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

[NT005 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg albendazole.

Each tablet contains about 569.6mg of lactose monohydrate and 3mg of colour FD & C yellow #6 (Lake sunset yellow FCF).

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Mottled, pale orange, oblong-shaped biconvex uncoated tablet with a score line on one side and "C541" on the other side.
The tablet can be divided into equal halves

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NT005 trade name] is a broad-spectrum anthelmintic used for the treatment of the following infections:

Cestode infections (tapeworms)

[NT005 trade name] is indicated for the treatment of *Echinococcus multilocularis* and *E. granulosus* infections before or after surgery or where surgery is not suitable.

[NT005 trade name] is also indicated for the treatment of neurocysticercosis caused by larval forms of the pork tapeworm, *Taenia solium.*

Lymphatic filariasis
[NT005 trade name] is indicated together with ivermectin and/or diethylcarbamazine for the elimination of lymphatic filariasis.

Treatment is given to the entire eligible population in endemic areas through a mass drug administration programme.

Other nematode infections (roundworms)

[NT005 trade name] is indicated for the treatment of nematode infections including ascariasis, capillariasis, enterobiasis, hookworm infections (necatoriasis and ancylostomiasis), strongyloidiasis, trichostrongyliasis, trichuriasis, cutaneous larva migrans and trichinellosis.

[NT005 trade name] can also be used, alone or in combination with other medicines, for the control of soil-transmitted helminthiasis (ascariasis, trichuriasis and hookworm infections) through mass drug administration programmes.

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

4.2 Posology and method of administration

Cestode infections (tapeworms)

Adults

In adults over 60 kg, the dose is 400 mg twice a day.

In adults up to 60 kg, the dose is 15 mg/kg daily in 2 divided doses (maximum 800 mg daily).

For *cystic echinococcosis*, [NT005 trade name] is taken for a course of 28 days followed by 14 tablet-free days. Up to 3 courses may be given.

For *alveolar echinococcosis*, [NT005 trade name] is taken for a course of 28 days followed by 14 tablet-free days, and treatment cycles may need to be continued for months or years.

For *neurocysticercosis*, [NT005 trade name] is taken for 8–30 days.

Children

Only limited data are available on the use of [NT005 trade name] in children for cestode infections.

Nematode infections

Doses for the treatment of nematode infections are shown in the following table.

Infection	**Dose and frequency**		**Treatment duration**
	Adult and child over 2 years	**Child 1–2 years**	
Ascariasis Enterobiasis Hookworm infections Trichostrongyliasis	400 mg once	200 mg once	Single dose
Trichuriasis, moderate	400 mg once	200 mg once	Single dose
Trichuriasis, severe	400 mg once daily	200 mg once daily	3 days
Strongyloidiasis	400 mg once or twice daily	Not recommended	3 days
Trichinellosis	400 mg once daily	Not recommended	3 days
Capillariasis	400 mg once daily	Not recommended	10 days
Cutaneous larva migrans	400 mg once or twice daily	Not recommended	3-7 days

Mass drug administration

For the elimination of *lymphatic filariasis* and the control of *soil-transmitted helminthiasis* (ascariasis, trichuriasis, or hookworm disease), [NT005 trade name] is taken once or twice a year as needed (see WHO guidelines).

Adults and children aged over 2 years

In adults and children aged over 2 years, the dose of [NT005 trade name] for mass drug administration is 400 mg once a year.

Children aged 1–2 years

In children aged 1–2 years, the dose of [NT005 trade name] for the control of soil-transmitted helminthiasis is 200 mg.

[NT005 trade name] is not used in children below 2 years for the elimination of lymphatic filariasis.

Special populations

Renal impairment

No dose adjustment is required.

Hepatic impairment

Caution should be used if [NT005 trade name] is given to patients with liver disease, since albendazole is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity.

Method of administration

For oral use. [NT005 trade name] is not a chewable tablet, but may be crushed or swallowed whole.

For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately

For intestinal infections, where absorption into the blood is not required, albendazole should be given on an empty stomach. For systemic effect, albendazole should be given with or after a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Uncovering pre-existing neurocysticercosis

Treatment with albendazole may uncover pre-existing neurocysticercosis, particularly in areas with high taenia infection. Patients may experience neurological symptoms such as seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, and appropriate steroid and anticonvulsant therapy should be started.

Risk of retinal damage in patients with retinal neurocysticercosis

Cysticercosis may, in rare cases, involve the retina. Before initiating therapy for neurocysticercosis, the patient should be examined for the presence of retinal lesions. If such lesions are visualised, the need for anticysticeral therapy should be weighed against the possibility of retinal damage caused by albendazole-induced changes to the retinal lesion.

Hepatic effects

Mild to moderate elevations of liver enzymes have been reported with albendazole. In prolonged higher dose albendazole therapy for hydatid disease there have been rare reports of severe hepatic abnormalities such as jaundice and histological hepatocellular damage, which may be irreversible. Enzyme abnormalities are usually reversible on discontinuation of treatment.

Patients with disturbed liver function tests prior to commencing albendazole therapy should be carefully evaluated, since the medicine is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity. If enzymes are significantly increased (greater than twice the upper limit of normal) during treatment, [NT005 trade name] should be discontinued. [NT005 trade name] treatment may be reinstituted when levels have returned to normal limits, but liver function should be monitored frequently during repeat therapy.

Bone marrow suppression

Albendazole can cause bone marrow suppression and therefore blood counts are needed at the start and every two weeks during each 28 day cycle for treating echinococcosis. Patients with liver disease, including hepatic echinococcosis, may be more susceptible to bone marrow suppression leading to pancytopenia,

aplastic anaemia, agranulocytosis and leucopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur.

Excipients

[NT005 trade name] contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

[NT005 trade name] contains FD & C yellow #6 (Lake sunset yellow FCF). This may cause allergic reactions.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Dexamethasone, praziquantel and cimetidine may increase the plasma concentration of the active metabolite of albendazole, albendazole sulphoxide.

Ritonavir, phenytoin, carbamazepine and phenobarbital may have the potential to reduce plasma concentrations of the active metabolite of albendazole. The clinical relevance of this is unknown, but may result in decreased efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and may require alternative dose regimens or therapies.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential
Pregnancy should be avoided in women treated with albendazole. Adequate contraceptive measures should be taken.

Pregnancy
There are no adequate and well-controlled studies of [NT005 trade name] administration in pregnant women. Animal studies have revealed evidence of teratogenicity in rats and rabbits (see section 5.3).

[NT005 trade name] should be used in pregnant women only if there are no alternatives and the potential benefit justifies the potential risk to the fetus.

Lactation
Albendazole acts primarily in the intestinal system of the mother and little is absorbed systemically; therefore, it is compatible with breastfeeding.

Fertility
There are no data on the effects of [NT005 trade name] on human male or female fertility.
Animal studies indicate no effects of albendazole on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness (see sections 4.8) while taking albendazole and should be advised not to drive or operate machines if this occurs.

4.8 Undesirable effects

Data from clinical trials and post-marketing surveillance were used to estimate the frequency of adverse events linked to albendazole.

The adverse reactions considered related to albendazole are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), and very rare (< 1/10 000).

Short duration of treatment

Blood and the lymphatic system disorders

Rare	Low red cell count

Immune system disorders

Rare	Hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders

Uncommon	Headache, dizziness

Gastrointestinal disorders

Common	Upper gastrointestinal symptoms (e.g. epigastric or abdominal pain, nausea, vomiting)
Uncommon	Diarrhoea

Hepatobiliary disorders

Rare	Elevations of hepatic enzymes

Skin and subcutaneous tissue disorders

Uncommon	Itchiness, skin rashes
Very rare	Erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders

Rare	Bone pain

Renal and urinary disorders

Rare	Proteinuria

Longer duration of treatment

Blood and the lymphatic system disorders

Uncommon	Leucopenia
Rare	Low red cell count
Very rare	Pancytopenia, aplastic anaemia, agranulocytosis

Immune system disorders

Uncommon	Hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders

Very common	Headache
Common	dizziness

Gastrointestinal disorders

Common	Gastrointestinal disturbances (abdominal pain, nausea, vomiting)

Hepatobiliary disorders

Very common	Mild to moderate elevations of hepatic enzymes
Uncommon	Hepatitis[1]

Skin and subcutaneous tissue disorders

Common	Reversible alopecia (thinning of hair, and moderate hair loss)
Very rare	Erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders

Rare Bone pain

Renal and urinary disorders

Rare Proteinuria

General disorders

Common Fever

[1] With prolonged albendazole treatment for hydatid disease there have also been reports of severe hepatic abnormalities, including jaundice and hepatocellular damage which may be irreversible

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

In case of overdosage, symptomatic therapy and general supportive measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihelmintics, benzimidazole derivatives, ATC code: P02CA03.

Mechanism of action

Albendazole is a benzimidazole derivative that causes degenerative alterations in the tegument and intestinal cells of the parasite and blocks their energy production, ultimately leading to immobilisation and death of the parasite. It works by binding to the colchicine-sensitive site of tubulin, thus inhibiting its assembly into microtubules. As cytoplasmic microtubules are critical in promoting glucose uptake, the glycogen stores of the parasites are depleted.

5.2 Pharmacokinetic properties

The absorption characteristics of [NT005 trade name] have been determined in healthy volunteers for albendazole and summarised in the following tables

Albendazole

Characteristic	**Arithmetic mean ± Standard deviation (Geometric mean)**
Maximum concentration (C_{max})	84 ± 89 (56)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	314 ± 368
Time to attain maximum concentration (T_{max})	4.0 (1.33 – 5.0)

Pharmacokinetics of albendazole

General	
	Albendazole concentrations are negligible or undetectable in plasma as it is rapidly converted into the sulfoxide metabolite prior to reaching the systemic circulation. The systemic anthelmintic activity has been attributed to this primary metabolite, albendazole sulfoxide. Maximal plasma concentrations of albendazole sulfoxide are typically achieved 2 to 5 hours after dosing.
Absorption	
Absolute bioavailability	NA*
Oral bioavailability	Albendazole is poorly absorbed from the gastrointestinal tract (<5%) due to its low aqueous solubility.
Food effect	Absorption is significantly enhanced (approximately 5-fold) if albendazole is administered with a fatty meal.
Distribution	
Volume of distribution (mean)	NA*
Plasma protein binding *in vitro*	Albendazole sulfoxide is 70% bound to plasma protein.
Tissue distribution	Albendazole sulfoxide is widely distributed throughout the body; it has been detected in urine, bile, liver, cyst wall, cyst fluid, and cerebral spinal fluid.
Metabolism	
	Albendazole rapidly undergoes extensive first-pass metabolism in the liver to albendazole sulfoxide, and is generally not detected in plasma. Albendazole sulfoxide is further metabolized to albendazole sulfone and other primary oxidative metabolites.
Active metabolite(s)	Albendazole sulfoxide
Elimination	
Elimination half life	The terminal elimination half-life of albendazole sulfoxide typically ranges from 8 to 12 hours.
Mean systemic clearance (Cl/F)	
Excretion	Following oral administration, albendazole has not been detected in human urine. Albendazole sulphoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine.

Pharmacokinetic linearity	Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range following ingestion of a fatty meal.
Drug interactions *(in vitro*)	
Transporters	NA*
Metabolizing enzymes	NA*

* Information not available

Special populations

Renal impairment

Since renal elimination of albendazole and its primary metabolite, albendazole sulfoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients.

Liver impairment

In patients with evidence of extrahepatic obstruction, the systemic availability of albendazole sulfoxide was increased 7-fold.

Elderly patients

Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data suggest that the pharmacokinetics is similar to those in young healthy subjects.

Paediatrics

Following single-dose administration of 200 to 300 mg (approximately 10 mg/kg) albendazole to paediatric patients with hydatid cyst disease (age range 6 to 13 years), albendazole sulfoxide pharmacokinetics were similar to those observed in fed adults.

5.3 Preclinical safety data

General toxicity
Studies of up to 6 months in mice, rats and dogs recognised the haematopoietic system and the liver as target organs of toxicity.

Genotoxicity
In genotoxicity tests, albendazole was found negative in an Ames Salmonella/microsome plate mutation assay, Chinese hamster ovary chromosomal aberration test, and *in vivo* mouse micronucleus test. In the *in vitro* BALB/3T3 cells transformation assay, albendazole produced weak activity in the presence of metabolic activation while no activity was found in the absence of metabolic activation.

Carcinogenicity
Long-term carcinogenicity studies in mice and rats found no evidence of increased incidence of tumours was found in the mice or rats at up to 400 mg/kg/day and 20 mg/kg/day, respectively.

Toxicity to reproduction
Albendazole did not affect male or female fertility in the rat at an oral dose level of 30 mg/kg/day.

Albendazole has been shown to be teratogenic (to cause embryotoxicity and skeletal malformations) in pregnant rats and rabbits. The teratogenic response in the rat was shown at oral doses of 10 and 30 mg/kg/day during gestation days 6 to 15, and in pregnant rabbits at oral doses of 30 mg/kg/day administered during gestation days 7 to 19. In the rabbit study, maternal toxicity (33% mortality) was noted

at 30 mg/kg/day. In mice, no teratogenic effects were observed at oral doses up to 30 mg/kg/day administered during gestation days 6 to 15.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Corn starch
Sodium starch glycolate
Sodium lauryl sulphate
Povidone
Microcrystalline cellulose
Saccharin sodium
Magnesium stearate
Colour FD & C yellow #6 (Lake sunset yellow FCF)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC.
Discard the product 30 days after initial opening.

6.5 Nature and contents of container

White HDPE bottle with blue child-resistant polypropylene cap, heat seal liner and rayon sani coil. Pack size: 60 tablets.
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6.6 Special precautions for disposal

No special requirements.

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

7. SUPPLIER

Cipla Limited
Cipla House
Peninsula Business park
Ganpatrao Kadam Marg
Lower Parel
Mumbai 400 013
India.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

NT005

9. DATE OF PREQUALIFICATION

31 March 2021

10. DATE OF REVISION OF THE TEXT

May 2021

References

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Section 4.6
REPROTOX® is a service of The Reproductive Toxicology Center, A Non-Profit Foundation located at: 2737 Devonshire Pl NW #120 https://reprotox.org/contact Washington DC 20008-3459 (2018)

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