Final Approval Date:
19 October 2007

SCHEDULING STATUS S4

PROPRIETARY NAME (AND DOSAGE FORM): **Biltricide® Tablets**

COMPOSITON:

Each lacquered tablet contains 600 mg praziquantel.

List of excipients: Corn starch, magnesium stearate, microcrystalline cellulose, Polyvidone 25, sodium lauryl sulphate, polyethyleneglycol 4000, methylhydroxypropylcellulose, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 12. Anthelmintics, Bilharzia medicines, Filaricides, etc.

PHARMACOLOGICAL ACTION:

Praziquantel is a trematodicide.

Pharmacodynamic properties

In vitro studies on trematodes and cestodes (tapeworms) have shown that praziquantel induces a rapid contraction of schistosomes by a specific effect on the permeability of the cell membranes. The medicine further causes vacuolisation and disintegration of the schistosome tegument. 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 limited very specifically to trematodes and cestodes; nematodes (including filariae) are not affected.

Pharmacokinetic properties

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

The medicine'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. The half-life of unchanged praziquantel is 1-2,5 hours. The half-life of total radioactivity (praziquantel plus metabolites) after administration of 14C-praziquantel is 4 hours. For attaining a therapeutic effect plasma levels of 0,6 µM/L (= 0.19 mg/L) have to be maintained for 4-6 (up to 10) hours.

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

Metabolism: Praziquantel is rapidly and extensively metabolised by a first pass effect. Main metabolites are hydroxylated degradation products of praziquantel.

Excretion: Praziquantel is eliminated predominantly via the kidneys as metabolites. More than 80% of the dose administered is eliminated renally within 4 days, 90% of this amount within the first 24 hours.

INDICATIONS:

Infections due to organisms of the following species pathogenic to man:
Schistosoma haematobium; Schistosoma mansoni.

CONTRA-INDICATIONS:

Biltricide must not be used in cases of known hypersensitivity to praziquantel or to any of the excipients.

Biltricide should not be taken during the first trimester of pregnancy. (See Pregnancy and Lactation)

Since parasite destruction within the eye may cause irreversible lesions, ocular cysticercosis must not be treated with this compound.
The concomitant administration of strong inducers of Cytochrome P 450 such as rifampicin must be avoided as therapeutically effective plasma levels may not be achieved. (See Interactions)

WARNINGS:

Since 80% of Biltricide and its metabolites are excreted in the kidneys, excretion might be delayed in patients with impaired renal function.

In uncompensated liver insufficiency and in patients with hepatosplenic schistosomiasis, caution should be taken, since due to reduced drug metabolisation in the liver, considerably higher and longer lasting concentrations of unmetabolised Biltricide can occur in vascular and/or collateral circulation, leading to prolonged plasma half-life. If necessary, the patient may be hospitalised for the duration of the treatment.

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 advised to hospitalise the patient for the duration of treatment. (See Special Precautions)

As Biltricide can exacerbate central nervous system pathology due to schistosomiasis, paragonimiasis

or Taenia solium cysticercosis, as a general rule this medicine 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.

Ability to drive and use machines: Because of possible effects on vigilance patients should be warned not to drive a car and not to operate machinery on the day of treatment (and during the subsequent 24 hours).

INTERACTIONS

Concomitant administration of drugs increasing the activity of drug metabolising liver enzymes (Cytochrome P450), e.g. antiepileptic drugs, dexamethasone may reduce plasma levels of Biltricide.

Concomitant administration of strong inducers of Cytochrome P450 such as rifampicin must be avoided. (See Contraindications)

Concomitant administration of drugs decreasing the activity of drug metabolising liver enzymes (Cytochrome P 450) e.g. cimetidine, may increase plasma levels of Biltricide.

Chloroquine, when taken simultaneously, can lead to lower concentrations of Biltricide in blood.

PREGNANCY AND LACTATION

Safety in pregnancy has not been established.

Biltricide appears in the milk of breastfeeding women at a concentration of 20-25**%** of maternal serum. It is not known, whether a pharmacological effect is likely to occur in children. For short-term therapy breastfeeding should be discontinued for the day(s) of treatment and the following 24 hours.

DOSAGE AND DIRECTIONS FOR USE:

For the treatment of Schistosomiasis, caused by S. haematobium and S. mansoni, the intake of 40 mg/kg body mass once or 20 mg/kg body mass twice, on a single day is recommended.

Administration:

The tablets should be swallowed whole with a little liquid, preferably during or after meals. With single daily doses it is recommended to take the tablets in the evening. If ingestion of tablets several times a day is prescribed, the interval between administrations should not be less than 4 hours and not more than 6 hours.

Special monitoring advice: 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 bodyweight.
Children: Safety in children under 4 years of age has not been established
Hepatic impairment: see Warnings.
Renal impairment: see Warnings.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects vary according to dose and duration of Biltricide; furthermore, they are dependent on the parasite species, extent of parasitisation, duration of infection and localisation 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. Status: 2004 (publication year of last literature source used).

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	Anorexia Diarrhea (very rarely bloody			

Vomiting	diarrhea)			
Skin and Subcutaneous Tissue Disorders				
Urticaria				Pruritus
Musculoskeletal, Connective Tissue and Bone Disorders				
	Myalgia			
General Disorders and Administration Site Conditions				
	Asthenia Feeling unwell			

Special precautions:

The patient's ability to drive or to operate machinery may be temporarily impaired. (See Warnings)

Caution should be exercised where there is a possibility of a simultaneous occurrence of both Schistosomiasis and CNS-cysticercosis infection, as cerebral cysticercosis requires hospital-based treatment by a specialist. (See Warnings)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Pronounced dizziness, "hang-over" feelings. There is no specific antidote and symptomatic measures should be applied.

No data are available in humans. In the event of overdose a fast acting laxative should be given.

Final Approval Date:
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IDENTIFICATION:

A white to orange-tinged oblong tablet with 4 equal segments, marked with LG on the one side and BAYER on the other.

PRESENTATION:

Packs of 4's or 10's and tins of 1000 lacquered tablets of 600 mg each.

STORAGE INSTRUCTIONS:

Store below 25°C. Keep out of reach of children.

REGISTRATION NUMBER: P/12/23

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

BAYER (PTY) LTD

27 Wrench Road, Isando, 1609

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