1. Name of the medicinal product

Praziquantel 600mg tablet

2. Qualitative and quantitative composition

Each film coated tablet contains Praziquantel 600mg

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications
Praziquantel tablets are 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)

4.2 Posology and method of administration
Recommended Dosage
Schistosomiasis The recommended dosage for the treatment of schistosomiasis is 20 mg/kg body weight 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 body weight administered orally three times a day separated by 4 to 6 hours for 1 day only.

Method of 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.

Praziquantel 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 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.

4.3 Contraindications
Praziquantel is contraindicated in:

- Patients who previously have shown hypersensitivity to praziquantel or any of the excipients in praziquantel tablets.
- 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 praziquantel.
- Patients taking strong Cytochrome P450 (CYP450) inducers, such as rifampin,

4.4 Special warnings and precautions for use
Clinical Deterioration

The use of praziquantel 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.

Central Nervous System (CNS) Effects
Praziquantel can exacerbate central nervous system pathology due to schistosomiasis, paragonimiasis, or *Taenia solium* cysticercosis. As a general rule, consider whether to administer praziquantel 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.

Potential Lack of Efficacy During the Acute Phase of Schistosomiasis
Data from two observational cohort studies in patients indicate that treatment with praziquantel 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.

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

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. Monitor patients for adverse reactions when administering the recommended dose of praziquantel to hepatosplenic schistosomiasis patients with moderate or severe liver impairment (Child-Pugh Class B or C).

Concomitant Administration with Strong Cytochrome P450 Inducers
Concomitant administration of strong CYP450 inducers, such as rifampin with praziquantel is contraindicated since therapeutically effective levels of praziquantel may not be achieved.

In patients receiving rifampin who need immediate treatment for schistosomiasis, alternative agents for schistosomiasis should be considered. However, if treatment with praziquantel is necessary, discontinue rifampin 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment.

4.5 Interaction with other medicinal products and other forms of interaction
CYP450 Inducers

- *Rifampin*

Concomitant administration of rifampin, a strong CYP450 inducer, with praziquantel 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 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.

- *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.

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 Cmax and a 1.9-fold increase in the AUC of praziquantel. The effect of this exposure increase on the therapeutic effect and safety of praziquantel has not been systematically evaluated.

4.6 Pregnancy, and lactation

Pregnancy Category B: 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 fetus due to praziquantel. There are, however, no adequate and well-controlled studies in pregnant women. An increase of the abortion rate was found in rats at three times the single human therapeutic dose. While animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers: Praziquantel appeared in the milk of nursing women at a concentration of about 1/4 that of maternal serum. Women should not nurse on the day of Praziquantel treatment and during the subsequent 72 hours.

4.7 Effects on ability to drive and use machines.

Avoid driving or hazardous activity on the day you take this medicine, and also the day after. Your reactions could be impaired. Grapefruit may interact with praziquantel and lead to unwanted side effects.

4.8 Undesirable effects

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

- Clinical Deterioration
- Central Nervous System (CNS) Effects.
- Potential Lack of Efficacy During the Acute Phase of Schistosomiasis
- Cardiac Arrhythmias.
- Hepatic Impairment in Hepatosplenic Schistosomiasis Patients.
- Concomitant Administration with Strong Cytochrome P450 Inducers.

The following adverse reactions associated with the use of praziquantel 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 praziquantel 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 praziquantel tablets and various formulations of praziquantel experienced similar adverse reactions as those observed in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Kindly contact www.fidson.com to report adverse reactions.

4.9 Overdose
In rats and mice, the acute LD50 was about 2,500 mg/kg. No data are available in humans. In the event of overdose a fast-acting laxative should be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Praziquantel is an anthelmintic used in most schistosome and many cestode infestations. Praziquantel effects the permeability of the cell membrane resulting in the contraction of schistosomes. 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.

Mechanism of Action
Praziquantel works by causing severe spasms and paralysis of the worms' muscles. This paralysis is accompanied - and probably caused - by a rapid Ca 2+ influx inside the schistosome. Morphological alterations are another early effect of praziquantel. These morphological alterations are accompanied by an increased exposure of schistosome antigens at the parasite surface. The worms are then either completely destroyed in the intestine or passed in the stool. An interesting quirk of praziquantel is that it is relatively ineffective against juvenile schistosomes. While initially effective, effectiveness against schistosomes decreases until it reaches a minimum at 3-4 weeks. Effectiveness then increases again until it is once again fully effective at 6-7 weeks. Glutathione S-transferase (GST), an essential detoxification enzyme in parasitic helminths, is a major vaccine target and a drug target against schistosomiasis. Schistosome calcium ion channels are currently the only known target of praziquantel.

5.2 Pharmacokinetic properties
Absorption

Rapidly absorbed (80%)

Distribution

Praziquantel was readily absorbed from the gastrointestinal tract of the fish. Absorption was more rapid at 18‡ C than at 12‡ C. Only in the liver, however, did the peak values reach significantly higher levels at the higher temperature. The peak values in different tissues (10.2–31.8 Mg/g) were reached 4–16 h after administration of the drug. The elimination of the drug from the tissues was less dependent on temperature than absorption. By 32 h p.a., 67%–96% of the maximum amounts had been eliminated from the tissues. Praziquantel was excreted partly with bile fluid and partly as water-soluble metabolites through the kidneys.

Elimination

Praziquantel and its metabolites are mainly excreted renally; within 24 h after a single oral dose, 70 to 80% is found in urine, but less than 0.1% as the unchanged drug. Praziquantel is metabolized through the cytochrome P450 pathway via CYP3A4.

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, 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.

Table 1: Pharmacokinetic parameters of praziquantel in four groups of patients with varying degrees of liver function following administration of 40 mg/kg of praziquantel tablets under fasting conditions.

Patient Group	Half-life (hr)	Tmax (hr)	Cmax (mcg/mL)	AUC (mcg/mL* hr)
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 ± 2.16a	2.21 ± 0.78a,b	1.47 ± 0.74a,b	10.72 ± 5.53a,b
Child-Pugh C (Group 4)	8.45 ± 2.62a,b,c	3.2 ± 1.05a,b,c	3.57 ± 1.30a,b,c	45.35 ± 17.50a,b,c

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

5.3 Preclinical safety data

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).

6. Pharmaceutical particulars

6.1 List of excipients
6.2 Incompatibilities
Not applicable

6.3 Shelf life
6.4 Special precautions for storage

- Store in the original package.
- Do not store above 30°C. Keep medicine away from direct sunlight
- Keep all medicine out of the reach of children.

6.5 Nature and contents of container
1 X 10 tablets packed in ALU/PVC blisters placed in a inner carton with insert.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. **SUPPLIER AND MANUFACTURER**
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