PRODUCT NAME
VERMOX® (mebendazole) tablets.

DOSAGE FORMS AND STRENGTHS
VERMOX® 500 mg tablet: white to faintly cream-colored, circular, flat, bevel-edged tablet.
Each tablet contains 500 mg mebendazole.
For excipients, see List of Excipients.

CLINICAL INFORMATION
Indications
VERMOX® 500 mg is indicated for the mass treatment of single or mixed gastrointestinal infestations by *Enterobius vermicularis* (pinworm); *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); *Ancylostoma duodenale*, *Necator americanus* (hookworm).
In patients living in heavily endemic areas, regular treatment with VERMOX® 500 mg (1-2 times a year) will substantially reduce the overall wormload and keep it well below the level of clinical significance.

Dosage and Administration
Dosage
1 single tablet of VERMOX® 500 mg.
Special populations
Pediatrics
VERMOX® 500 mg given as a single dose.
Pediatrics < 2 years of age
Because of the risk of convulsions, VERMOX® is contraindicated in children below the age of 1 year for the mass treatment of single or mixed gastrointestinal infestations (see Contraindications, Warnings and Precautions).
VERMOX® has not been extensively studied in children below the age of 2 years. Therefore, VERMOX® should be used in children aged 1-2 years only if the potential benefit justifies the potential risk (see Warnings and Precautions).
Administration
No special procedures, such as diet or use of laxatives, are required.

Contraindications
VERMOX® is contraindicated in children below the age of 1 year for the mass treatment of single or mixed gastrointestinal infestations. In addition, VERMOX® is contraindicated in persons with a known hypersensitivity to the drug or its excipients.

Warnings and Precautions
Convulsions in children, including in infants below one year of age, have been reported very rarely during post-marketing experience with VERMOX® (see Adverse Reactions). VERMOX® has not been extensively studied in children below the age of 2 years. Therefore, VERMOX® should be used in children aged 1-2 years only if the potential benefit justifies the potential risk (e.g. if their worm infestation interferes significantly with their nutritional status and physical development).
To reduce the risk of choking, VERMOX® oral suspension should be considered for patients such as young children who are unable to swallow the tablet.
There have been rare reports of reversible liver function disturbances, hepatitis, and neutropenia described in patients who were treated with mebendazole at standard dosages for indicated conditions (see Adverse Reactions – Postmarketing data). These events, along with glomerulonephritis and agranulocytosis, have also been reported with dosages substantially above those recommended and with treatment for prolonged periods of time.

Results from a case-control study investigating an outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) suggested a possible relationship between SJS/TEN and the concomitant use of mebendazole and metronidazole. Further data suggesting such a drug-drug interaction are not available. Therefore, concomitant use of mebendazole and metronidazole should be avoided.

Interactions

Concomitant treatment with cimetidine may inhibit the metabolism of mebendazole in the liver, resulting in increased plasma concentrations of the drug especially during prolonged treatment.

Concomitant use of mebendazole and metronidazole should be avoided (see Warnings and Precautions).

Pregnancy, Breast-feeding and Fertility

Pregnancy

Mebendazole has shown embryotoxic and teratogenic activity in rats and in mice. No harmful effects on reproduction were noted in other animal species tested (see Non-clinical Information).

The possible risks associated with prescribing VERMOX® 500 mg during pregnancy, particularly during the first trimester, should be weighed against the expected therapeutic benefits.

Breast-feeding

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. Therefore, caution should be exercised when VERMOX® 500 mg is administered to breast-feeding women.

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 Non-clinical Information).

Effects on Ability to Drive and Use Machines

VERMOX® 500 mg does not affect the mental alertness or driving ability.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of mebendazole based on the comprehensive assessment of the available adverse event information. A causal relationship with mebendazole cannot be reliably established in individual cases. Further, 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 clinical practice.

Clinical trial data

The safety of VERMOX® was evaluated in 6276 subjects who participated in 39 clinical trials for the treatment of single or mixed parasitic infestations of the gastrointestinal tract. In these 39 clinical trials, no adverse reactions occurred in ≥1% of VERMOX®-treated subjects. Adverse reactions occurring in <1% of VERMOX®-treated subjects are shown in Table 1.

Table 1: Adverse Reactions Reported by <1% of VERMOX®-Treated Subjects in 39 Clinical Trials

System/Organ Class Adverse Reaction
Gastrointestinal Disorders
Abdominal Discomfort
Diarrhea
Flatulence
Skin and Subcutaneous Tissue Disorders
Rash

Postmarketing data

Adverse reactions first identified during postmarketing experience with VERMOX® (mebendazole) are included in Table 2. In this table, adverse reactions are based on spontaneous reporting rates, and presented by frequency category according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000, including isolated reports.

Table 2: Adverse Reactions Identified During Postmarketing Experience with VERMOX® by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class Frequency Category	Adverse Reaction
Blood and Lymphatic System Disorders	
Very Rare	Agranulocytosis*, Neutropenia
Immune System Disorders	
Very Rare	Hypersensitivity including anaphylactic reaction and anaphylactoid reaction
Nervous System Disorders	
Very Rare	Convulsions, Dizziness
Gastrointestinal Disorders	
Very Rare	Abdominal pain, Nausea, Vomiting
Hepatobiliary Disorders	
Very Rare	Hepatitis, Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders Very Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Exanthema, Angioedema, Urticaria, Alopecia
Renal and Urinary Disorders	
Very rare	Glomerulonephritis*

* Observed in higher and prolonged doses

Overdose

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported rarely: alopecia, reversible liver function disturbances, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis. With the exception of agranulocytosis and glomerulonephritis, these also have been reported in patients

who were treated with mebendazole at standard dosages (see Adverse Reactions – Postmarketing data).

Signs and symptoms

In the event of accidental overdose, abdominal cramps, nausea, vomiting and diarrhea may occur.

Treatment

There is no specific antidote. Activated charcoal may be given if considered appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Mechanism of action

In therapeutic indications mebendazole acts locally in the lumen of the gut by interfering with cellular tubulin formation in the intestines of worms. Mebendazole binds specifically to tubulin and causes ultrastructural degenerative changes in the intestine. As a result, the glucose uptake and the digestive functions of the worm are disrupted to such an extent that an autolytic process occurs.

Pharmacokinetic Properties

Absorption

Following oral administration, <10% of the dose reaches the systemic circulation, due to incomplete absorption and to extensive pre-systemic metabolism (first-pass effect). The majority of an orally administered dose remains in the gastrointestinal tract. Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Dosing with a high fat meal increases the bioavailability of mebendazole, although the overall effect of food on the amount of drug remaining in the gastrointestinal tract is not expected to be substantial.

Distribution

The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that mebendazole penetrates areas outside the vascular space. This is supported by data in patients on chronic mebendazole therapy (e.g., 40 mg/kg/day for 3-21 months) that show drug levels in tissue.

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 and are excreted in the urine and bile. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients.

Steady-state pharmacokinetics

During chronic dosing (e.g., 40 mg/kg/day for 3-21 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately 3-fold higher exposure at steady-state compared to single dosing.

NON-CLINICAL INFORMATION

The single-dose toxicity evaluations in multiple species revealed that mebendazole was well tolerated and has a large margin of safety. Repeated-dose, oral, chronic toxicity results in rats, at toxic dose levels of 40 mg/kg (240 mg/m^2) and above, showed altered liver weights with some

slight centrilobular swelling and hepatocellular vacuolation, and altered testicular weights with some tubular degeneration, desquamation and marked inhibition of spermatogenic activity.

Carcinogenicity and Mutagenicity

No carcinogenic effects were observed in the mouse or rat. No mutagenic activity was shown in *in vitro* gene-mutagenicity studies.

In vivo tests revealed no structural chromosome damaging activity. Micronucleus test results have shown aneugenic effects in mammalian somatic cells above a threshold plasma concentration of 115 ng/mL.

Reproductive Toxicology

At maternal toxic doses, embryo toxic and teratogenic activity has been shown in pregnant rats at a single dose of 10 mg/kg (60 mg/m^2) and above. Teratogenic and fetotoxic effects have also been observed in mice at maternally toxic doses of 10 mg/kg (60 mg/m^2) and higher. No harmful effects on reproduction were noted in other animal species tested.

Fertility

Male rat fertility was not affected with doses up to 40 mg/kg (240 mg/m^2) for 60 days. When female rats were dosed at up to 10 mg/kg body weight for 14 days before gestation and during pregnancy, no significant effect upon fetuses and offspring were observed. However, when female rats were dosed at 40 mg/kg (240 mg/m^2) a reduction in the pregnancy rate was observed.

PHARMACEUTICAL INFORMATION

List of Excipients

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, methylcellulose, microcrystalline cellulose, sodium starch glycolate.

Incompatibilities

None known.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

See storage conditions on the outer pack.

Keep out of the sight and reach of children.

Nature and Contents of Container

VERMOX® 500 mg is supplied in packs containing one tablet or in bottles containing 150 tablets.

Not all pack sizes may be available.

Instructions for Use and Handling

Not applicable.

Instructions for Disposal

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

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

30 May 2017