



NDA 18-714/S-008, S-009

Bayer Pharmaceuticals Corporation  
Attention: Margaret Foley  
Associate Director  
400 Morgan Lane  
West Haven, CT 06516

Dear Ms. Foley:

Please refer to your supplemental new drug applications dated December 8, 2003 and April 30, 2004, received December 9, 2003 and May 4, 2004, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Biltricide® (praziquantel) Tablets, 600 mg.

Your submission dated June 17, 2004 constitutes a complete response to our June 9, 2004 action letter.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

## 1. CLINICAL PHARMACOLOGY

- The first sentence was revised to read:  
BILTRICIDE® Praziquantel induces a rapid contraction of schistosomes by a specific effect on the permeability of the cell membrane.
- The following paragraph and table were added:

Special Populations: The pharmacokinetics of praziquantel were studied in 40 patients with *Schistosoma mansoni* infections with varying degrees of hepatic dysfunction (See table1). In patients with schistosomiasis, the pharmacokinetic parameters did not differ significantly between those with normal hepatic function (Group 1) and those with mild (Child-Pugh B) hepatic impairment. However, in patients with moderate-to-severe hepatic dysfunction (Child-Pugh Class B and C), praziquantel half-life,  $C_{max}$ , and AUC increased progressively with the degree of hepatic impairment. In Child-Pugh class B, the increases in mean half-life,  $C_{max}$ , and AUC relative to Group 1 were 1.58-fold, 1.76-fold, and 3.55-fold, respectively. The corresponding increases in Child-Pugh class C patients were 2.82-fold, 4.29-fold, and 15-fold for half-life,  $C_{max}$ , and AUC.

Table 1: Pharmacokinetic parameters of praziquantel in four groups of patients with varying degrees of liver function following administration of 40 mg/kg under fasting conditions.

<u>Patient Group</u>	<u>Half-life (hr)</u>	<u>T<sub>max</sub> (hr)</u>	<u>C<sub>max</sub> (µg/mL)</u>	<u>AUC (µg/mL* hr)</u>
<b><u>Normal hepatic function (Group 1)</u></b>	<u>2.99 ± 1.28</u>	<u>1.48 ± 0.74</u>	<u>0.83 ± 0.52</u>	<u>3.02 ± 0.59</u>
<b><u>Child-Pugh A (Group 2)</u></b>	<u>4.66 ± 2.77</u>	<u>1.37 ± 0.61</u>	<u>0.93 ± 0.58</u>	<u>3.87 ± 2.44</u>
<b><u>Child-Pugh B (Group 3)</u></b>	<u>4.74 ± 2.16<sup>a</sup></u>	<u>2.21 ± 0.78<sup>a,b</sup></u>	<u>1.47 ± 0.74<sup>a,b</sup></u>	<u>10.72 ± 5.53<sup>a,b</sup></u>
<b><u>Child-Pugh C (Group 4)</u></b>	<u>8.45 ± 2.62<sup>a,b,c</sup></u>	<u>3.2 ± 1.05<sup>a,b,c</sup></u>	<u>3.57 ± 1.30<sup>a,b,c</sup></u>	<u>45.35 ± 17.50<sup>a,b,c</sup></u>

a) p<0.05 compared to Group 1

b) p<0.05 compared to Group 2

c) p<0.05 compared to Group 3

## 2. CONTRAINDICATIONS

- The first sentence in this section was revised to read:

BILTRICIDE<sup>®</sup> should ~~should~~ must not be given to patients who previously have shown hypersensitivity to the drug.

## 3. WARNINGS

- This section was added to read as follows:

Therapeutically effective levels of praziquantel may not be achieved with concomitant administration of strong inducers of cytochrome P450 such as rifampin.

## 4. PRECAUTIONS

- This section was revised to read:

### General:

Approximately 80% of a dose of praziquantel is excreted in the kidneys, almost exclusively (>99%) in the form of metabolites. Excretion might be delayed in patients with impaired renal function, but accumulation of unchanged drug would not be expected. Therefore, dose adjustment for renal impairment is not considered necessary. Nephrotoxic effects of praziquantel or its metabolites are not known.

Caution should be exercised in the administration of the usual recommended dose of praziquantel to hepatosplenic schistosomiasis patients with moderate to severe liver impairment (Child Pugh Class B and C). Reduced metabolism of praziquantel by the liver in these patients may lead to considerably higher and longer lasting plasma concentrations of unmetabolized praziquantel (See **CLINICAL PHARMACOLOGY/Special Populations**).

Minimal increases in liver enzymes have been reported in some patients.

Patients suffering from cardiac irregularities should be monitored during treatment.

When schistosomiasis or fluke infection is found to be associated with cerebral cysticercosis it is advised to hospitalize the patient for the duration of treatment.

**Information for the Patients:**

Patients should be warned not to drive a car and not to operate machinery on the day of BILTRICIDE<sup>®</sup> treatment and the following day.

**Drug Interactions:**

~~No data are available regarding interaction of Biltricide with other drugs.~~

Concomitant administration of drugs that increase the activity of drug metabolizing liver enzymes (Cytochrome P450), e.g. antiepileptic drugs (phenytoin, phenobarbital and carbamazepine), dexamethasone, may reduce plasma levels of praziquantel. Concomitant administration of rifampin must should be avoided (see **CONTRAINDICATIONS WARNINGS**). Concomitant administration of drugs that decrease the activity of drug metabolizing liver enzymes (Cytochrome P 450), e.g. cimetidine, ketoconazole, itraconazole, erythromycin may increase plasma levels of praziquantel. Chloroquine, when taken simultaneously, can may lead to lower concentrations of praziquantel in blood. The mechanism of drug-drug interaction is unclear. Grapefruit was reported to produce a 1.6-fold increase in the C<sub>max</sub> and a 1.9-fold increase in the AUC of praziquantel. However, the effect of this exposure increase on the therapeutic effect and safety of praziquantel has not been systematically evaluated.

**Mutagenesis, Carcinogenesis:**

Mutagenic effects in Salmonella tests found by one laboratory have not been confirmed in the same tested strain by other laboratories. Long term carcinogenicity studies in rats and golden hamsters did not reveal any carcinogenic effect.

**Pregnancy Category B:**

Reproduction studies have been performed in rats and rabbits at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ~~Biltricide<sup>®</sup>~~ praziquantel. There are, however, no adequate and well-controlled studies in pregnant women. An increase of the abortion rate was found in rats at three times the single human therapeutic dose. While animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing mothers:**

~~Biltricide<sup>®</sup>~~ Praziquantel appeared in the milk of nursing women at a concentration of about 1/4 that of maternal serum. Women should not nurse on the day of BILTRICIDE<sup>®</sup> treatment and during the subsequent 72 hours.

**Pediatric use:**

Safety in children under 4 years of age has not been established.

**Geriatric use:**

Clinical studies of praziquantel did not include a sufficient number of subjects ages 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in these patients.

## 5. ADVERSE EFFECTS-~~EVENTS~~

- The last sentence in the first paragraph was deleted as follows:

~~In patients with liver impairment caused by the infection, no adverse effects of Biltricide® have occurred which would necessitate restriction in use.~~

- A new **Post-Marketing Adverse Event Reports** subsection was added to read:

### **Post Marketing Adverse Event Reports:**

Additional adverse events reported from worldwide post marketing experience and from publications with praziquantel include:

abdominal pain, allergic reaction (generalized hypersensitivity) including polyserositis, anorexia, arrhythmia (including bradycardia, ectopic rhythms, ventricular fibrillation, AV blocks), asthenia, bloody diarrhea, convulsion, myalgia, somnolence, vertigo, vomiting

## 6. DOSAGE AND ADMINISTRATION

- This section was revised to read:

The dosage recommended for the treatment of schistosomiasis is: ~~3~~20 mg/kg bodyweight three times a day as a one day treatment, at intervals of not less than 4 hours and not more than 6 hours. The recommended dose for clonorchiasis and opisthorchiasis is: ~~3~~25 mg/kg bodyweight three times a day as a one day treatment, at intervals of not less than 4 hours and not more than 6 hours. The tablets should be washed down unchewed with ~~some liquid~~ water during meals. Keeping the tablets or segments thereof in the mouth can reveal a bitter taste which can promote gagging or vomiting. ~~The interval between the individual doses should not be less than 4 and not more than 6 hours.~~

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon enclosed draft labeling (text for the package insert submitted June 17, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. Please submit the copies of the final printed labeling (FPL) electronically to each application according to the guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). These guidances specify that labeling should be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in

paper. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 18-714/S-008, S-009". Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drugs products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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 call Robin Anderson, R.N., M.B.A., Labeling Reviewer, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Renata Albrecht  
7/14/04 02:46:19 PM