

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BILTRICIDE safely and effectively. See full prescribing information for BILTRICIDE.

**BILTRICIDE (praziquantel) tablets, for oral use**

Initial U.S. Approval: 1982

### INDICATIONS AND USAGE

Biltricide is an anthelmintic indicated in patients aged one year and older for the treatment of the following infections:

- Schistosomiasis due to all species of schistosoma (for example, *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and,
- Clonorchiasis and Opisthorchiasis due to the liver flukes, *Clonorchis sinensis* and *Opisthorchis viverrini*

### DOSAGE AND ADMINISTRATION

- Schistosomiasis:** 20 mg/kg bodyweight 3 times a day separated by 4 to 6 hours for 1 day only. (2.1)
- Clonorchiasis and Opisthorchiasis:** 2.5 mg/kg 3 times a day separated by 4 to 6 hours for 1 day only. (2.1)
- Take with water during meals. Do not chew or keep segments in the mouth. (2.2)
- For pediatric patients under 6 years of age, the tablets may be crushed or disintegrated and mixed with semi-solid food or liquid. (2.2)
- For additional administration instructions see the full prescribing information.

### DOSAGE FORMS AND STRENGTHS

- Tablets: 600 mg (with three scores (notches) on the tablet) (3)

### CONTRAINDICATIONS

- Known hypersensitivity to Biltricide or any of its ingredients. (4.1)
- Concomitant administration with strong Cytochrome P450 (CYP450) inducers such as rifampin. (4., 5.4, 7.1)

### WARNINGS AND PRECAUTIONS

- Clinical Deterioration:** Potentially life threatening clinical deterioration can occur in patients treated during the acute phase of schistosomiasis. (5.1)

- Central Nervous System (CNS) Effects:** Biltricide can exacerbate central nervous system pathology due to schistosomiasis. Consider whether to administer to individuals reporting a history of epilepsy and/or other signs of potential central nervous systems involvement such as subcutaneous nodules suggestive of cysticercosis. (5.2)
- Potential Lack of Efficacy for Acute Schistosomiasis:** This has been reported in observational studies (5.3).
- Cardiac Arrhythmias:** Bradycardia, ectopic rhythms, ventricular fibrillation, and AV blocks has been observed with Biltricide administration. Monitor patients with cardiac arrhythmias during treatment (5.4).

### ADVERSE REACTIONS

The adverse reactions reported were malaise, headache, dizziness, abdominal discomfort (with or without nausea), pyrexia and urticaria. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- Other CYP 450 Inducers:** Concomitant administration of other CYP450 inducers, for example, antiepileptic drugs and dexamethasone, may also reduce plasma levels concentrations of praziquantel. (7.1)
- CYP450 Inhibitors:** Concomitant administration of CYP450 inhibitors, for example, cimetidine, ketoconazole, itraconazole, erythromycin. (7.2)

### USE IN SPECIFIC POPULATIONS

- Pediatrics:** Safety has not been established in pediatric patients younger than 1 year of age. (8.4)
- Hepatic Impairment:** Monitor patients for adverse reactions when administering the recommended dose of Biltricide to hepatosplenic schistosomiasis patients with moderate to severe liver impairment (Child-Pugh Class B or C). (8.6)

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Revised: 1/2019

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Biltricide is indicated in patients aged 1 year and older for the treatment of the following infections:

- Schistosomiasis due to all species of schistosoma (for example, *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and
- Clonorchiasis and Opisthorchiasis 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 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

Schistosomiasis The recommended dosage for the treatment of schistosomiasis is 20 mg/kg bodyweight administered orally three times a day separated by 4 to 6 hours, for 1 day only.

#### Clonorchiasis and Opisthorchiasis

The recommended dosage for the treatment of clonorchiasis and opisthorchiasis is 25 mg/kg bodyweight administered orally three times a day separated by 4 to 6 hours for 1 day only.

#### 2.2 Administration

Take tablets with water during meals. Do not chew or keep the tablets (or parts of tablets) in the mouth; the bitter taste may cause gagging or vomiting. To prevent choking in pediatric patients under 6 years of age, the tablets may be crushed or disintegrated and mixed with semi-solid food or liquid. Use crushed or disintegrated tablets within 1 hour of mixing.

Biltricide 600 mg tablets have three scores which can be split into four segments at the scores. When broken, each of the four segments contains 150 mg of praziquantel so that the dosage can be adjusted to the patient's bodyweight. Segments are broken off by pressing the score (notch) with thumbnails. If one-quarter of a tablet is required, this is best achieved by breaking the segment from the outer end.

### 3 DOSAGE FORMS AND STRENGTHS

Biltricide tablets contain 600 mg of praziquantel. The tablets are white to orange tinged, film-coated, oblong with three scores (notches), imprinted with "BAYER" on one side and "LG" on the other side.

### 4 CONTRAINDICATIONS

Biltricide is contraindicated in:

- Patients who previously have shown hypersensitivity to praziquantel or any of the excipients in Biltricide.
- Patients with ocular cysticercosis; since parasite destruction within the eye that occurs because of hypersensitivity reaction to the dead parasite after treatment may cause irreversible lesions, ocular cysticercosis must not be treated with Biltricide.
- Patients taking strong Cytochrome P450 (CYP450) inducers, such as rifampin, [*see Warnings and Precautions (5.6) and Drug Interactions (7.1, 7.2)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Clinical Deterioration

The use of Biltricide in patients with schistosomiasis may be associated with clinical deterioration (for example, paradoxical reactions, serum sickness Jarisch-Herxheimer like reactions: sudden inflammatory immune response

suspected to be caused by the release of schistosomal antigens). These reactions predominantly occur in patients treated during the acute phase of schistosomiasis. They may lead to potentially life-threatening events, for example, respiratory failure, encephalopathy, papilledema, and/or cerebral vasculitis.

## 5.2 Central Nervous System (CNS) Effects

Biltricide can exacerbate central nervous system pathology due to schistosomiasis, paragonimiasis, or *Taenia solium* cysticercosis. As a general rule, consider whether to administer Biltricide to individuals reporting a history of epilepsy and/or other signs of potential central nervous systems involvement such as subcutaneous nodules suggestive of cysticercosis unless the potential benefit justifies the potential risk. Hospitalize the patient for duration of treatment when schistosomiasis or fluke infection is found to be associated with cerebral cysticercosis.

## 5.3 Potential Lack of Efficacy During the Acute Phase of Schistosomiasis

Data from two observational cohort studies in patients indicate that treatment with Biltricide in the acute phase of infection may not prevent progression from asymptomatic infection to acute schistosomiasis, or from asymptomatic infection/acute schistosomiasis into chronic phase.

## 5.4 Cardiac Arrhythmias

Bradycardia, ectopic rhythms, ventricular fibrillation, and AV blocks has been observed with Biltricide administration. Monitor patients with cardiac arrhythmias during treatment.

## 5.5 Hepatic Impairment in Hepatosplenic Schistosomiasis Patients

Reduced hepatic metabolism of praziquantel results in higher and sustained plasma concentrations of unmetabolized praziquantel in patients with liver impairment [see *Clinical Pharmacology* (12.3)]. Monitor patients for adverse reactions when administering the recommended dose of Biltricide to hepatosplenic schistosomiasis patients with moderate or severe liver impairment (Child-Pugh Class B or C).

## 5.6 Concomitant Administration with Strong Cytochrome P450 Inducers

Concomitant administration of strong CYP450 inducers, such as rifampin with Biltricide is contraindicated since therapeutically effective levels of praziquantel may not be achieved. [see *Contraindications (4) and Drug Interactions (7.1)*].

In patients receiving rifampin who need immediate treatment for schistosomiasis, alternative agents for schistosomiasis should be considered. However, if treatment with Biltricide is necessary, discontinue rifampin 4 weeks before administration of Biltricide. Treatment with rifampin can then be restarted one day after completion of Biltricide treatment [see *Drug Interactions (7.1, 7.2)*].

# 6 ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are discussed elsewhere in the labeling:

- Clinical Deterioration [see *Warnings and Precautions (5.1)*]
- Central Nervous System (CNS) Effects [see *Warnings and Precautions (5.2)*]
- Potential Lack of Efficacy During the Acute Phase of Schistosomiasis [see *Warnings and Precautions (5.3)*]
- Cardiac Arrhythmias [see *Warnings and Precautions (5.4)*]
- Hepatic Impairment in Hepatosplenic Schistosomiasis Patients [see *Warnings and Precautions (5.5)*]
- Concomitant Administration with Strong Cytochrome P450 Inducers [see *Warnings and Precautions (5.6)*]

The following adverse reactions associated with the use of Biltricide were identified in clinical studies, published literature or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions were observed in both adults and pediatric patients:

*General disorders and administration site conditions:* malaise, pyrexia

*Nervous system disorders:* headache, dizziness

*Gastrointestinal disorders:* abdominal discomfort, nausea

*Skin and subcutaneous tissue disorders:* urticaria

Such adverse reactions may be more frequent and/or serious in patients with a heavy worm burden.

Additional adverse reactions reported from worldwide post marketing experience and from publications with Biltricide and various formulations of praziquantel include:

*Blood and lymphatic system disorders:* eosinophilia

*Cardiac disorders:* arrhythmia (including bradycardia, ectopic rhythms, ventricular fibrillation, AV blocks)

*Ear and labyrinth disorders:* vertigo, tinnitus

*Eye disorders:* visual disturbance

*Gastrointestinal disorders:* abdominal pain, bloody diarrhea, vomiting

*General disorders and administration site conditions:* polyserositis, asthenia, fatigue, gait disturbance

*Hepatobiliary disorders:* hepatitis

*Immune system disorders:* allergic reaction, generalized hypersensitivity, anaphylactic reaction

*Metabolism and nutrition disorders:* anorexia

*Musculoskeletal and connective tissue disorders:* myalgia

*Nervous system disorders:* convulsion, somnolence, intention tremor

*Respiratory, thoracic and mediastinal disorders:* pneumonitis, dyspnea, wheezing

*Skin and subcutaneous tissue disorders:* pruritus, rash, Stevens-Johnson syndrome

Pediatric patients 1 to 17 years of age treated with Biltricide and various formulations of praziquantel experienced similar adverse reactions as those observed in adult patients.

## **7 DRUG INTERACTIONS**

### **7.1 CYP450 Inducers**

#### *Rifampin*

Concomitant administration of rifampin, a strong CYP450 inducer, with Biltricide is contraindicated. In patients receiving rifampin, for example, as part of a combination regimen for the treatment of tuberculosis, alternative drugs for schistosomiasis should be considered. If treatment with Biltricide 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. [See *Contraindications* (4), *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3).]

#### *Other CYP 450 Inducers*

Concomitant administration of other drugs that are CYP450 inducers, for example, antiepileptic drugs (phenytoin, phenobarbital and carbamazepine), and dexamethasone, may also reduce plasma concentrations of praziquantel. [See *Warnings and Precautions* (5.6).]

### **7.2 CYP450 inhibitors**

Concomitant administration of drugs that decrease the activity of drug metabolizing liver enzymes (CYP450 inhibitors), for example, cimetidine, ketoconazole, itraconazole, erythromycin may increase plasma concentrations of

praziquantel. In addition, grapefruit juice was also reported to produce a 1.6-fold increase in the  $C_{max}$  and a 1.9-fold increase in the AUC of praziquantel. The effect of this exposure increase on the therapeutic effect and safety of Biltricide has not been systematically evaluated [*see Dosage and Administration (2.2)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

Published studies have not identified an association with Biltricide use during pregnancy and major birth defects, miscarriage or adverse maternal or fetal outcomes (*see Data*). In animal reproduction studies conducted in pregnant rats and rabbits no adverse developmental outcomes were observed with oral administration of praziquantel during organogenesis at approximately 0.65 times (rats) or 1.3 times (rabbits) the highest recommended human daily dose of 75 mg/kg/day, based on body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Data

#### Human Data

Two randomized controlled clinical trials have been conducted using praziquantel for the treatment of schistosoma infection in pregnant women. In one randomized controlled trial in pregnant women with schistosoma (*S. japonicum*) infection, 186 pregnant women were treated with praziquantel compared to 184 women who received placebo. Treatment with praziquantel during pregnancy had no effect on birthweight, and there were no differences in rates of miscarriage, fetal death and major birth defects between the praziquantel-treated and control patients. In another randomized controlled trial that included 2507 pregnant women in Uganda, 18% of women were infected with schistosoma infection. Treatment with praziquantel during pregnancy had no effect on mean birth weight, perinatal mortality or major birth defects.

In other published studies, including a retrospective observational study, case series and case reports, there have been no reports of major birth defects, stillbirths or other adverse pregnancy outcomes associated with the use of praziquantel during pregnancy.

#### Animal Data

No evidence of fetal harm was observed in rats and rabbits at praziquantel dose levels of 30 to 300 mg/kg body weight given repeatedly by oral administration during the period of organogenesis. These doses were up to 0.65 times (rats) or 1.3 times (rabbits) the highest recommended human daily dose of 75 mg/kg/day, based on body surface area.

### 8.2 Lactation

#### *Risk Summary*

Limited data from published literature reports the presence of praziquantel in human milk at low concentrations. There is no information on the effects of praziquantel in the breastfed infant or effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Biltricide and any potential adverse effects on the breastfed infant from Biltricide or from the underlying maternal condition.

### 8.4 Pediatric Use

Safety and dosing recommendations of Biltricide in pediatric patients 1 to 17 years have been established. Safety of Biltricide in pediatric patients younger than 1 year of age has not been established.

Post-marketing experience and published literature indicates that pediatric patients 1 to 17 years of age treated with praziquantel experience similar adverse reactions as adults treated with praziquantel [see *Adverse Reactions* (6)].

### 8.5 Geriatric Use

Clinical studies of Biltricide 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 [see *Clinical Pharmacology* (12.3)].

### 8.6 Hepatic Impairment

Following oral administration of Biltricide to patients with liver impairment, reduced hepatic metabolism of praziquantel results in higher and sustained plasma concentrations of unmetabolized praziquantel [see *Clinical Pharmacology* (12.3)]. Monitor patients for adverse reactions when administering the recommended dose of Biltricide to hepatosplenic schistosomiasis patients with moderate or severe liver impairment (Child-Pugh Class B or C).

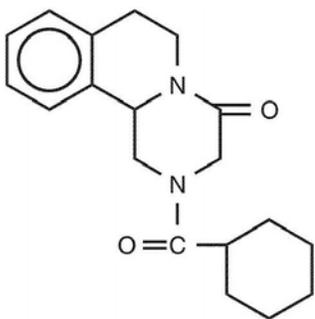
### 8.7 Renal Impairment

No dosage adjustment of Biltricide is necessary in patients with renal impairment. Nephrotoxic effects of Biltricide or its metabolites are not known [see *Clinical Pharmacology* (12.3)].

## 11 DESCRIPTION

Biltricide (praziquantel) is an anthelmintic, trematodicide provided in tablet form for oral administration.

Praziquantel is 2-(cyclohexylcarbonyl)-1,2,3,6,7, 11b-hexahydro-4H-pyrazino [2, 1-a] isoquinolin-4-one with the molecular formula; C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>. The structural formula is as follows:



Praziquantel is a white to nearly white crystalline powder of bitter taste. The compound is stable under normal conditions and melts at 136 to 140°C with decomposition. The active substance is hygroscopic. Praziquantel is easily soluble in chloroform and dimethylsulfoxide, soluble in ethanol and very slightly soluble in water.

Biltricide tablets contain 600 mg of praziquantel. Inactive ingredients: corn starch, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, and titanium dioxide .

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Praziquantel is an anthelmintic drug [see *Microbiology* (12.4)].

### 12.3 Pharmacokinetics

#### *Absorption*

After oral administration, 80% of an administered Biltricide dose is absorbed, with maximal serum

concentrations of praziquantel achieved 1 to 3 hours after dosing.

### Elimination

Following oral administration of Biltricide, the elimination half-life of praziquantel in serum ranges between 0.8 to 1.5 hours.

### Metabolism

Praziquantel is rapidly metabolized by the cytochrome P450 enzyme system and undergoes a first pass effect after oral administration of Biltricide.

### Excretion

Approximately 80% of an oral dose of Biltricide is excreted in the kidneys, almost exclusively (greater than 99%) in the form of praziquantel metabolites.

### Specific Populations

#### Patients with Hepatic Impairment

The pharmacokinetics of praziquantel were studied in 40 patients with *Schistosoma mansoni* infections with varying degrees of hepatic impairment (See Table 1). 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 class A) hepatic impairment. However, in patients with moderate-to-severe hepatic impairment (Child-Pugh class B and C), praziquantel half-life, C<sub>max</sub>, and AUC increased progressively with the degree of hepatic impairment. In Child-Pugh class B, the increases in mean half-life, C<sub>max</sub>, 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<sub>max</sub>, 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 of Biltricide under fasting conditions.**

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

a) p<0.05 compared to Group 1

b) p<0.05 compared to Group 2

c) p<0.05 compared to Group 3

#### Patients with Renal Impairment

Excretion of praziquantel following oral administration of Biltricide might be delayed in patients with impaired renal function, but accumulation of unchanged drug would not be expected.

### Drug Interaction Studies

#### Rifampin (CYP450 Inducer)

In a crossover study with a 2-week washout period, 10 healthy subjects ingested a single 40 mg/kg oral dose of Biltricide 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 oral dose of Biltricide was administered to these same healthy subjects two weeks after discontinuation of rifampin, the mean praziquantel AUC and C<sub>max</sub> were 23% and 35% lower, respectively, than when Biltricide was given alone.

## 12.4 Microbiology

Praziquantel induces a rapid contraction of schistosomes by a specific effect on the permeability of the cell membrane. The drug further causes vacuolization and disintegration of the schistosome tegument. However, the mechanism of action is unknown.

Praziquantel is active against schistosoma (for example, *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini* [see *Indications and Usage* ([1](#))]. Published *in vitro* data have shown a potential lack of efficacy of praziquantel against migrating schistosomulae [see *Warnings and Precautions* ([5.3](#))].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity studies of praziquantel published in the scientific literature are inconclusive. Long term oral carcinogenicity studies in rats and golden hamsters did not reveal any carcinogenic effect at doses up to 250 mg/kg/day (about half of the human daily dose based on body surface area). Praziquantel had no effect on fertility and general reproductive performance of male and female rats when given at oral doses ranging from 30 to 300 mg/kg body weight (up to 0.65 times the human daily dose based on body surface area).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Biltricide is supplied as 600 mg tablets containing praziquantel. The tablets are white to orange tinged, film-coated, oblong tablets with three scores. The tablet is coded with “BAYER” on one side and “LG” on the reverse side.

Biltricide is available in bottles of six 600 mg tablets, NDC 50419-747-01.

Store below 86°F (30°C).

## 17 PATIENT COUNSELING INFORMATION

- Advise patients to take Biltricide during meals as directed [see *Dosage and Administration* ([2.2](#))].
- Advise patients not to chew tablets and to take them with water [see *Dosage and Administration* ([2.2](#))].
- Advise patients that tablets may be crushed or disintegrated and mixed with semi-solid food or liquid or disintegrated to prevent choking in children under 6 years of age. Crushed or disintegrated tablets should be used within 1 hour of mixing [see *Dosage and Administration* ([2.2](#))].
- Advise patients not to take Biltricide if they are allergic to Biltricide or any of its components [see *Contraindications* ([4](#))].
- Advise patients not to take Biltricide if they are taking rifampin [see *Contraindications* ([4](#)) and *Warnings and Precautions* ([5.6](#), [7.1](#), [7.2](#))].
- Advise patients that the use of praziquantel can be associated with clinical deterioration during the acute phase of schistosomiasis [see *Warnings and Precautions* ([5.1](#))].
- Advise patients that Biltricide should not be used if they have epilepsy or other CNS effects [see *Warnings and Precautions* ([5.2](#))].
- Advise patients to report any cardiac irregularities to their healthcare provider [see *Warnings and Precautions* ([5.4](#))].

- Advise patients not to drive a car and not to operate machinery on the day of Biltricide treatment and the following day.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.

Whippany, NJ 07981 USA

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