DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18-714/S-012

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Bradley Jones, RAC
Associate Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Jones:

Please refer to your Supplemental New Drug Application (sNDA) dated June 13, 2010, received June 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Biltricide® (praziquantel) 600 mg, Tablets.

We acknowledge receipt of your amendment dated July 28, 2010.

Your February 15, 2010, submission constituted a complete response to our December 15, 2008, action letter.

This Prior Approval supplemental new drug application provides for revisions to the U.S. Prescribing Information (USPI) based on the content of the Company Core Data Sheet (CCDS) for this product. In addition, this supplemental new drug application provides for labeling revisions to contraindicate the concurrent use of rifampin with praziquantel.

This supplemental application provides for the following revisions to the package insert for Biltricide: (~~strikethrough~~ = deleted information and underlined = added information)

1. Under the **INDICATIONS AND USAGE** section:

   BILTRICIDE is indicated for the treatment of infections due to: all species of schistosoma (~~e.g.~~ for example, *Schistosoma mekongi, Schistosoma japonicum, Schistosoma mansoni* and *Schistosoma hematobium),* and infections due to the liver flukes, *Clonorchis sinensis/Opisthorchis viverrini* (approval of this indication was based on studies in which the two species were not differentiated).

2. Under the **CONTRAINDICATIONS** section:

   BILTRICIDE ~~must not be given to~~ is contraindicated in patients who previously have shown hypersensitivity to the drug or any of the excipients. Since parasite destruction

within the eye may cause irreversible~~irreparable~~ lesions, ocular cysticercosis must~~should~~ not be treated with this compound.

Concomitant administration with strong Cytochrome P450 (P450) inducers, such as rifampin, is contraindicated since therapeutically effective blood levels of praziquantel may not be achieved (see **PRECAUTIONS/Drug Interactions**). In patients receiving rifampin who need immediate treatment for schistosomiasis, alternative agents for schistosomiasis should be considered. However, if treatment with praziquantel is necessary, rifampin should be discontinued 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment (see **PRECAUTIONS/Drug Interactions**).

3. Under the **WARNINGS** section:

Therapeutically effective levels of BILTRICIDE~~praziquantel~~ may not be achieved when administered concomitantly with ~~concomitant administration of~~ strong ~~inducers of cytochrome~~ P450 inducers, such as rifampin (see **CONTRAINDICATIONS**).

4. Under the **PRECAUTIONS/General** subsection:

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

Patients suffering from cardiac irregularities should be monitored during treatment.

As BILTRICIDE can exacerbate central nervous system pathology due to schistosomiasis, as a general rule this drug should not be administered to individuals reporting a history of epilepsy and/or other signs of potential central nervous systems involvement such as subcutaneous nodules suggestive of cysticercosis.

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.

5. Under the **PRECAUTIONS/Drug Interactions** subsection:

~~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 should be avoided (see **WARNINGS).**~~

Concomitant administration of rifampin, a strong P450 inducer, with praziquantel is contraindicated and must be avoided (see **CONTRAINDICATIONS**). In a crossover study with a 2-week washout period, 10 healthy subjects ingested a single 40 mg/kg dose of praziquantel following pre-treatment with oral rifampin (600 mg daily for 5 days). Plasma praziquantel concentrations were undetectable in 7 out of 10 subjects. When a single 40 mg/kg dose of praziquantel was administered to these healthy subjects two

weeks after discontinuation of rifampin, the mean praziquantel AUC and Cmax were 23% and 35% lower, respectively, than when praziquantel was given alone. In patients receiving rifampin, for example, as part of a combination regimen for the treatment of tuberculosis, alternative agents for schistosomiasis should be considered. However, if treatment with praziquantel is necessary, treatment with rifampin should be discontinued 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment.

Concomitant administration of other drugs that increase the activity of drug metabolizing liver enzymes (P450 inducers), for example, antiepileptic drugs (phenytoin, phenobarbital and carbamazepine), and dexamethasone, may also reduce plasma levels of praziquantel.

Concomitant administration of drugs that decrease the activity of drug metabolizing liver enzymes (~~Cytochrome~~ P-450 inhibitors), ~~e.g.~~ for example, cimetidine, ketoconazole, itraconazole, erythromycin may increase plasma levels of praziquantel.

Chloroquine, when taken simultaneously, may lead to lower concentrations of praziquantel in blood. The mechanism of this drug-drug interaction is unclear.

Grapefruit juice was reported to produce a 1.6-fold increase in the C_{max} 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.

6. Under the **PRECAUTIONS/Nursing mothers** subsection:

   Praziquantel appeared in the milk of nursing women at a concentration of about 1/4 that of maternal serum although it is not known whether a pharmacological effect is likely to occur in children. Women should not nurse on the day of BILTRICIDE treatment and during the subsequent 72 hours.

7. Under the **ADVERSE EVENTS/Post Marketing Adverse Events Reports** subsection:

   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, eosinophilia, myalgia, pruritis, somnolence, vertigo and vomiting.

8. Under the **HOW SUPPLIED** Section:

   BILTRICIDE® is available in bottles of 6 tablets.

	Strength	**NDC**
Bottles of 6~~:~~	600 mg	~~0026-2521-06~~ 0085-1747-01

Store below 86°F (30°C).

~~Bayer HealthCare~~

~~Bayer Pharmaceuticals Corporation~~
~~400 Morgan Lane~~
~~West Haven, CT 06516 USA~~
~~Made in Germany~~

Manufactured by:

Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Made in Germany

Distributed and Marketed by:
Schering Corporation, a subsidiary of

MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

BILTRICIDE is a registered trademark of Bayer Aktiengesellschaft and is used under license by Schering Corporation.

9. Minor Editorial Changes were made, including removal of the registered symbol for Biltricide, updates to package insert copyright date, and package insert version.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling, text for the package insert, and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., M.P.H.
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-18714	SUPPL-12	BAYER HEALTHCARE PHARMACEUTICALS INC	BILTRICIDE TABLETS

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

/s/

OZLEM A BELEN
08/16/2010