WHO-PQ RECOMMENDED
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VERMOX CHEWABLE 500 mg chewable tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains 500 mg of mebendazole.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Round, flat radius-edged white to yellowish chewable tablet that is debossed with “M” over “500” on one side and “J” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vermox Chewable is indicated for the mass treatment of subjects one year of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and *Ancylostoma duodenale* (hookworms).

In subjects living in heavily endemic areas, regular treatment with mebendazole 500 mg chewable tablets (1-2 times a year) will reduce the overall worm burden.

For further information on the appropriate use of Vermox Chewable 500 mg tablets in the context of mass drug administration for the control of soil transmitted helminths, consideration should be given to official guidelines and recommendations.
Official guidance will normally include WHO and local health authorities’ guidance.

4.2 Posology and method of administration

Adults and Paediatric Population
The recommended dosage in subjects one year of age and older is one mebendazole 500 mg chewable tablet taken as a single dose. This dose may be repeated on an annual or biannual basis, according to programmatic recommendations.

Chew Vermox Chewable 500 mg tablet completely before swallowing.
For subjects who have difficulty chewing the tablet, approximately 2 mL to 3 mL of drinking water can be added to a suitably sized spoon and the Vermox Chewable 500 mg tablet placed into the water. Within 2 minutes, the tablet absorbs water and turns into a soft mass with semi-solid consistency, which can then be swallowed.

Vermox Chewable 500 mg tablet can be taken without regard to food intake (see section 5.1).

* 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.

Special populations
Hepatic Impairment
Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Renal impairment
There is no need for dosing adjustment in renal insufficiency. Less than 2% of an orally administed dose of mebendazole is renally excreted.

Elderly patients
Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

Paediatric patients
The safety and effectiveness of mebendazole 500 mg chewable tablets have been established in paediatric patients 1 to 16 years of age. Safety and efficacy of mebendazole in children less than 1 year of age have not been established (see section 4.3).

4.3 Contraindications

Mebendazole 500 mg chewable tablets are contraindicated in children below the age of 1 year for the mass treatment of single or mixed gastrointestinal infestations (see section 4.4).

Vermox Chewable should not be given when the subject has a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of Convulsions
Convulsions have been reported in infants below the age of 1 year during postmarketing experience with mebendazole (see section 4.8).

Haematologic Effects
Agranulocytosis and neutropenia have been reported with mebendazole use at higher doses and for more prolonged durations than is recommended for the treatment of soil-transmitted helminth infections. Monitor blood counts if Vermox Chewable is used at higher doses or for prolonged duration.

Metronidazole Drug Interaction and Serious Skin Reactions
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole. Avoid concomitant use of mebendazole and metronidazole.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of mebendazole and metronidazole should be avoided (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The available published literature on mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages. There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy.

Breast-feeding
Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant, and the limited reports on the effects on milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of Vermox Chewable to a breastfed infant; therefore, developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mebendazole and any potential adverse effects on the breastfed infant from mebendazole or from the underlying maternal condition.

Fertility
Results of mebendazole reproduction studies showed no effects on fertility up to and including doses of 10 mg/kg/day (60 mg/m^2) (see section 5.3).

4.7 Effects on ability to drive and use machines

Vermox Chewable 500 mg does not affect mental alertness or driving ability.

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of mebendazole was evaluated in 6276 adult and paediatric subjects one year of age and older who participated in 39 clinical trials for treatment of single or mixed parasitic infections of the gastrointestinal tract. In these trials, the formulations, dosages and duration of mebendazole treatment varied. Adverse reactions reported in mebendazole-treated subjects from the 39 clinical trials are shown in Table 1 below.

Table 1: Adverse Reactions Reported in Mebendazole-Treated Subjects from 39 Clinical Trials*

Adverse Reaction(s)
Gastrointestinal Disorders
Anorexia
Abdominal Pain
Diarrhoea
Flatulence
Nausea
Vomiting
Skin and Subcutaneous Tissue Disorders
Rash

* Includes mebendazole formulations, dosages and treatment duration other than Vermox Chewable 500 mg tablet

Clinical Studies with Mebendazole Chewable 500 mg Tablet
The safety profile of mebendazole chewable 500 mg tablets administered as a single dose was evaluated in 677 paediatric subjects aged 1 to 16 years and in 34 adults. The safety profile was consistent with the known safety profile of mebendazole.

Postmarketing Experience
The following adverse reactions have been identified in adult and paediatric patients postmarketing with mebendazole formulations and dosages other than the Vermox Chewable 500 mg tablet. Because these reactions are 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.

Table 2: Adverse Reactions Identified During Postmarketing Experience with Mebendazole*

	Adverse Reaction(s)
Blood and Lymphatic System Disorders	Agranulocytosis, Neutropenia
Immune System Disorders	Hypersensitivity including anaphylactic reactions
Nervous System Disorders	Convulsions, Dizziness
Hepatobiliary Disorders	Hepatitis, Abnormal liver tests
Renal and Urinary Disorders	Glomerulonephritis
Skin and Subcutaneous Tissue Disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Exanthema, Angioedema, Urticaria, Alopecia

* Includes mebendazole formulations, dosages and treatment durations other than Vermox Chewable 500 mg tablet

4.9 Overdose

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported: alopecia, reversible transaminase elevations, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis.

Signs and Symptoms
In the event of accidental overdose, gastrointestinal signs and symptoms may occur.

Treatment
There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anthelmintic for oral administration, benzimidazole derivatives;
ATC code: P02CA01.

Mechanism of action
Mebendazole interferes with cellular tubulin formation in the helminth and causes ultrastructural degenerative changes in its intestine. As a result, its glucose uptake and the digestive and reproductive functions are disrupted, leading to immobilization, inhibition of egg production and death of the helminth.

Antimicrobial Activity
Mebendazole is active against:
Ascaris lumbricoides
Trichuris trichiura
Necator americanus
Ancylostoma duodenale

Resistance
There is a potential for development of resistance to mebendazole. The mechanism of resistance to mebendazole is likely due to mutations of the beta-tubulin gene, leading to changes of beta-tubulin protein, which results in reduced binding of mebendazole to beta-tubulin; however, the clinical significance of this is not known.

Clinical results

The efficacy of Vermox Chewable 500 mg tablets was evaluated in a double-blind, randomized, placebo controlled trial conducted in Africa in 295 paediatric patients between the ages of 1 year to 16 years of age with *A. lumbricoides* and/or *T. trichiura* infections.
Patients were stratified by worm type and randomized to receive either mebendazole 500 mg chewable tablet (N=149) or placebo (N=146) at the baseline visit (double-blind period). After the 19 day double-blind period, all subjects received a single mebendazole 500 mg chewable tablet (open-label period).

Clinical cure was defined as zero egg count (*A. lumbricoides* and/or *T. trichiura*) at the end of the double-blind period (Day 19) in patients with positive egg count for the respective worm(s) at baseline. Patients with missing stool sample at Day 19 were considered not cured (Table 3).

Table 3: Clinical Response at the End of the Double-Blind Period (Day 19) for *A. lumbricoides* and *T. trichiura*

Infection Type	mebendazole 500 mg chewable tablet All Patients=149*	Placebo All Patients=146*	Difference[1] (95% CI)
A. lumbricoides	**N=86 n (%)**	**N=81 n (%)**	
Cure	72 (83.7)	9 (11.1)	**72.6 (62.3, 82.7)**[2]
Failure[3]	9 (10.5)	67 (82.7)	
Missing[4]	5 (5.8)	5 (6.2)	
T. trichiura	**N=124 n (%)**	**N=119 n (%)**	
Cure	42 (33.9)	9 (7.6)	**26.2 (16.7, 35.6)**[2]
Failure[3]	76 (61.3)	103 (86.6)	
Missing[4]	6 (4.8)	7 (5.8)	

[1] Difference in cure rates, expressed in percentages, and based on Mantel Haenszel methods to account for stratification by site.
[2] P-value <0.001 based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
[3] Failures include patients who tested positive for the worm at Visit 3 (Day 19, i.e. test-of-cure).
[4] Patients with missing stool sample at Day 19.
***** Some patients had mixed infection.

In patients treated with mebendazole 500 mg chewable tablets, clinical cure rates at the end of the double blind period (Day 19) in patients with *A. lumbricoides* and/or *T. trichiura* were statistically significant (p<0.001) compared to placebo: 84% compared to 11% for *A.lumbricoides* (N=167), respectively, and 34% compared to 7% for *T. trichiura* (N=243), respectively.

In patients treated with mebendazole 500 mg chewable tablets, egg count reduction rates at the end of the double-blind period (Day 19) in patients with *A. lumbricoides* and/or *T. trichiura* were statistically significant (p<0.001) compared to placebo, 100% compared to 30.0% for *A. lumbricoides*, respectively, and 81.2% compared to 27.4% for *T. trichiura*, respectively.

Overall, 13 randomized patients had hookworm infection in addition to *A. lumbricoides* and/or *T. trichiura* infection. Of these patients, 4/4 patients in the mebendazole chewable tablet group (100%) and 2/9 patients in the placebo group (22.2%) were cured of hookworm infection at the end of the double-blind treatment period.

The efficacy of mebendazole 500 mg single oral dose for the treatment of mixed and/or single infestations with *Ancylostoma duodenale* or *Necator americanus* (hookworm) has been documented in 24 published reports from the world literature, of which 8 studies were placebo-controlled trials (see Table 4).

Table 4: Summary of Cure Rates and Egg Count Reductions in the treatment of mixed and/or single infestations with *Ancylostoma duodenale* or *Necator americanus*

	All Studies (24 studies)	**Placebo-controlled Studies (8 Studies)**	
Treatment Arm	**Mebendazole 500 mg**	**Mebendazole 500 mg**	**Placebo**
Overall Cure Rate	N=4600	N=1211	N=965
Weighted Mean % (range)	25.5 (2.9 – 91.1)	20.5 (2.9 – 91.1)	7.6 (0 – 33.0)
Overall Egg Count Reduction	N=4872	N=1211	N=965
Weighted Mean % (range)*	72.0 (-6.5 – 98.3)	61.2 (-6.5 – 98.3)	18.2 (-38.9 – 41.0)

* Individual egg count reduction calculation methods varied based on study

5.2 Pharmacokinetic properties

Absorption

Following oral administration of mebendazole 500 mg chewable tablet, the majority of the dose remains in the gastrointestinal tract where it exerts an anthelmintic effect locally. Dosing the mebendazole 500 mg chewable tablet with a high fat meal increases the bioavailability of mebendazole. In the clinical studies conducted in paediatric patients with soil transmitted helminth infections, the majority of these patients were administered Vermox Chewable 500 mg tablets with food.

Mean plasma pharmacokinetic parameters of mebendazole in healthy adult subjects under fasted and fed conditions are summarized in Table 5.

Table 5: Mean (SD) Plasma Pharmacokinetic Parameters After a Single Vermox Chewable 500 mg Dose in Healthy Adult Subjects (n=16) Under Fasted and Fed (High-fat Meal) Conditions

Parameter	**Fasted**	**Fed**
C_{max} (ng/mL)	14.0 (9.17)	56.2 (35.8)
T_{max} (h)*	1.5 (0.5-3.0)	4.0 (2.0-6.0)
AUC_{last} (ng.h/mL)	175 (129)	456 (249)

* median (range)

Distribution

The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that absorbed mebendazole penetrates areas outside the vascular space.

Metabolism

Orally administered mebendazole is extensively metabolized primarily by the liver. Plasma concentrations of its major metabolites (hydrolyzed and reduced forms of mebendazole) are higher than those of mebendazole. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Elimination

Mebendazole, the conjugated forms of mebendazole, and its metabolites likely undergo some degree of enterohepatic recirculation. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients. Less than 2% of orally administered mebendazole is excreted in urine and the remainder in the faeces as unchanged drug or its metabolites.

Specific Populations

Paediatric

Based on a limited number of blood samples, the pharmacokinetic results following single-dose administration of a 500 mg mebendazole chewable tablet to paediatric patients (age 1 to 16 years) with single or mixed infections of *T. trichiura* and/or *A. lumbricoides* indicated that children aged 1 to 3 years have approximately four-fold higher systemic exposure than adults.

5.3 Preclinical safety data

In carcinogenicity tests of mebendazole in mice and rats, no carcinogenic effects were seen at doses as high as 40 mg/kg (0.4 to 0.8-fold the maximum recommended human dose [MRHD], based on mg/m^2) given daily over two years. No mutagenic activity was observed with mebendazole in a bacterial reverse gene mutation test. Mebendazole was mutagenic in the absence of S-9 when tested using a continuous (24 hour) treatment incubation period in the mouse lymphoma thymidine kinase assay. Mebendazole was aneugenic *in vitro* in mammalian somatic cells. In the *in vivo* mouse micronucleus assay, orally administered mebendazole induced an increased frequency of micronucleated polychromatic erythrocytes with evidence suggestive of aneugenicity. Doses up to 40 mg/kg in rats (0.8-fold the MRHD, based on mg/m^2), given to males for 60 days and to females for 14 days prior to gestation, had no effect upon fetuses and offspring.

In animal reproduction studies, adverse developmental effects (i.e. skeletal malformations, soft tissue malformations, decreased pup weight, embryolethality) were observed when mebendazole was administered to pregnant rats during the period of organogenesis at single oral doses as low as 10 mg/kg (approximately 0.2-fold the MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chewable tablet
Crospovidone
Magnesium stearate
Microcrystalline cellulose
Povidone
Strawberry flavour
Sucralose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

Unused tablets should be discarded 3 months after the bottle is first opened. When the bottle is first opened this date (Date opened) should be written on the bottle label in the space provided.

6.4 Special precautions for storage

Do not store above 30°C. Keep container tightly closed.

6.5 Nature and contents of container

200 tablets packed in an HDPE bottle with HDPE cap with safe-seal induction liner.

6.6 Special precautions for disposal

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

7. SUPPLIER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

NT006

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF THE PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

April 2019
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Detailed information on this product is available on the website of the WHO Prequalification program hhttps://extranet.who.int/prequal/.

Reference List

WHO Guideline: Preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups. Geneva, World Health Organization, 2017; available at: https://www.who.int/nutrition/publications/guidelines/deworming/en/ (accessed April 13, 2019)

United States Prescribing Information for Vermox Chewable 500 mg chewable tablets, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208398s000lbl.pdf (accessed April 13, 2019)