

PRODUCT MONOGRAPH

BILTRICIDE®

(Praziquantel)

Tablets

Anthelmintic

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PRODUCT MONOGRAPH**BILTRICIDE[®]****(Praziquantel)****Tablets****THERAPEUTIC CLASSIFICATION**

Antihelminthic Agent

ACTIONS AND CLINICAL PHARMACOLOGYMechanism of Action

BILTRICIDE[®] (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. The effect is more marked on adult worms compared to young worms. An increased calcium influx may play an important role.

Secondary effects are inhibition of glucose uptake, lowering of glycogen levels and stimulation of lactate release. The action of praziquantel is limited very specifically to trematodes and cestodes; nematodes (including filariae) are not affected.

Clinical Pharmacology

After oral administration, praziquantel is rapidly absorbed (approximately 80%), subjected to a first pass effect, metabolized and eliminated by the kidneys. Maximal serum concentration is achieved 1 to 3 hours after dosing. The half-life of praziquantel in serum is 0.8 to 1.5 hours.

INDICATIONS AND CLINICAL USE

BILTRICIDE[®] (praziquantel) is indicated for the treatment of infections due to the following species of schistosoma: (Schistosoma haematobium, Schistosoma japonicum, Schistosoma mansoni, and Schistosoma mekongi), 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).

CONTRAINDICATIONS

BILTRICIDE[®] (praziquantel) is contraindicated in patients who have previously shown hypersensitivity to the drug or to any of the excipients. Since parasite destruction within the eye may cause irreversible lesions, ocular cysticercosis must not be treated with BILTRICIDE[®].

The concomitant administration of praziquantel with strong inducers of Cytochrome P450 such as rifampin must be avoided as therapeutically effective plasma levels of BILTRICIDE[®] (praziquantel) may not be achieved.

WARNINGS

Information to the Patient

There may possibly be effects on vigilance. Patients should be warned not to drive a car and not to operate machinery on the day of BILTRICIDE[®] (praziquantel) treatment and during the subsequent 24 hours as their ability to do so may be temporarily impaired by the use of praziquantel.

Children

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

Pregnancy

No adequate and well-controlled studies have been conducted with BILTRICIDE[®] (praziquantel) in pregnant women (see [PRECAUTIONS](#)).

PRECAUTIONS

General

Nephrotoxic effects of BILTRICIDE[®] (praziquantel) have not been observed. Since 80% of praziquantel and its derivatives are excreted in the kidneys, excretion may be delayed in patients with impaired renal function.

Caution should be taken in patients with uncompensated liver insufficiency or with hepatosplenic schistosomiasis. Because of reduced drug metabolism in the liver, considerably higher and longer lasting concentrations of unmetabolized praziquantel can occur in the vascular system and/or collateral circulation, leading to prolonged plasma half-life. If necessary, the patient may be hospitalized for the duration of treatment. Mild increases in liver enzymes have also been reported in some patients.

Patients suffering from cardiac irregularities should be monitored during treatment.

When schistosomiasis or fluke infection is found in patients living in or coming from areas with endemic human cysticercosis, it is advisable to hospitalize the patient for the duration of treatment.

As BILTRICIDE[®] (praziquantel) can exacerbate central nervous system pathology due to schistosomiasis, paragonimiasis, or *Taenia solium* cysticercosis, 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.

Pregnancy

An increase in the abortion rate was found in rats at three times the single human therapeutic dose. Although animal reproduction studies have not brought to light any evidence that the mother or the unborn child might be harmed, these studies are not always predictive of human response. Praziquantel should not be used in pregnancy unless the potential benefit of treating women of reproductive age and pregnant women far outweighs the risk to their health and to the health of their babies (see [WARNINGS](#)).

Nursing Mothers

Praziquantel appears in the milk of nursing women at a concentration of 20-25% that of maternal serum. Breastfeeding should be suspended for the day(s) of treatment and the following 72 hours. The physician should evaluate if the potential benefit clearly outweighs the potential risk (taking into consideration the quality of available alternative artificial nutrition).

Drug Interactions

Many categories of drugs are known to inhibit or induce the drug metabolizing family of P450 enzymes located in the liver and intestine. Co-administration of such drugs may impact upon their metabolisms. In some cases serum concentration or bioavailability may be increased and in others decreased. Care must therefore be exercised when co-administering such drugs. Praziquantel is believed to be metabolized via the P450 enzyme system. The following lists some of the drug interactions which have been reported so far with praziquantel. Other causes such as effects upon absorption among others may also exist.

Concomitant administration of praziquantel with strong inducers of Cytochrome P450 such as rifampin must be avoided because therapeutically effective levels of praziquantel may not be achieved.

Co-administration with praziquantel of anticonvulsants like phenytoin, fosphenytoin, carbamazepine and phenobarbital or with chloroquine or dexamethasone has been reported to lower praziquantel bioavailability and serum levels. Similar trends have been reported with glucose and bicarbonate.

Cimetidine, miconazole and ketoconazole have been shown to inhibit P450 enzyme mediated metabolism. When co-administered with praziquantel, increased bioavailability and serum levels of praziquantel have been reported. Praziquantel on the other hand has been shown to reduce albendazole bioavailability and serum levels.

ADVERSE REACTIONS

Adverse reactions vary according to dose and duration of BILTRICIDE® (praziquantel) medication. Furthermore, they are dependent on the parasite species, extent of parasitization, duration of infection and localization of the parasites in the body.

Adverse reactions are based on publications and on spontaneous reports sorted by CIOMS III categories of frequency and MedDRA System Organ Classes (in internationally agreed order). Frequencies of adverse reactions are mainly based on data from medical literature.

The following adverse reactions have been observed after praziquantel administration. It is often not clear whether the complaints reported by patients or the undesired effects recorded by the physician are caused by praziquantel itself (direct relation), or may be considered to be an endogenous reaction to the death of the parasites (indirect relation) or are symptomatic observations of the infestation (no relation). It may be difficult to differentiate between the possible variations.

Table 1: Adverse Drug Reactions

Very Common ≥10%	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%	Very Rare <0.01%
Immune System Disorders				
				Allergic reaction Polyserositis Eosinophilia
Nervous System Disorders				
Headache Dizziness	Vertigo Somnolence (including drowsiness)			Seizures
Cardiac Disorders				
				Unspecific arrhythmias
Gastrointestinal Disorders				
Gastrointesitnal and abdominal pains Nausea Vomiting	Anorexia Diarrhea (very rarely bloody diarrhea)			
Skin and Subcutaneous Tissue Disorders				
	Urticaria			Puritus
Musculoskeletal, Connective Tissue and Bone				
	Myalgia			
General Disorders and Administration Site Conditions				
	Feeling unwell Fever			

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data is available regarding overdosage in humans. In the event of an overdose, a fast-acting laxative is recommended. In rats and mice the acute oral LD₅₀ was approximately 2500 mg/kg and in dogs the oral LD₅₀ was less than 200 mg/kg.

DOSAGE AND ADMINISTRATION

Dosage

Doses should be individualized depending on the diagnosis. Based on clinical experience, the following dosages are recommended:

Schistosomiasis: 3 x 20 mg/kg body weight as a 1-day treatment. Using the following table, the number of tablets to be taken 3 times on the same day can be determined.

	Body Weight in kg								
	20-25	26-33	34-41	42-48	49-56	57-63	64-70	71-78	79-86
Dose (mg)	450	600	750	900	1050	1200	1350	1500	1650
Number of tablets corresponding to 1 x 20 mg/kg *	3/4	1	1 1/4	1 1/2	1 3/4	2	2 1/4	2 1/2	2 3/4

* Note: Each 600 mg oblong tablet has 3 scores. When broken, each of the four segments contains 150 mg of active ingredient.

The recommended dose for clonorchiasis and opisthorchiasis is 3 x 25 mg/kg body weight as a 1-day treatment.

	Body Weight in kg								
	22-26	27-33	34-38	39-44	45-50	51-56	57-62	63-68	69-75
Dose (mg)	600	750	900	1050	1200	1350	1500	1650	1800
Number of tablets corresponding to 25 mg/kg*	1	1 1/4	1 1/2	1 3/4	2	2 1/4	2 1/2	2 3/4	3

*Each 600 mg oblong tablet has 3 scores. When broken, each of the four segments contains 150 mg of active ingredient.

Administration

The tablets should be swallowed whole with a little liquid, preferably during or after meals. Keeping the tablets (or segments thereof) in the mouth may reveal a bitter taste which can cause gagging or vomiting.

The interval between administrations should be at least 4 hours and not more than 6 hours. When broken, each of the four segments contains 150 mg of active ingredient so that the dosage can be easily adjusted to the patient's body weight.

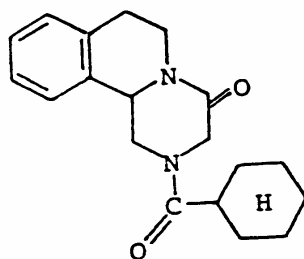
Safety and efficacy in children under 4 years of age have not been established (see [WARNINGS](#)).

PHARMACEUTICAL INFORMATION**DRUG SUBSTANCE**

Proper Name: Praziquantel

Chemical Name: 2-(cyclohexylcarbonyl)-1, 2, 3, 6, 7, 11b-hexahydro4H-pyrazino [2,1-a]isoquinolin-4-one

Structural Formula:



Molecular Formula: C₁₉H₂₄N₂O₂

Molecular Weight: 312.4

Description: Praziquantel is a colourless crystalline powder of bitter taste. The compound is stable under normal conditions and melts at 136°C-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.

Composition

Each tablet contains:

- Praziquantel
- Corn starch
- Magnesium stearate
- Microcrystalline cellulose
- Polyvidone 25
- Sodium lauryl sulphate

Polyethylene glycol 4000
Methylhydroxypropylcellulose
Titanium dioxide

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature below 30°C. Protect from light and excessive humidity.

AVAILABILITY OF DOSAGE FORMS

BILTRICIDE[®] (praziquantel) is supplied as a 600 mg white, film-coated, oblong tablet with three scores on both sides. Each tablet is engraved BAYER on one side and LG on the other. When broken each of the four segments contains 150 mg of the active ingredient so that the dosage can be easily adjusted to the patient's body weight.

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.

BILTRICIDE[®] (praziquantel) is available in bottles of 6 tablets.

INFORMATION TO THE PATIENT

Please read this leaflet carefully before you start to take your medicine. If you still have any questions after reading this, talk to your doctor or pharmacist.

BILTRICIDE[®] (praziquantel) can only be obtained with a prescription from your doctor. This drug has been prescribed by your doctor to treat the infection you have that is caused by worms and/or liver flukes. Do not give this medicine to other people.

Important Points to Note Before Taking Your Medicine

1. Tell your health-care provider about all medications (prescription or non-prescription) that you are currently taking.
2. You should not use BILTRICIDE[®] (praziquantel) if you took it before and had an allergy to it.
3. You should not take BILTRICIDE[®] (praziquantel) and rifampin at the same time because the amount of praziquantel in your body may be lowered below the level required to treat your infection.
4. You should not drive or operate machinery on the day of your treatment and during the next 24 hours as your reflexes may be impaired.
5. If any of the following apply to you, make sure you tell your doctor:
 - (i) you are pregnant or think you may be
 - (ii) you are breastfeeding
 - (iii) you have impaired renal (kidney) function, uncompensated liver insufficiency or suffer from cardiac irregularities.
6. The safety and effectiveness of BILTRICIDE[®] (praziquantel) in children under 4 years of age has not been established.
7. Keep this medicine out of the reach of children.

How to Take Your Medicine

1. The dose depends on your weight. You must take the medicine exactly as it is prescribed by your doctor. If you are not sure how many tablets to take or how often to take them, consult your doctor or pharmacist.
2. You should not change the dose prescribed by your doctor.
3. The tablets should be swallowed unchewed with some liquid, preferably during or after meals. Keeping the tablets (and pieces of the tablets) in your mouth may release a bitter taste which can cause you to gag or vomit.
4. The space between doses should be at least 4 hours and not more than 6 hours.
5. BILTRICIDE[®] (praziquantel) is supplied as a 600 mg white, oblong tablet with three notches. It is marked BAYER on one side and LG on the other. When broken, each of the four pieces that result contains 150 mg of active ingredient (praziquantel). This allows your doctor to easily adjust the dose depending on your weight.

6. Pieces are broken off by pressing the notch with your thumbnails. If only one quarter of a tablet is required, this is best achieved by breaking the tablet from the outer end.

Side Effects

After taking your medicine you may experience some side effects. These vary according to the dose and duration of your treatment. They also depend on the type of infection you have, how long you have had the infection, and where in your body the infection is. The side effects, if there are any, are most often one or more of the following: abdominal pain, loss of appetite, nausea, vomiting, headache, weakness, dizziness, drowsiness, muscle pain or fever. Often it is hard to tell if the side effects are due to the medicine or the infection itself. If you are concerned about how you are feeling after you take the medicine, or if you feel noticeably worse, contact your doctor or pharmacist as soon as possible.

What to Do If You Take an Overdose

It is important to follow exactly the dosage instructions on the label of your medicine. If you do take too much of the medicine, contact your doctor or the nearest hospital emergency department immediately.

Storing Your Medicine

Store this medicine at room temperature below 30°C. Keep this and all medicine in a safe place out of the reach of children. Do not store in a damp place and keep away from light.

Further Information

This leaflet is only a brief information summary about your medicine. If you still have any questions, you should ask your doctor or pharmacist.

MICROBIOLOGY

The effect of praziquantel on all species pathogenic to man, such as S. haematobium, S. mekongi, S. mansoni and S. japonicum was proven by extensive animal experiments in mice, mastomys, hamsters, and different primates.

Table 2: ED₉₅-values of praziquantel (total dose in mg/kg) against schistosome species in 3 different rodent hosts.

Host Animal	Mouse	Mastomys	Syrian Hamster				
			S. mansoni	S. haematobium	S. japonicum	S. intercalatum	S.-mattheei
SchistosomaSpecies	S. mansoni	S. mansoni	S. mansoni	S. haematobium	S. japonicum	S. intercalatum	S.-mattheei
Route, duration of treatment							
5 x p.o., 1 day	479	411	469	500*	250*	--	--
3 x p.o., 1 day	796	251	194	>300*	<100*	<300*	<150*
2 x p.o., 1 day	1059	308	197	>200*	<100*	--	<200*
1 x p.o., 1 day	685	278	249	>250*	100*	--	--
3-10 x p.o., 1 day	200	187	63	150*	--	>150*	--

* estimated values

Praziquantel proved to be equally effective against all tested Schistosoma mansoni strains from different geographical areas.

As can be seen in the following table, all intra-mammalian stages of S. mansoni are equally susceptible to praziquantel in vitro.¹

Table 3: Effect in vitro of various concentrations of praziquantel on schistosomula, immature and mature Schistosoma mansoni.

Location and Sex of Worms	Age of Worms in Days	µg Praziquantel/mL						
		100	10	1	0.3	0.1	0.03	0
Lung	7	+	+	+	t	t	n	n
Liver	14			+	t	n		
	21	+	+	+	t	t	n	n
	35			+/t	t	t	n	n
Mesentery ♂	48	+	+	+	+/t	t/n	n	n
Mesentery ♀	48	+/t	+/t	+	t	t	n	n
Liver ♀	300	+	+	+	t	t	n	n

+ = full effect

t = trace effect

n = no effect

Praziquantel is also effective against other trematode species such as the liver flukes Clonorchis sinensis and Opisthorchis viverrini.

PHARMACOLOGY

Pharmacodynamics

In vitro studies on trematodes and cestodes (tapeworms) have shown that BILTRICIDE® (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. The effect is more marked on adult worms compared to young worms. An increased Ca^{2+} -influx may play an important role.

Secondary effects are inhibition of glucose uptake, lowering of glycogen levels and stimulation of lactate release. The action of praziquantel is specific to trematodes and cestodes; nematodes (including filariae) are not affected.

Kinetic examinations were carried out with radiolabelled praziquantel in different animal species (rat, dog, rhesus monkey and sheep). A rapid absorption, distribution and elimination after oral application, independent of the animal species, was observed.

Pharmacokinetics

After oral administration, praziquantel is rapidly and completely absorbed. Maximal plasma concentrations are achieved within 1-2 hours.

The drug's concentration is 0.05 to 5.0 mg/L in peripheral blood after administration of 5 to 50 mg/kg; the concentration in the mesenteric vein is 3 to 4 times higher compared to peripheral blood.

Unchanged praziquantel passes the blood-brain barrier; its concentration in cerebrospinal fluid is estimated to be 10% to 20% of the plasma concentration.

The half-life of unchanged praziquantel is 1-2.5 hours. The half-life of total radioactivity (praziquantel plus metabolites) after administration of ^{14}C -praziquantel is 4 hours.

Praziquantel is rapidly metabolized by a first pass effect. Both the unchanged drug and the metabolites are eliminated predominantly via the kidneys. More than 80% of the dose administered is eliminated renally within 4 days, 90% of this amount within the first 24 hours. Main metabolites are hydroxylated degradation product of praziquantel.

Based on animal and human studies at the plasma level of 0.6 $\mu\text{mol/L}$ (0.19 mg/L), a therapeutic effect is achieved for 4-6 hours, and in some cases may last as long as 10 hours.

TOXICOLOGY

Acute Toxicity

The acute toxicity of BILTRICIDE[®] (praziquantel) is low as demonstrated in uninfected mice, rats, and rabbits after oral application and in mice and rats after subcutaneous, intraperitoneal, and intramuscular injection. The acute toxicity for dogs could not be evaluated owing to the emetic effect of higher doses of the compound in this species.

Table 4: Acute toxicity of praziquantel.

Route of Administration	Species	LD ₅₀ in mg/kg Number of Days	
		1	7 and 14
p.o.	Mouse	2454	2454
	Rat	2976	2840
	Rabbit	1100	1050
	Dog	> 200	> 200
s.c.	Mouse	7268	7172
	Rat	> 16000	> 16000
i.m.	Mouse	> 2000	> 2000
	Rat	> 1000	> 1000
i.p.	Rat	796	796

In mice infected with Schistosoma mansoni, the acute toxicity of praziquantel was within the same range as found in healthy animals.

Praziquantel proved to be well tolerated in tests carried out in rabbits for primary skin tolerance and for mucosal tolerance in the eye. Furthermore, the substance showed no sensitizing effect in intracutaneous tests in guinea-pigs and in epicutaneous tests in man.

Long-Term Toxicity

In the four-week study in rats and dogs and a three-month study in dogs, the only consistent toxicities observed were enlarged liver and thyroid glands in rats (at 300 mg/kg/day and above), enlarged liver in dogs (180 mg/kg/day after 4 weeks of exposure) and increased absolute and relative liver weight (180 mg/kg/day after 3 months of exposure). These changes were not associated with abnormal findings in clinical chemistry or histopathological examination.

Reproduction Toxicity

In reproduction tests with doses up to 40 times the human dose (300 mg/kg body weight/day), praziquantel had no effect either on the fertility of male and female rats or on the embryonal and fetal development of the offspring. Even with daily oral administration during organogenesis, praziquantel did not show any embryotoxic or teratogenic effects. An increase in the abortion rate was found in rats receiving three times the single human therapeutic dose.

Reproduction studies in rabbits at doses up to 40 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to praziquantel.

Carcinogenicity

Long-term carcinogenicity studies were conducted in Sprague-Dawley rats and golden hamsters. Praziquantel was not considered to be carcinogenic in rats. In hamsters, praziquantel might be considered to be a weak carcinogen based on a slight increase in percent malignant tumours in the female.

Mutagenicity

Extensive studies in various test systems (both in vitro and in vivo) have yielded no evidence of mutagenicity. Mutagenic effects in Salmonella tests observed by one laboratory have not been confirmed in the same tested strain by other laboratories.

REFERENCE

1. Andrews P. A summary of the efficacy of praziquantel against schistosomes in animal experiments and notes on its mode of action. *Arzneim-Forsch (Drug Res.)*. 1981; 31: 538-541.
2. Buhning KU, Diekmann HW, Muller H, Narbe A, Nowak H. Metabolism of praziquantel in man. *Eur. J. Drug Metabolism and Pharmacokinetics*. 1978; 3: 179-190.
3. Diekmann HW, Buhning KU. The fate of praziquantel in the organism III. Metabolism in rat, beagle dog and rhesus monkey.
4. Froberg H, Schencking MS. Toxicological profile of praziquantel, a new drug against cestode and schistosome infections, as compared to some other schistosomicides. *Arzneim-Forsch (Drug Res.)*. 1981; 31: 555-565.
5. Leopold G, Ungethum W, Groll E, Diekmann HW, Nowak H, Wegrier DHG. Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes. *Eur. J. Clin. Pharmacol.* 1978; 14: 281-291.
6. Mehlhorn H, Becker B, Andrews P, Thomas H, Frenkel JK. In vivo and in vitro experiments on the effects of praziquantel on Schistosoma mansoni. *Arzneim-Forsch (Drug Res.)* 1981; 31: 544-554.
7. Putter J, Held F. Quantitative studies on the occurrence of praziquantel in milk and plasma of lactating women. *Eur. J. Drug Metabolism and Pharmacokinetics*. 1979; 4: 193-198.
8. Steiner K, Garbe A, Diekmann HW, Nowak H. The fate of praziquantel in the organism I. Pharmacokinetics in animals. *Eur. J. Drug Metabolism and Pharmacokinetics*. 1976; 2: 85-95.
9. Webbe G, James C. A comparison of the susceptibility to praziquantel of Schistosoma haematobium, S. japonicum, S. mansoni, S. intercalatum and S. mattheei in hamsters. *Z. Parasitenk.* 1977; 52: 169-177.