1.3

PRODUCT INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

PRAZIQUANTEL TABLETS USP 600MG

2. Qualitative and Quantitative Composition

Each tablet contains:

Praziquantel USP 600mg

3. Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Praziquantel 600mg Tablets is indicated in adults and children for large scale preventive chemotherapy interventions for the control of schistosoma infections due to various types of blood fluke worms (Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum) following the recommendations of the WHO Global Programme to Eliminate Schistosomiasis.

Groups targeted for treatment are:

- School-age children (6-15 years of age) in endemic areas.
- Adults (> 15 years) considered to be at risk in endemic areas.

from special groups: pregnant and lactating women and groups with occupations involving contact with infested water, such as fishermen, farmers, irrigation workers, or women whose domestic tasks bring them in contact with infested water.

- Entire communities living in highly endemic areas.

4.2 Posology and method of administration

Posology

Dose recommendations in preventive chemotherapy interventions

Height (cm/inches)	**Number of tablets (mg) of Praziquantel 600mg Tablets**
94-109 cm (37-42 inches) 1 tablet (600 mg)	1 tablet (600 mg)
110-124 cm (43-48 inches)	1 ½ tablets (900 mg)
125-137 cm (49-53 inches)	2 tablets (1200 mg)
138-149 cm (54-58 inches)	2 ½ tablets (1500 mg)
150-159 cm (59-62 inches)	3 tablets (1800 mg)
160-177 cm (63-69 inches)	4 tablets (2400 mg)
≥178 cm (>70 inches)	5 tablets (3000 mg)

Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Recommended treatment strategy for preventive chemotherapy interventions

Intervention frequency is determined by the prevalence of infection in school-age children or visible haematuria. In high-transmission areas, treatment may have to be repeated every year for a number of years. Monitoring is essential to determine the impact of control interventions.

Praziquantel 600mg Tablets should be taken once a year in high-risk communities, once every 2 years in moderate-risk communities, and twice during the period of primary schooling age in low-risk communities (e.g. once at entry and once on exit). In low risk communities adults should be treated only if infection is suspected.

High-risk community is defined as detection of intestinal and urinary schistosomiasis ≥50% by parasitological methods or ≥ 30 % by questionnaire for visible haematuria in 50 children from the upper classes of a selection of schools in areas around water.

Moderate-risk community is defined as detection of intestinal and urinary schistosomiasis ≥10% but < 50% by parasitological methods or < 30% by questionnaire for visible haematuria. Low-risk community is defined as detection of intestinal and urinary schistosomiasis <10% by parasitological methods.

Method of administration
Oral use.
Praziquantel 600mg Tablets should be taken unchewed during meals.

Special populations

Liver Disease Praziquantel 600mg Tablets should be administered with caution to patients with moderate to severe liver impairment. Renal Impairment No dose adjustments for renal impairment are necessary. Elderly No special precautions are required in the elderly. Children < 4 years There is no documented information on the safety of praziquantel for children under 4 years of age (or under 94 cm height). In principle, these children should therefore be excluded from treatment or mass preventive treatment but can be treated on an individual case by case basis by medical personnel.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Ocular cysticercosis - parasite destruction within the eye may cause serious ocular damage. Concomitant administration of strong inducers of Cytochrome P450 such as rifampicin.

4.4 Special warnings and precautions for use

Caution should be exercised in administering 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 in these patients may lead to considerably higher and longer lasting plasma concentrations of unmetabolized praziquantel.

Approximately 80% of a dose of praziquantel is excreted in the kidneys, almost exclusively (>99%) in the form of metabolites. Excretion may 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.

Patients suffering from cardiac arrhythmias or cardiac insufficiency treated with digoxin should be monitored during treatment.

Praziquantel should not be used in patients with a history of or suffering from epilepsy and/or other signs of potential central nervous system involvement due to schistosomiasis, paragonimiasis or Taenia solium cysticercosis such as subcutaneous nodules of cysticercosis.

Patients with neurocysticercosis should always be treated in hospital because of the risk of pericystic oedema.

The intensity and the severity of the undesirable effects that appear after administration of Praziquantel 600mg Tablets may be associated with the level of worm burden.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of rifampicin should be avoided. Rifampicin should be discontinued 4 weeks before administration of praziquantel. Rifampicin can be restarted one day after praziquantel treatment.

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 and concomitant use is not recommended.

Concomitant administration of drugs that decrease the activity of drug metabolizing liver enzymes (Cytochrome P450), e.g. cimetidine, ketoconazole, itraconazole, or 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.

Patients should be advised not to drink grapefruit juice on the day of administration of Praziquantel 600mg Tablets.

4.6 Fertility, Pregnancy and lactation

Pregnancy

In areas where schistosomiasis is endemic, risk-benefit analyses have revealed that the health advantages of treating women of reproductive age and pregnant women far outweigh the risk to their health and to their babies. Evidence also shows that women can be treated with praziquantel at any stage of pregnancy or lactation.

Breastfeeding

Praziquantel has been reported to be excreted in the milk of nursing women. Women should not breastfeed on the day of treatment with Praziquantel 600mg Tablets and during the subsequent 24 hours.

Fertility

Reproduction studies performed so far in rat and rabbits have revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. Patients should be warned about the potential for dizziness, somnolence or seizures. while taking Praziquantel 600mg Tablets and should be advised not to drive or operate machines if any of these symptoms occur on the day of treatment.

4.8 Undesirable effects

The following adverse reactions have been observed and reported during treatment with praziquantel with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to<1/100); rare (≥1/10,000 to<1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The most frequently (>1/10) reported adverse reactions are headache, dizziness, fatigue, abdominal pain, nausea, vomiting, and urticaria.

System Organ Class	Very common	Common	Rare	Very Rare
Immune system disorders				Allergic reaction Polyserositis Eosinophilia
Nervous system disorders*	Headache Dizziness	Vertigo Somnolence		Seizures
Cardiac disorders				Unspecified Arrhythmias
Gastrointestinal disorders	Gastrointestinal and abdominal pains Nausea Vomiting	Anorexia Diarrhoea		Bloody diarrhoea
Hepatobiliary disorders			Liver function tests increased	
Skin and subcutaneous tissue disorders	Urticaria			
Musculoskeletal and connective tissue disorders		Myalgia		
General disorders and administration site condition	Fatigue	Feeling unwell (asthenia, malaise) Feve		

* In cysticercosis, death of the cysts results in local inflammation and oedema. Within the brain, this oedema can simulate an acute space-occupying lesion.

Side effects may be more frequent and/or serious in patients with a heavy worm burden. It is often not clear whether the complaints reported by patients or the undesirable effects reported by the health care provider are caused by praziquantel itself, or may be considered to be an endogenous reaction to the death of the parasites produced by praziquantel, or are symptomatic observations of the infestation.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

Symptoms

Information on overdosage in humans is not available.

Treatment

Treatment should be supportive and provide symptomatic care. Activated charcoal may reduce absorption of the medicine if given within one to two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: P02B A01

Mechanism of action

Praziquantel is a chinolin derivative and 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 than on young worms.

5.2 Pharmacokinetic properties

Absorption and bioavailability

After oral administration praziquantel is rapidly absorbed. It undergoes first-pass metabolism and 80% of the dose is excreted mainly as metabolites in the urine within 24 hours. Following single dose administration of 2 tablets Praziquantel 600mg Tablets in two sequences (full replicate design), used to compare the bioavailability of this product with the same dose of the reference formulation, mean Cmax (± SD) values of praziquantel were 1363 ng/ml (±880) at T1 and 1372 ng/ml (±962) at T2 and the corresponding AUC values were 2938 ng.h/ml (±1607) at T1 and 3098 ng.h/ml (±1936) at T2. The mean (± SD) tmax values were 2.44 (±1.74) hours and 2.55 (±1.36) hours at T1 and T2, respectively.

Distribution

Praziquantel is 80% bound to serum proteins. It passes the blood-brain barrier and liquor concentration is about 14–20% of the concurrent total (free plus protein-bound) plasma concentration. Praziquantel is excreted in the milk of nursing mothers in concentrations about 25% of maternal serum concentrations.

Biotransformation

Praziquantel is subject to first pass effect and extensive metabolism in the liver, mainly via the cytochrome P450 isoenzymes CYP2B1 and CYP3A4. One hour after administration only approximately 6% of the medicine in serum is in the unmetabolised form.

Elimination

Approximately 80% of a dose of praziquantel is excreted in the kidneys within four days, 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.

Pharmacokinetics in hepatic impairment

The pharmacokinetics of praziquantel were studied in 40 patients with Schistosoma mansoni infections with varying degrees of hepatic dysfunction. 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, Cmax, and AUC increased progressively with the degree of hepatic impairment. In Child-Pugh class B, the increases in mean half-life, Cmax, 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, Cmax, and AUC.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

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.

Reproductive toxicity

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 foetus due to praziquantel. An increase of the abortion rate was found in rats at three times the single human therapeutic dose.

6. Pharmaceutical particulars

6.1 List of excipients

1. Starch BP
2. Microcrystalline Cellulose BP
3. P.V.P.K-30 BP
4. Sodium Lauryl Sulphate BP
5. Sodium Starch Glycolate BP
6. Magnesium Stearate BP
7. Crospovidone BP
8. Croscarmellose BP
9. Colloidal Silicon dioxide BP
10. Purified Water BP
11. Instacoat White I.H.
12. Isopropyl Alcohol BP
13. Dichloromethane BP

6.2 Incompatibilities

None applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

None stated.

6.5 Nature and contents of container

Blister packs containing 1 X 10 Tablets

6.6 Special precautions for disposal and other handling

Not applicable