine was albendazole sulfoxide; the sulfone and 2-aminosulfone metabolites were present in lesser quantities, and several other minor metabolites were in even lesser quantities. In contrast to the animal studies, total human urinary metabolites account for <1% of the totaled applied dose.

Albendazole has been shown to be poorly absorbed upon oral dosing in humans, probably due to its very low aqueous solubility (0.2 ug/mL at pH 7.4, with phosphate buffer) (reference [3], in Confidential Attachment 4). Albendazole that is absorbed from the gut is metabolized rapidly, with unchanged albendazole at concentrations below the detection limit in plasma, urine and bile during one study (reference [2], in Confidential Attachment 4). Albendazole sulfoxide, the primary metabolite in humans and other species, is known to be anthelmintically active.

Metabolites are largely eliminated from blood within 72 hours and the half-life for albendazole sulfoxide in plasma has been determined to be 8.38 hours (reference [4], in Confidential Attachment 4). Seven of nine animal metabolites have also been identified in human urine (reference [4], in Confidential Attachment 4), which suggests that the pattern of metabolism is qualitatively similar to that determined for other animals. See Figure 1 for the proposed metabolic pathway of albendazole in man. In Figure 1, Metabolite C is albendazole sulfoxide, Metabolite A is albendazole sulfone, and Metabolite I is albendazole 2-aminosulfone, the three major urinary metabolites.

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In animals, metabolism of albendazole occurs mainly in the liver, which is also likely to be the site for metabolism in humans (reference [2], in Confidential Attachment 4). Sulfoxidation of albendazole may also occur in the intestines, as indicated by an *in vitro* sulfoxidation study using rat intestinal microsomes (reference [5], in Confidential Attachment 4). Albendazole sulfoxide has also been found in bile (reference [6], in Confidential Attachment 4) indicating biliary excretion as a contributing route of depletion of albendazole sulfoxide from the human body.

## 7.2 Physical Properties

The following physical properties were determined for albendazole and the major metabolites [1]. Details are provided in the following sections.

| Property | Albendazole | Albendazole sulfone | Albendazole sulfoxide | Albendazole 2-aminosulfone |
|---|---|---|---|---|
| Aqueous Solubility (mg/L, pH 7) | 0.53 | 6.82 | 67.5 | 511 |
| $K_{ow}$ | 501 | 26 | 14 | 0.62 |
| $pK_a$ | ND | 6.78 | 7.87 | 9.35 |
| Soil Adsorption (maximum adsorption $K_{oc}$) | 27500 | ND | 2900 | ND |
| UV/vis ($\lambda$max, nm, pH 7) | 295 | 291 | 292 | 290 |
| ($\varepsilon$, M-1.cm-1) | 1.11E4 | 1.10E4 | 2.36E4 | 1.22E4 |

ND = Not Determined

### 7.2.1 Aqueous Solubility

The aqueous solubilities of albendazole and the major metabolites were determined in pH 5, 7, and 9 buffers. Data are summarized in the following table.

**Aqueous solubility of albendazole and selected metabolites (mg/L)**

| Chemical | pH 5.0 | pH 7.0 | pH 9.0 |
|---|---|---|---|
| Albendazole | 0.579 | 0.530 | 0.564 |
| Albendazole sulfone | 8.05 | 6.82 | 7.51 |
| Albendazole sulfoxide | 71.7 | 67.5 | 72.1 |
| Albendazole 2-aminosulfone | 1343 | 511 | 488 |

As shown in the table, albendazole metabolites are much more soluble in water than albendazole itself. Oxidation of the sulfur atom causes the sulfoxide and sulfone metabolites to be more polar than albendazole. In addition, ionization of the benzimidazole nitrogen atom is expected to increase the aqueous solubility of the molecules at pH < $pK_a$.

7.2.2 Octanol/Water Partition Coefficient (Kow)

The $K_{ow}$ values for albendazole and the major metabolites are summarized in the following table.

| Chemical | $K_{ow}$ | log $K_{ow}$ | % Solute in Water Phase |
|---|---|---|---|
| Albendazole | 501 | 2.70 | 0.2 |
| Albendazole sulfone | 26 | 1.41 | 3.6 |
| Albendazole sulfoxide | 14 | 1.15 | 6.5 |
| Albendazole 2-aminosulfone | 0.62 | -2.08 | 60.8 |

As expected from the aqueous solubility data, albendazole metabolites are more hydrophilic than albendazole itself.

7.2.3 Volatility

No experiments were conducted to determine the volatility of albendazole or the major metabolites. Both albendazole and the metabolites have the potential to hydrogen bond with water. Based on the aqueous solubility and $K_{ow}$ data, the metabolites are hydrophilic. These data strongly suggest that neither albendazole or the metabolites are prone to volatilization from water.

7.2.4 Soil Adsorption

The equilibrium distribution of albendazole and the sulfoxide metabolite was investigated using three soils and 0.01 M $CaCl_2$ aqueous phase. As would be expected from the aqueous solubility and octanol/water partitioning data, albendazole distributed more strongly to the soils than did the sulfoxide metabolite. The effect was especially pronounced during desorption experiments; desorption log $K_{oc}$ values for albendazole were all high, ranging from 4.7 to 7.5. Results for albendazole and the sulfoxide metabolite are summarized below.

**Albendazole**

| | Adsorption | | | Desorption | | | |
|---|---|---|---|---|---|---|---|
| Soil | log $K_d$ | log $K_{oc}$ | 1/n | log $K_d$ | log $K_{oc}$ | 1/n | pH |
| TXSTLM | 2.04 | 4.13 | 1.21 | 5.44 | 7.27 | 2.86 | 8.0 |
| ILSTLM | 2.70 | 4.44 | 0.770 | 3.02 | 4.76 | 0.915 | 5.5 |
| NYLM | 2.15 | 3.89 | 0.936 | 2.96 | 4.70 | 1.33 | 6.5 |

**Albendazole Sulfoxide**

| | Adsorption | | | Desorption | | | |
|---|---|---|---|---|---|---|---|
| Soil | log $K_d$ | log $K_{oc}$ | 1/n | log $K_d$ | log $K_{oc}$ | 1/n | pH |
| TXSTLM | 0.08 | 2.18 | (a) | (a) | (a) | (a) | 8.0 |
| ILSTLM | 1.72 | 3.46 | 0.611 | 1.58 | 3.32 | 0.576 | 5.5 |
| NYLM | 0.80 | 2.54 | 0.771 | 0.81 | 2.56 | 0.657 | 6.5 |

(a) Screening tests demonstrated that < 25% adsorbed, therefore advanced tests were not required.

The soil mobility classification scheme of Hamaker [7] ranks chemicals, based on $K_{oc}$, on scale of 1 (immobile) to 5 (very mobile). Based on this scale and the experimental adsorption $K_{oc}$ values shown above, albendazole is in mobility class 2 (moderately immobile) and the sulfoxide metabolite is in mobility class 4-5 (mobile to highly mobile).

### 7.2.5 UV/vis Spectrum and Direct Sunlight Photolysis

Albendazole and all three primary metabolites exhibit absorption maxima between 290 and 295 nm at pH 7, suggesting that all four compounds may be susceptible to direct photolysis (see section 7.3.2).

## 7.3 Transformation and Depletion Mechanisms

### 7.3.1 Biodegradation

The binding, volatilization, and mineralization of $^{14}$C-albendazole in feedlot soil was investigated [1] under both aerobic and aerobic/anaerobic conditions. Headspace gasses were periodically analyzed for volatile $^{14}$C organics and $^{14}CO_2$. Soil aliquots were extracted with ethyl acetate and a pH 5 aqueous buffer solution.

Volatile organics accounted for <0.1 percent of the applied $^{14}$C activity while $^{14}CO_2$ accounted for <2 percent. The balance of the $^{14}$C activity was accounted for as follows: organic soluble - 7 to 15 percent; aqueous soluble - 5 to 16 percent; bound to soil - 69 to 89 percent. The degree of soil binding increased with time. The data indicate minimal volatilization and mineralization of the compounds in the test system. The significant amount of $^{14}$C activity that was aqueous extractable suggests that $^{14}$C-albendazole may have been metabolized by the soil microflora to more polar metabolites. Based on the soil adsorption data, little or no $^{14}$C-albendazole would be expected to be aqueous extractable.

No experimental data are available concerning the biodegradation of albendazole in aquatic systems. However, literature data indicate extensive oxidation of benzyl sulfides to the corresponding sulfoxides and sulfones by the yeast, *Aspergillus niger* [14]. It is highly probable that sulfoxidation of albendazole to sulfoxide and/or sulfone degradants by activated sludge microflora will occur in wastewater treatment plants.

### 7.3.2 Direct Sunlight Photolysis

Direct sunlight photolysis experiments were conducted on albendazole and the three primary metabolites under autumn irradiance conditions (September 26 to October 8). Photodegradation half-lives, calculated based on the experimental irradiance conditions and 24 hour days, are summarized below.

| Compound | Photodegradation Half-Lives ($t_{1/2}$, days) pH 5 | pH 7 | pH 9 |
|---|---|---|---|
| Albendazole | 0.525 | 0.516 | 0.704 |
| Albendazole sulfoxide | 0.525 | 0.502 | 0.096 |
| Albendazole sulfone | 1.31 | 0.516 | 0.050 |
| Albendazole 2-aminosulfone | 4.12 | 1.60 | 1.44 |

Half-lives extrapolated from the experimental data for summer and winter irradiance conditions were faster and slower than the experimental data shown above, respectively (range of 0.106 to 1.65 days). These data indicate that albendazole and the three primary metabolites are susceptible to direct sunlight photolysis with half-lives on the order of approximately one day.

7.4 Summary: Predicted Environmental Fate of Albendazole in the Environment

For the purposes of this assessment, it is assumed that the primary route of introduction of the drug substance into the environment is through wastewater treatment plants (WWTPs). Metabolism data suggest that albendazole excreted in urine will consist primarily of the sulfoxide, sulfone, and 2-aminosulfone metabolites. However, urinary metabolites account for only ~1 % of the dose in humans. Given the poor bioavailability of albendazole, a significant proportion of the total albendazole dose will be excreted via feces, presumably as unmetabolized albendazole. Available data lead to the following conclusions regarding the fate of albendazole and its metabolites in WWTPs.

- Albendazole, having a low aqueous solubility and high $K_{ow}$ and $K_{oc}$ values, will partition significantly to activated sludge solids.
- Albendazole is likely to be biologically oxidized to sulfoxide and/or sulfone degradants by activated sludge microflora but probably not mineralized.
- Albendazole degradants are much less hydrophobic than albendazole and are expected to adsorb to a lesser extent than albendazole.
- Adsorbed albendazole will leave the WWTP and enter the terrestrial environmental compartment primarily in land-farmed waste activated sludge.
- Albendazole biodegradants will remain primarily in the aqueous phase and be released to receiving waters in WWTP effluent.
- Once released to a receiving water via WWTP effluent, albendazole degradants are expected to be relatively mobile in the aquatic environment and be subject to photodegradation.

ENVIRONMENTAL ASSESSMENT
Albendazole Tablets

## 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

Results of environmental effects studies pertinent to the use of albendazole by humans are presented below. These study summaries were obtained from an earlier comprehensive environmental assessment by SmithKline Beecham for NADA 110-048, for the use of albendazole in cattle, entitled *Environmental Assessment of Albendazole: A Broad-Spectrum Anthelmintic*, dated March 7, 1989 [1]. The Freedom of Information Act summary of that assessment is thus used as a reference herein. Additional information presented below may be found in the Freedom of Information Summary - *Albendazole Suspension for Use in Cattle*, NADA 110-048 [8].

### 8.1 Human and Mammalian Health Effects Summary

#### 8.1.1 Acute Toxicity Studies

##### 8.1.1.1 Oral Toxicity [9]

The oral $LD_{50}$ was between 1320 and 2400 mg/kg in rats, greater than 3000 mg/kg in mice, greater than 10,000 mg/kg in hamsters, and greater than 500 mg/kg in rabbits.

##### 8.1.1.2 Inhalation Toxicity [9]

The inhalation toxicity has not been determined.

##### 8.1.1.3 Skin Irritation [9]

Albendazole is classified as a non-irritant to rabbit skin. There was no evidence of skin irritation following direct application in rabbits.

##### 8.1.1.4 Eye Irritation [9]

Albendazole is classified as a non-irritant to rabbit eyes. There was no evidence of irritation following direct application in rabbits.

##### 8.1.1.5 Sensitization [9]

Albendazole is categorized as a non-sensitiser to guinea pig skin (Buehler Test). Allergic reactions rarely occur in humans.

8.1.2 Chronic Toxicity Studies

8.1.2.1 Teratogenicity [9]

Teratogenic effects (birth defects) or toxicity to developing offspring occurred in studies with rats, rabbits, sheep and swine. These effects usually occurred at dose levels that also produced maternal toxicity. Rat reproductive toxicity studies showed only minimal effects on male and female reproduction. No observed effect levels (NOEL) determined during teratogenicity studies are presented in the table in Item 8.1.2.5 below.

8.1.2.2 Mutagenicity [9]

Albendazole was not observed to be mutagenic in bacteria (Ames test) or animal cells (cell-mediated Chinese hamster ovary test).

8.1.2.3 Carcinogenicity [9]

Albendazole is not listed as a carcinogen by SB, IARC, NTP, or US OSHA. Lifetime studies with mice and rats demonstrated no evidence of carcinogenicity.

8.1.2.4 Other Effects [9]

No target organ effects are known to occur in humans. Numerous subchronic and chronic toxicity studies were conducted to demonstrate the safety of this material.

8.1.2.5 Summary of Human Safety Studies

The following studies were performed and results obtained to determine the safety threshold of albendazole and any metabolites in animal tissues used for human food. Details of these studies may be found in the Freedom of Information Summary - *Albendazole Suspension for Use in Cattle*, NADA 110-048 [8].

| Study | NOEL |
|---|---|
| Teratogenicity in mice | 30 mg/kg/day |
| Teratogenicity in rats | 5 mg/kg/day |
| Teratogenicity in rabbits | 5 mg/kg/day |
| Three generation reproduction in rats | 150 ppm |
| Chronic/Carcinogenicity in rats | 7.0 mg/kg/day |
| Chronic/Carcinogenicity in mice | 25 mg/kg/day |
| Six month dog study | 5 mg/kg/day |
| Peri/Postnatal reproduction in rats | 20 mg/kg/day |

## 8.2 Aquatic Toxicity Studies

### 8.2.1 Acute Aquatic Toxicities of Albendazole

#### 8.2.1.1 Acute Toxicity to *Daphnia magna* [1]

Static acute toxicity tests of albendazole and its three major metabolites were performed with *Daphnia magna*, following the FDA Environmental Assessment Technical Assistance Document 4.08 Daphnia Acute Toxicity. Results of these studies are found in the table below; albendazole itself showed the highest level of toxicity.

**Daphnia Acute Toxicity**

| Compound | $EC_{50}$ | NOEC* |
|---|---|---|
| Albendazole | 24 ug/L | 17 ug/L |
| Albendazole sulfoxide | 30 mg/L | 11 mg/L |
| Albendazole sulfone | >14 mg/L** | 6.1 mg/L |
| Albendazole 2-aminosulfone | 110 mg/L | 53 mg/L |

* NOEC is equivalent to zero immobilization relative to controls.
** Estimated, above albendazole sulfone water solubility of 6.82 to 8.05 ppm.

#### 8.2.1.2 Acute Toxicity to Fresh Water Fish [1]

The effects of a mixture of the three major bovine urinary metabolites of albendazole on fresh water fish have also been investigated. These compounds are also the major urinary

metabolites found in man. Static, acute exposures were performed with the cold water rainbow trout, *Salmo gairdneri*, and warm water bluegill sunfish, *Lepomis macrochirus*. From 96 hour exposures at metabolite concentrations combined to simulate the relative proportions found in cattle urine (45:45:10 for albendazole sulfoxide, albendazole sulfone and albendazole 2-aminosulfone, respectively), the $LC_{50}$ values and confidence limits are presented below. These values are considerably higher than those expected to be found in the environment from the use of albendazole in cattle, and are also even higher than those concentrations expected to be found in the environment from use of albendazole by humans (see MEEC and PEC values in Confidential Attachment 3).

**Freshwater Fish Acute Toxicity**

| Species | $LC_{50}$ ~~$EC_{50}$~~ | Lower and Upper 95% Confidence Limits |
|---|---|---|
| Rainbow trout (*Salmo gairdneri)* | 86 ppm | 53 and 110 ppm |
| Bluegill sunfish (*Lepomis macrochirus)* | 222 ppm | 201 and 250 ppm |

8.2.1.3 Bioaccumulation in Bluegill Sunfish [1]

To assess the potential for albendazole and its metabolites to bioaccumulate, a bioaccumulation study was performed with Bluegill Sunfish (*Lepomis macrochirus*) to assess concentrations in edible and non-edible tissues [1]. Fish were added to water containing a total concentration of 100 ppb of radiolabeled albendazole and its metabolites; on day 44 they were transferred to a tank containing no radiolabeled material. Study results are summarized in the following table.

**Bluegill Sunfish Tissue Bioaccumulation**

| Sampling Period | Edible Tissue (ppb) | Non-edible Tissue (ppb) |
|---|---|---|
| One week | 90 | 1179 |
| 22 days | 22 | 174 |
| 44 days | 30 | 116 |
| After transfer | 13 | 29 |
| From 44 to 76 days | <20 | <40 |

Radioactivity levels rapidly decreased after day 44, indicating that the radiolabeled compounds were not persistent in the tissues.

## 8.3 Other Toxicity Studies

### 8.3.1 Acute Terrestrial Toxicities of Albendazole

#### 8.3.1.1 Acute Toxicity to Microorganisms

Several studies to determine the inhibitory effects of albendazole, albendazole sulfoxide and albendazole 2-aminosulfone (two of the three major metabolites of cattle and sheep) on bacteria, fungi and algae have been performed to assess the possible impact of albendazole and its metabolites on their growth, the results of which are presented below [1]. The minimum inhibitory effects were observed for 2 fungi species exposed to albendazole itself.

**Minimum Inhibitory Concentration of Albendazole and Two Metabolites to Soil Microflora**

| Species | Albendazole | Metabolites: Albendazole Sulfoxide | Metabolites: Albendazole 2-aminosulfone |
|---|---|---|---|
| Bacteria (ug/disc) [a,b] | | | |
| *Aerobacter levanicum* | NI | NI | NI |
| *Arthrobacter globiformis* | NI | NI | NI |
| *Bacillus subtilis* | NI | NI | NI |
| *Pseudomonas fluorescens* | NI | NI | NI |
| *Streptomyces albus* | NI | NI | NI |
| Fungi (ug/disc) [a,b] | | | |
| *Aspergillus niger* | 0.1 | 10 | 10 |
| *Chaetomium globosum* | 1 | 10 | NI |
| *Penicillium chrysogenum* | 0.1 | 3 | 3 |
| *Trichoderma viridi* | NI | NI | NI |
| Algae (ppm) [a,c] | | | |
| *Microcystis aeruginosa* | NI | 50 | 50 |
| *Selenastrum capricornutum* | NI | NI | NI |

[a] NI = No Inhibition, at any of the doses tested.

[b] Bacterial and fungal species were tested at 30, 10, 3, 1, 0.3, and 0.1 ug/ filter paper discs, which were placed on agar surfaces inoculated with the bacteria of fungi.

[c] Algae species were grown in liquid cultures containing 50, 10 or 1 ppm of the specified test compound.

The potential toxicity of albendazole to activated sludge microbes from a waste water treatment plant and to *Photobacterium* (via Microbics Microtox® test) was also evaluated, at the Corporate Environmental Research Laboratory of SmithKline Beecham. A summary of the results of these tests are included in reference [10], in Confidential Attachment 4. Albendazole, tested at a nominal concentration of 50% of water solubility (the water solubility is reported to be 0.53 mg/L at pH 7), was not inhibitory to sludge microorganisms, as determined by measurements of sludge respiration rates. Results of the test with *Photobacterium* indicated that the production of light by the bacteria was inhibited at the

maximum test concentration of 45% of water solubility, and that a calculated albendazole concentration of 68% (equivalent to 0.36 mg/L) would reduce light production of the *Photobacterium* by 50%.

### 8.3.2 Chronic Terrestrial Toxicities of Albendazole

#### 8.3.2.1 Toxicity to Earthworms [8]

A 60 day toxicity study with earthworms was performed, using agricultural soils treated at levels of albendazole and its metabolites equivalent to those estimated to occur following the incorporation of animal feedlot wastes and mixtures of the parent drug and metabolites. Mixtures were prepared in the proportions of metabolites expected following excretion from treated animals. Results of this study indicated that albendazole and its metabolites had no effect on the reproductive capability of the earthworms at the environmentally expected concentrations.

## 8.4 Summary: Predicted Environmental Effects of Albendazole in the Environment

Calculations to determine the Maximum Expected Emitted Concentrations (MEEC) and the Predicted Environmental Concentrations (PEC) of albendazole and of albendazole sulfoxide (a representative human metabolite) from human use of albendazole is presented in Confidential Attachment 3.

Based upon the studies summarized above, which were performed for the Environmental Assessment for use of albendazole in cattle [1], the use of albendazole by humans for the hydatid disease indication is also not expected to result in the release of albendazole or any of its metabolites at concentrations that may be expected to produce adverse effects upon organisms or ecosystems in the environment (see Confidential Attachment 3). To evaluate the worst-case potential ecological risk posed by introduction of albendazole into the environment, the MEEC and PEC values for albendazole may be compared to the lowest no-observed effect concentration (NOEC) obtained during ecotoxicology testing. For albendazole, the lowest NOEC value was 1.7E-2 mg/L (0.017 mg/L), obtained during the *Daphnia magna* 48-hour acute study. This NOEC value is greater than the terrestrial and aquatic MEEC and PEC values for albendazole (see Confidential Attachment 3). Therefore, introduction of albendazole parent compound into the environment at projected fifth year production levels should not result in adverse effects to aquatic or terrestrial biota.

Also, the main metabolites of albendazole have been found to be more soluble and less toxic than the parent molecule [1], and all have been experimentally determined to have short photolytic half-lives (see Item 7.3.2). Thus, albendazole and its metabolites entering the environment are not expected to bioaccumulate or be persistent.

## 9. USE OF RESOURCES AND ENERGY

### 9.1 Use of Resources And Energy At Cuernavaca

Of the total electricity, fuel and water used at the Cuernavaca facility on a yearly basis, approximately 0.067% of each is estimated to be used per production batch of albendazole drug substance.

#### 9.1.1 Effect Upon Endangered Species And Historic Places

The production of albendazole substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by albendazole substance production or waste disposal activities since the production is taking place outside of the United States.

### 9.2 Use of Resources and Energy to Produce Drug Product at Cidra

The Cidra facility for albendazole product manufacture is a 52 acre site located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico.

For the production of Albendazole Tablets at the expected 5th year level of production, the Cidra facility is estimated to use 0.14% of the electricity, fuel oil and water the facility currently uses.

#### 9.2.1 Effect Upon Endangered Species And Historic Places

The production of albendazole product and the disposal of associated wastes should have no effect on threatened or endangered species. Details on the environmental characteristics of the Cidra community are given in Appendix III. Property listed in or eligible for listing in

the National Register of Historic Places will also not be impacted by albendazole product production or waste disposal activities.

## 10. MITIGATION MEASURES

### 10.1 Mitigation At Cuernavaca

Potential adverse environmental impacts associated with the proposed action are minimized at the Cuernavaca facility by the following:

Many solvent waste streams are recovered either on or off site and recycled back to the process, representing 38% of the total wastes (by weight) produced during albendazole substance production.

No air or water emissions are directly discharged. The aqueous waste is pre-treated in neutralization cisterns before being discharged into the activated sludge wastewater plant. The volatile organic compounds present in the process air emissions are filtered and further absorbed by alkaline solutions. Dust airstreams from the process are directed to dust extractors.

The site has a spill control plan that has been effective in the prevention of environmental accidents.

### 10.2 Mitigation Measures at Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

The activated carbon from the biotreatment filters is returned to the manufacturer for regeneration approximately every three months.

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units.

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%.

A holding tank is designed to allow for the capture and treatment of any spills or oil contaminated water before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

## 11. ALTERNATIVE TO THE PROPOSED ACTION:

No potentially adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of Albendazole Tablets will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

## 12. LIST OF PREPARERS:

### 12.1 List of Contributors:

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### 12.2 Preparers:

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SmithKline Beecham
(See Appendix V for Curricula Vitae)

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## 13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the SmithKline Beecham Corporate Environmental Research Laboratory.

Date: September 1, 1995

Signature: James Hagan

James R. Hagan, P.E.
Vice President & Director
Corporate Environment & Safety
SmithKline Beecham

## 14. REFERENCES:

1. Freedom of Information Summary, SmithKline Beecham - Albendazole Suspension for Cattle, NADA 110-048. *Environmental Assessment of Albendazole: A Broad-Spectrum Anthelmintic*, for use of albendazole in cattle, March 7, 1989.

2. Marriner, S.E., Morris, D.L., Dickson, B., and Bogan, J.A. (1986). "Pharmacokinetics of Albendazole in Man." *Eur J Clin Pharmacol* 30: 705-708.

3. Bogan, J.A. and Marriner, S.E., (1984), "Pharmacodynamic and toxicological aspects of albendazole in man and animals," In: Albendazole in helminthiasis. M. Firth, (ed) Royal Society of Medicine International Congress and Symposium Series no. 61. Royal Society of Medicine 13-21.

4. Penicaut, B., Maugein, Ph., Maisonneuve, H. and Rossignol, J.F. (1983). "Pharmacokinetics and Urinary Metabolism of Albendazole in Man." *Bull. Soc. Pathol. Exot.-Filiales* 76: 698-708. Translated from the French by the Medical Documentation Service College of Physicians, Philadelphia, Pennsylvania.

5. Villaverde, C., Alvarez, A.I., Redondo, P., Voces, J., del Estal, J.L. and Prieto, J.G. "Small Intestinal Sulphoxidation of Albendazole." *Xenobiotica*. University of Surrey, UK. In press.

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9. SmithKline Beecham Material Safety Data Sheet (MSDS) Number 10000100; Albendazole; Date revised: 21 December 1993.

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11. U.S. EPA, "1984 Need Survey: Report to Congress: Assessment of Needed Publicly Owned Waste Water Treatment Facilities in the U.S.", EPA 430-9-84-011, U.S. EPA, 1984.

12. Vincent, P. G. "FDA NEPA Strategy Perspective," Invitational Paper Presentation, American Institute of Chemical Engineers, August 18-21, 1991, Pittsburgh, PA.

13. Barton, D.A. and McKeown, J.J., "Field Verification of Predictive Modeling of Organic Compound Removal by Biological Wastewater Treatment Processes", *Environmental Progress*, Vol. 10, No. 2, May 1991, p. 96.

14. Keislich, K. *Microbial Transformations of Non-Steroid Cyclic Compounds*. Stuttgart, Germany: Georg Thieme Publishers, 1976

MSDS NUMBER: 10000100 MATERIAL SAFETY DATA SHEET

## 1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

**SUBSTANCE/PREPARATION:**
ALBENDAZOLE

**TRADENAMES/SYNONYMS:**
(5-(PROPYLTHIO)-1H-BENZIMIDAZOL-2-YL-)CARBAMIC ACID METHYL ESTER * VALBAZEN * ZENTEL * ANALGON * ALBAZENE * MONIL * VALBOVINO * ALBENDAZOLUM * ABZ * SK&F 62979 * SKF-62979 * PROFTRIL * PROFTRIL SHEEP * (5-(PROPYLTHIO)-1H-BENZIMIDAZOL-2-YL-)CARBAMIC ACID METHYLESTER * METHYL 5-(PROPYLTHIO)-2-BENZIMIDAZOLECARBAMATE * ((PROPYLTHIO)-5 1H-BENZIMIDAZOLYL-2) CARBAMATE DE METHYLE (FRENCH) * (5-(PROPYLTHIO)-1H-BENZIMIDAZOL-2-YL)CARBAMIC ACID METHYL ESTER * 5-(PROPYLTHIO)-2-CARBOMETHOXYAMINOBENZIMIDAZOLE * SKF 62979 * ZENTAL * 62979 (SK&F) * 62979 (SKF) * A4673 (SIGMA-ALDRICH)

**CHEMICAL FAMILY:**
BENZIMIDAZOLE CARBAMATE ANTHELMINTIC

**MOLECULAR FORMULA:**
C12-H15-N3-O2-S

**MOLECULAR WEIGHT:**
265.342

**EINECS NUMBER:**
2594147

**ELINCS NUMBER:**
Not Assigned

**COMPANY:**
SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

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709 SWEDELAND ROAD
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**PHONE NUMBERS:**
++1-610-270-7807

++44-(0)903-822650

**EMERGENCY AND AFTER HOURS CONTACT:**
++1-800-228-5635 (EXTENSION 157)

## 2.COMPOSITION/INFORMATION ON INGREDIENTS

| INGREDIENTS | CAS REGISTRY NO | PERCENT |
|---|---|---|
| ALBENDAZOLE | 54965-21-8 | 100% |

**CONTAMINANTS:**
None identified.

## 3. HAZARDS IDENTIFICATION

**PRIMARY ROUTES OF EXPOSURE:**
Avoid breathing dust, eye contact, skin contact, ingestion.

**SKIN CONTACT:**
Irritation and allergic skin reaction are not expected following direct contact with this material, based on results of animal studies. However, skin contact should be avoided.

**EYE CONTACT:**
Irritation following direct contact with this material is not expected. However, eye contact should be avoided.

**INHALATION:**
Effects of breathing dust are not known. Avoid inhaling this material.

INGESTION:
Toxicity following ingestion can occur. Effects after over exposure are not known.

CONDITIONS AGGRAVATED BY EXPOSURE:
This material produced developmental toxicity in studies with animals. Over exposure during pregnancy might have an adverse effect on developing offspring.

## 4. FIRST-AID MEASURES

SKIN CONTACT:
Remove contaminated clothing and remaining material by flushing with water. Obtain medical assistance if immediate or delayed symptoms of skin reaction develop.

NOTE TO PHYSICIAN:
Rare instances of idiosyncratic hypersensitivity have been reported in humans following skin contact.

EYE CONTACT:
Flush eyes continuously with water for at least 15 minutes and obtain medical assistance.

NOTE TO PHYSICIAN:
None.

INHALATION:
Move exposed subject to fresh air. Seek medical assistance in case of known or possible over exposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ASSISTANCE.

NOTE TO PHYSICIAN:
For combustion products, refer to section number 5.

INGESTION:
In the event of swallowing this material, seek immediate medical assistance.

NOTE TO PHYSICIAN:
This material is not a corrosive agent.

ANTIDOTES:
None known.

## 5.FIRE-FIGHTING MEASURES

FIRE CONTROL:
Toxic or corrosive gases are expected from fires involving this material. Use water, carbon dioxide, foam or dry chemical extinguishers.

SPECIAL FIREFIGHTING PROCEDURES:
Toxic or corrosive gases including oxides of carbon, nitrogen and sulfur are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

## 6. ACCIDENTAL RELEASE MEASURES

SPILLS:
Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Wear protective clothing and equipment consistent with the degree of hazard. Carefully scoop up the spillage and place in a suitable, properly labeled container for recovery or disposal. Wash down spillage area with copious amounts of water. This must only be undertaken in waste water can be directed to an on-site

waste water treatment system.

DECONTAMINATION PROCEDURES:
Not determined.

## 7. HANDLING AND STORAGE

HANDLING:
This material has not been tested for its dust explosion properties. However, like most organic dusts, it is expected to explode when ignited as a dust cloud. Care should be taken to avoid dispersion as a dust cloud. Ensure that all items of plant and equipment used for handling this material are bonded and earthed (grounded). The presence of isolated conductors should be avoided. Use only with adequate ventilation. Enclosure is recommended to routinely control airborne dust levels below published exposure limits.

STORAGE:
Store in a cool, dry place. Do not store above 40 to 45 degrees C for longer than 6 months.

## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:
ALBENDAZOLE:
SmithKline Beecham(PEL):
0.3 MG/M3 (8 HR TWA)
INDUSTRIAL HYGIENE METHOD:
SB/1202 analytical method.

PERSONAL PROTECTION:
RESPIRATORS:
If dust is present, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:
Wear impervious gloves.

EYE PROTECTION:
Wear safety glasses with sideshields when handling this material.

HYGIENE PRACTICES:
Wash hands and arms thoroughly after handling this material.
Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:
Wear lab coat or other protective clothing with long sleeves.

## 9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:
Odorless, off-white micronised powder.

FLASH POINT:
Expected to be greater than 55 degrees C.

AUTOIGNITION TEMP:
Not determined.

LOWER EXPLOSIVE LIMIT:
Not applicable for solids.

UPPER EXPLOSIVE LIMIT:
Not applicable for solids.

MELTING POINT:
208 to 210 degrees C.

BOILING POINT:
Not determined.

VAPOUR DENSITY:
Not applicable.
VAPOUR PRESSURE:
Not applicable.
EVAPORATION RATE:
Not applicable.
VOLATILE COMPONENTS (%):
None expected.
VISCOSITY:
Not applicable.
PH OF AQUEOUS SOLUTIONS:
Not applicable.
RELATIVE DENSITY:
Not determined.
CONDUCTIVITY:
Not applicable.
PARTITION COEFFICIENT:
Not determined.
SOLUBILITY:
Soluble in dimethyl sulfoxide, strong acids and strong bases.
Insoluble in water.
OXYGEN BALANCE:
This material is considered to be of medium energy hazard potential based on oxygen balance calculated as minus 178.
TRAIN FIRE TEST:
Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.
DUST EXPLOSIVITY:
Classification: Not determined.
Minimum explosive concentration (grams/cubic metre): Not determined.
Minimum ignition temperature - cloud (degrees C): Not determined.
Minimum ignition temperature - layer (degrees C): Not determined.
Minimum oxygen concentration (% v/v): Not determined.
Explosion characteristics:
Pmax (bar): Not determined.
dP/dT (bar/second): Not determined.
Kst (bar metre/second): Not determined.
St class: Not determined.
DUST ELECTRICAL PROPERTIES:
Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm meter): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

## 10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:
Avoid direct sunlight and conditions that might generate heat.
INCOMPATIBILITY:
Not identified.
STABILITY:
This material is expected to be stable at room temperatures for up to three years.
THERMAL STABILITY:
Capillary tube test: Not determined.
Differential scanning calorimetry: Not determined.
Accelerating rate calorimeter: Not determined.

HAZARDOUS POLYMERIZATION:
Not identified.
HAZARDOUS DECOMPOSITION PRODUCTS:
None expected.
FIRE AND EXPLOSION HAZARDS:
Not expected.

## 11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:
The oral LD50 was between 1320 and 2400 mg/kg in rats, greater than 3000 mg/kg in mice, greater than 10000 mg/kg in hamsters and greater than 500 mg/kg in rabbits.
INHALATION TOXICITY:
Not determined.
SKIN IRRITATION:
This material was classified as a non irritant to rabbit skin. There was no evidence of skin irritation following direct application in rabbits.
EYE IRRITATION:
This material was classified as a non irritant to rabbit eyes. There was no evidence of irritation folllowing direct application in rabbits.
SENSITISATION:
This material was categorised as a non-sensitiser to guinea pig skin (Buehler Test). Allergic reactions rarely occur in humans.
MUTAGENICITY:
This material was not mutagenic in bacteria (Ames test) or animal cells (cell-mediated Chinese hamster ovary test).
CARCINOGENICITY:
This material is not listed as a carcinogen by SB, IARC, NTP or US OSHA. Lifetime studies with mice and rats demonstrated no evidence of carcinogenicity.
REPRODUCTIVE EFFECTS:
Teratogenic effects (birth defects) or toxicity to developing offspring occurred in studies with rats, rabbits, sheep and swine. These effects usually occurred at dose levels that also produced maternal toxicity. Rat reproductive toxicity studies showed only minimal effects on male and female reproduction.
OTHER EFFECTS:
No target organ effects are known to occur in humans. Numerous subchronic and chronic toxicity studies were conducted to demonstrate the safety of this material.

## 12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
Not determined.
BIODEGRADATION:
Not determined.
ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.
SOIL ADSORPTION:
Not determined.
OTHER EFFECTS:
Not determined.

## 13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in

a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed contract chemical incinerator.

## 14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class: Not applicable
Sub Risk: Not applicable
Packing group: Not applicable
IMDG page number: Not applicable
MFAG number: Not applicable
EMS number: Not applicable
Marine Pollutant: Not applicable
Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable

FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.

EMERGENCY INFORMATION:
HAZCHEM code: Not applicable.
TREMCARD number: Not applicable.

## 15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE CLASSIFICATION
Not classified as a significant fire hazard
HEALTH CLASSIFICATION
Harmful

ENVIRONMENTAL CLASSIFICATION
(Leave blank)
RISK PHRASES:
Possible risk of harm to the unborn child. (R63)
SAFETY PHRASES:
Avoid exposure - obtain special instruction before use. (S53)

Wear suitable protective clothing and gloves. (S36/37)

SYMBOL:
Saint Andrew's Cross.(Xn)

## 16. OTHER INFORMATION

HAZARD LABEL:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** HARMFUL ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** POSSIBLE RISK OF HARM TO THE UNBORN CHILD.
** WEAR SUITABLE PROTECTIVE CLOTHING AND GLOVES.
** AVOID EXPOSURE - OBTAIN SPECIAL INSTRUCTION BEFORE USE.
** TARGET ORGAN- NO SPECIFIC TARGET ORGAN EFFECTS KNOWN.
** SYMBOL: SAINT ANDREW'S CROSS.(XN)

REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= 1 REACTIVITY = 0

# AMENDED PAGES

ENVIRONMENTAL ASSESSMENT
Albendazole Tablets

1. **DATE:** July 24, 1995

2. **NAME OF APPLICANT:** SmithKline Beecham Pharmaceuticals

3. **ADDRESS:** Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

## 4. DESCRIPTION OF THE PROPOSED ACTION:

### 4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for the manufacture, marketing and distribution of Albendazole Tablets (NDA# 20-666) for the treatment of hydatid disease in humans. Albendazole is a benzimidazole carbamate that has broad spectrum anthelmintic activity, and is effective against most nematodes and some cestodes. A 200 mg tablet has been commercially available in Europe and other international markets for the treatment of intestinal parasites since 1982 under the trade Zentel® Eskazole®, a 400 mg dosage form, became available in Europe in March 1992 for the treatment of *Echinococcus* infection or hydatid disease. In June 1989, SB Animal Health's albendazole suspension (Valbazen®) was approved in the U.S. to treat animal helmintic infections.

Albendazole is intended to be marketed in the U.S. for human use in a 200 mg strength tablet packaged in HPDE bottles.

### 4.2 Need for the Proposed Action

Albendazole is a synthetic benzimidazole carbamate substance which is effective against parasitic diseases. Albendazole has been used in the treatment of hydatid cyst disease, neurocysticercosis, and microsporidiosis. The manufacture of albendazole tablets is significantly important in the treatment of hydatid disease. Because of the wide spectrum of albendazole activity, the need of combination therapy is minimized. The mode of action of albendazole, as an anthelmintic substance, is presumed to be similar to other 2-amino substituted benzimidazole anthelmintics which eliminate helminths via interfering with the polymerization of microtubulin.

Amended page

ENVIRONMENTAL ASSESSMENT
**Albendazole Tablets**

This Environmental Assessment reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities in Cuernavaca (Mexico) for drug substance production, and Cidra (Puerto Rico) for drug product production. It also includes references to pertinent fate and effects data and evaluations that are available to date for albendazole.

The manufacture of albendazole drug substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Drug Substance will be Produced

Albendazole, the drug substance in the product which is the subject of the proposed action, is manufactured in five process stages at the site below.

4.3.1 Cuernavaca, Mexico

SmithKline Beecham Quimica, S.A. de C.V.
Calle 37-Este 126, Civac
Jiutepec, Morelos
Mexico

Julian Laboratories occupies a 10 acre site in C.I.V.A.C. (Ciudad Industrial del Valle de Cuernavaca). C.I.V.A.C. is a 240 acre industrial park comprised of approximately 100 industrial manufacturers and located in Cuernavaca, Mexico. Cuernavaca, at an elevation of 1,540 meters, is a residential city located 70 Km southwest of Mexico City, the capital of Mexico. Julian Laboratories is located 1 Km from the residential areas of Cuernavaca.

4.4 Location where Drug Product will be Produced

4.4.1 Cidra, Puerto Rico

Albendazole drug product (200 mg Tablets) will be prepared at the following facility:

Amended page

5.1.9 Impurities:

Five impurities have been identified in albendazole prepared by the current route of synthesis. The structural formula and description of impurities from the synthesis process are presented in Item 3.A/Drug Substance of the Chemical, Manufacturing, and Controls section of the Albendazole Tablets NDA.

The assay for albendazole is performed by a reversed phase HPLC analysis, or by a titrimetric method with 0.1 N perchloric acid. The HPLC analysis is run isocratically at room temperature. The flow rate is 0.7 mL/min and the detector wavelength is set at 254 nm. Under these conditions the retention time of albendazole is 12 minutes (the HPLC method is described in Item 3.A of the Chemical, Manufacturing, and Controls section of the Albendazole Tablets NDA).

The residual solvents are identified by gas chromatography. Impurities are identified by TLC and/or HPLC. Identification of albendazole is carried out by infra-red analysis and thin layer chromatography.

There are no impurities at levels > 1% found in the chemical substance.

## 6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

### 6.1 Introduction from Production of Albendazole

The production of albendazole drug substance and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. For this assessment, engineering estimation are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology that may be implemented before actual approval of the albendazole application.

#### 6.1.1 Drug Substance Production at Cuernavaca

Albendazole drug substance will be made in five process stages (regarding the environmental fate of the process compounds) at Cuernavaca, at the SmithKline Beecham Pharmaceuticals' facility in Cuernavaca, Mexico. The chemicals and the quantities expected to be used at Cuernavaca are presented in Tables 1, 2A and 2B in Confidential Attachment 1. The projected fifth year number of lots made per process stage is presented in Table 15 in Confidential Attachment 2. All data tables for the production of drug substance at

Consult #615 (HFD-520)

ALBENZA (albendazole tablets) 200 mg

The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name however, the Committee is concerned that so much of the USAN name appears in the trademark. The USAN Council discourages the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietay name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs. The LNC was consulted with the USAN Council and was advised there would be no objection by the Council to this use of the USAN syllables.

The LNC has no reason to find the proposed proprietary name unacceptable.

D Boring 6/20/96, Chair
CDER Labeling and Nomenclature Committee

(615)

# REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: ~~Mr. Kent Johnson~~, Chair, (HFD-~~600~~ 530) MPN II
Dan Ewing

FROM: Division of Anti Infective DP HFD- 520
Attention: D. B. KATAGUE Phone: 827-2124

DATE: 5/15/96

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: ALBENZA Albyn Albenza NDA/~~ANDA~~ # 20,666

Established name, including dosage form: Albendazole Tablets, 200mg

Other trademarks by the same firm for companion products: Zentel for veterinary use

Indications for Use (may be a summary if proposed statement is lengthy): Treatment of hydatid cyst disease and neurocysticercosis

Initial comments from the submitter: (concerns, observations, etc.) I have no problem. a search of PDR revealed no generic or trade names that resemble either albendazole or ALBENZA. Furthermore, the name ALBENZA in no way implies safety or efficacy of the product

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Dec. 1990

Co. Corres

**SmithKline Beecham**
*Pharmaceuticals*

June 7, 1996

**NDA 20-666**
**Albendazole Tablets**

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research IV
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Re: Response to FDA Request for Information**

Dear Doctor Fanning:

We are writing with regard to our pending New Drug Application for albendazole (NDA 20-666), submitted December 8, 1995.

Reference is made to the facsimile received from the Food and Drug Administration (FDA), dated June 5, 1996, wherein draft labeling was provided and additional chemistry, manufacturing and controls information was requested as post-approval Phase IV commitments.

At this time we wish to amend the application in response to the FDA's request for information as described below. For your convenience, the FDA requests precede our responses and are presented in bold-faced type.

**FDA Request 1:**

**The applicant is requested to provide the following information as a phase IV commitment (post-approval):**

**Drug Substance:**

**1. Specification limits for impurities at or above 0.1% in the drug substance.**

**2. The reviewer recommends that the current USP monograph, titrimetric assay for albendazole be replaced by the more versatile and specific HPLC method described in the NDA.**

**FDA Request 1 (continued):**

**Drug Product:**

**1. The validated HPLC method is used for release and stability testing of drug product. Please provide specification limits for degradation products at or above 0.1%.**

**SB Response:**

SmithKline Beecham Pharmaceuticals hereby commits: 1) to establishing specification limits for impurities at or above 0.1% in the drug substance; 2) to revise the current USP monograph by replacing the titrimetric assay with the HPLC method for albendazole; and 3) to providing specification limits for the degradation products at or above 0.1%.

Results from our fulfillment of commitments numbered 1 and 3 will be submitted in the Annual Report for NDA 20-666 as it becomes available.

**FDA Request 2:**

**A statement for which marketing applications for this product for the indication of neurocysticercosis may have been rejected by any foreign regulatory authority.**

**SB Response:**

There has been no rejection of a marketing application for this product for the indication of neurocysticercosis in any country.

**FDA Request 3:**

**A statement that the formulation for albendazole used in all pharmacokinetic studies and clinical trials was manufactured at either France or China.**

**SB Response:**

SB hereby acknowledges that to the best of our knowledge the formulation used in the pharmacokinetic studies and clinical trials used the same formulation manufactured at our facilities in either France or China. We note one exception to this statement where we believe that the material used in three clinical trials was a generic formulation of albendazole.

Reference is made to our submission of April 16, 1996 wherein we informed the Agency that any study conducted prior to 1990 may have used the formulation from France. In addition, we provided comparative dissolution data to support the equivalence of the clinical batches (both China and France) to the new commercial formulation (Cidra).

If there are any questions, or if additional information is needed while reviewing this submission, please contact me at (215) 751-4455 (telephone) or (215) 751-4096 (FAX).

Sincerely

Debra Hackett

Debra Hackett
Manager
U.S. Regulatory Affairs

Desk Copy: Ms. Pauline Fogarty (2)
transmitted via facsimile