WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[NT011 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains praziquantel 600 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to orange tinged, oblong, film-coated tablet with three scores on one side and two scores on the other side. The tablet is debossed with "P8" on one side and "H" on the other side.

The tablet can be divided into either two or four equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NT011 trade name] is indicated in adults and children for the elimination through mass drug administration programmes 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)
- adults (> 15 years) considered to be at risk, including:
  - pregnant and breastfeeding women, groups with occupations involving contact with infested water, such as fishermen, farmers, irrigation workers, and people 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 mass drug administration programmes

The dose of [NT011 trade name] is based on the height of the person, as illustrated in the table below, with the aim of delivering a dose of at least 40 mg/kg.

Height (cm/inches)	Number of tablets (mg)
94-109 cm (37-42 inches)	1 tablet (600 mg)
110-124 cm (43-48 inches)	1½ tablets (900 mg)
125-137 cm (49-53 inches)	2 tablets (1200 mg)
138-149 cm (54-58 inches)	2½ 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 or taller (70 inches or taller)	5 tablets (3000 mg)

Recommended treatment strategy

Intervention frequency is determined by the prevalence of infection or visible haematuria in school-age children. Monitoring is essential to determine the impact of control interventions.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

In *high-risk communities*, the appropriate dose of [NT011 trade name] from the table above should be taken once a year. A high-risk community is defined as detection of intestinal and urinary schistosomiasis by parasitological methods in 50% or more school-age children, or detection by questionnaire of visible haematuria in 30% or more children from a selection of schools in areas around water.

In *moderate-risk communities*, the appropriate dose of [NT011 trade name] should be taken once every 2 years. A moderate-risk community is defined as detection of intestinal and urinary schistosomiasis by parasitological methods in between 10% and 50% of school-age children, or detection by questionnaire of visible haematuria in less than 30% of school-aged children.

In *low-risk communities*, the appropriate dose of [NT011 trade name] should be taken by children on two occasions during their period of primary schooling (e.g., once at entry and once on exit). Adults should be treated only if infection is suspected. A low-risk community is defined as detection of intestinal and urinary schistosomiasis by parasitological methods in less than 10% of school-age children.

Special populations

Liver disease

[NT011 trade name] should be administered with caution to patients with moderate to severe liver impairment (see section 4.4).

Renal impairment

No dose adjustments for renal impairment are necessary (see section 4.4.).

Elderly

No special precautions are required in the elderly.

Children less than 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 mass treatment but can be treated on an individual case-by-case basis by medical personnel.

Method of administration

Oral administration.

[NT011 trade name] should be taken with a meal. The medicine should be swallowed without chewing.

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 (see section 4.5).

4.4 Special warnings and precautions for use

Liver impairment

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 patients with liver impairment may lead to considerably higher and longer lasting plasma concentrations of unmetabolized praziquantel.

Renal impairment

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.

Cardiac impairment

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

Neurologic effects

Since praziquantel can exacerbate central nervous system pathology due to schistosomiasis, it 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 suggestive of cysticercosis.

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

4.5 Interaction with other medicinal products and other forms of interaction

Praziquantel is believed to be metabolized via the CYP450 enzyme system.

Concomitant use of rifampicin (a strong P450 inducer) is contraindicated as therapeutically effective plasma levels of praziquantel may not be achieved. In patients receiving rifampin who need immediate treatment for schistosomiasis, alternative agents for schistosomiasis should be considered.

If treatment with praziquantel is necessary, rifampin should be discontinued 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment

Concomitant administration of medicines that increase the activity of drug metabolizing liver enzymes (Cytochrome P450), e.g., antiepileptic drugs (phenytoin, phenobarbital, and carbamazepine) and dexamethasone, may reduce plasma levels of praziquantel; 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.

Concomitant administration of chloroquine 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 [NT011 trade name].

4.6 Fertility, pregnancy and breastfeeding

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 breastfeeding.

Breastfeeding

Praziquantel is secreted into breast milk 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.

Fertility

Reproduction studies performed so far in rat and rabbits have revealed no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness, somnolence, or seizures (see section 4.8) while taking [NT011 trade name] and should be advised not to drive or operate machines on the day of treatment and for the next 24 hours.

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				Jarisch-Herxheimer reaction 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 conditions	Fatigue	Feeling unwell (asthenia, malaise) Fever		

* 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, an endogenous reaction to the death of the parasites produced by praziquantel or are symptomatic observations of the infestation.

Reporting of 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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national 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 after ensuring the airway is protected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintics, 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. Praziquantel further causes vacuolization and disintegration of the schistosome tegument. The effect is more marked on adult than on young worms.

Secondary effects include 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.

5.2 Pharmacokinetic properties

The absorption characteristics of [NT011 trade name] have been determined after administration of tablets of [NT011 trade name] in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** (*)
Maximum concentration (C_{max}) ng/ml	773 ± 641 (527)
Area under the curve (AUC_{0-t}), a measure of the extent of absorption ng.hour/ml	1328 ± 1082 (892)
Time to attain maximum concentration (t_{max}) hour	2.40 ± 1.04

*geometric mean

Pharmacokinetics of praziquantel

Absorption	
Absorption	t_{max} 1-3 hours
Absolute bioavailability	NA
Oral Bioavailability	> 80%
Food effect	AUC is increased approximately 2- to 4-fold; glucose and bicarbonate lower praziquantel bioavailability
Distribution	
Volume of distribution (Vd/F)	NA
Plasma protein binding *in vitro*	80% almost exclusively to albumin
Tissue distribution	Extensively distributed. Crosses the blood-brain barrier with approximately 14-20% of the total (free plus protein-bound) plasma concentration. Excreted in breast milk in concentrations of approximately 25% of the maternal serum concentration.
Elimination	
Elimination half life	1.5 - 3h
Mean systemic clearance (Cl/F)	7.0 L/kg/hr
% of dose excreted in urine	Approximately 80% (>99% as metabolites)

% of dose excreted in faeces	NA
Drug interactions *(in vitro)*	Coadministration with inducers or inhibitors of P450 enzymes will decrease and increase respectively the exposure to praziquantel.
Metabolising enzymes	Extensive first pass hepatic metabolism mainly via CYP2B1 and CYP3A4. Approximately 6% of the dose is unmetabolized after one hour.
Special populations	
Renal impairment	Accumulation of unchanged drug is not expected with renal impairment due to extensive hepatic metabolism
Hepatic impairment	No effect on pharmacokinetics were seen with mild (Child-Pugh A) hepatic impairment. C_{max} and AUC increase progressively with moderate to severe hepatic impairment (Child-Pugh B 1.8- and 3.7-fold, respectively. and Child-Pugh C 4.3- and 15-fold, respectively)

5.3 Preclinical safety data

Harmful 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

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.

Mutagenesis

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.

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 fetus 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

Core tablet: Pregelatinized starch
Povidone
Sodium lauryl sulfate
Microcrystalline cellulose
Magnesium stearate

Film coat: Hydroxypropyl methylcellulose
Titanium dioxide
Macrogol/ PEG
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

HDPE bottle pack of 6 tablets and Blister pack of 1 x 6's tablets and 10 x 10's tablets

Do not store above 30ºC. Avoid excursions above 30ºC. Store in the original container.

HDPE bottle pack of 100, 500 and 1000 tablets

Do not store above 30ºC. Avoid excursions above 30ºC. Store in the original container.

Discard the product 180 days after initial opening.

6.5 Nature and contents of container

White to orange tinged, oblong, film-coated tablet with three scores on one side and two scores on the other side. The tablet is debossed with "P8" on one side and "H" on the other side.

The tablet can be divided into either two or four equal doses.

HDPE bottle

White opaque, HDPE container with a white opaque, polypropylene ribbed child resistant plastic cap closure with a pulp liner. The bottle also contains purified cotton as a space filler. Pack sizes: 6 and 100 tablets.

White opaque, HDPE container with a white opaque, polypropylene ribbed CT plastic cap closure with a pulp liner. The bottle also contains purified cotton as a space filler. Pack sizes: 500 and 1000 tablets.

Blister

Cold form PVC/Alu/OPA-Alu blister. Each blister card contains 6 tablets. Each blister card is packed in a carton. Pack size: 1 x 6's tablets.

Cold form PVC/Alu/OPA-Alu blister. Each blister card contains 10 tablets. Such 10 blister cards are packed in a carton. Pack size: 10 x 10's tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

NT011

9. DATE OF PREQUALIFICATION

23 August 2022

10. DATE OF REVISION OF THE TEXT

September 2022

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines