

## 1. NAME OF THE MEDICINAL PRODUCT

**VERMOX TABLETS**

**VERMOX SUSPENSION**

## 2. QUALITATIVE AND COMPOSITION

Each tablet contains 100 mg mebendazole.

The oral suspension contains 20 mg mebendazole per ml.

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

VERMOX 100 mg tablet: slightly orange, circular, flat, bevel-edged, half-scored tablet with inscription "JANSSEN" on one side and "Me/100" on the other.

VERMOX 20 mg/ml oral suspension: white homogeneous suspension..

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### **Vermox tablets**

Treatment of trichuris trichiura (whipworm)

*Ascaris lumbricoides* (roundworm)

*Ancylostoma duodenale* (common hookworm)

*Necator americanus* (american hookworm), strongyloidiasis, enterobius vermicularis (pinworm) and teniasis in single or mixed infections)

#### **Vermox suspension**

Treatment of single or mixed infections of *Trichuris trichura* (whipworm), *Ascaris lumbricoides* (large roundworm), *Ancylostoma duodenale*, *Necator americanus* (hookworm), *Strongyloides stercoralis*, ***Enterobius vermicularis* (threadworm/pinworm)** and *Taenia* spp.

Posology and method of administration

*Enterobiasis*: Adults and children over 2 years:

Take

1 tablet or 5 ml oral suspension given as a single dose. Since reinfections by *Enterobius vermicularis* are known to be very frequent, it is recommended that the treatment be repeated after 2 and 4 weeks, particularly in eradication programs.

*Ascariasis, trichuriasis, hookworm* and mixed infestations:

*Adults and children over 2 years*

Take 1 tablet or 5 ml oral suspension two times a day, in the morning and in the evening for 3 consecutive days.

**Taeniasis and strongyloidiasis:**

*Adults*

Although favorable results have been obtained with lower dosages, it is suggested to take 2 tablets or 10ml oral suspension two times a day in the morning and the evening for 3 consecutive days, to obtain complete cure. Even at this higher dosage undesirable effects are rare.

Children *over* 2 years.

Take 1 tablet. or 5 ml oral suspension two times a day in the morning and the evening for 3 consecutive days.

#### Administration:

No special procedures, such as diet or use of laxatives, are required.

For children < 2 years see section 4.4

Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine.

Vermox oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

## **4.2 Contraindications**

VERMOX is contraindicated in pregnancy and in patients with a known hypersensitivity to the product or any components.

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

## **4.3 Special warnings and special precautions for use**

Vermox is not recommended in the treatment of children under 2 years

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 section 4.8 'Undesirable effects'). 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.

A case-control study of a single outbreak of Stevens-Johnson syndrome /toxic epidermal necrolysis (SJS/TEN) suggested a possible association with the concomitant use of metronidazole with mebendazole. Although there are no additional data on this potential interaction, concomitant use of mebendazole and metronidazole should be avoided.

Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience (see section 4.8 'Undesirable effects'). Vermox has not been extensively studied in children below the age of 2 years. .

Because of the lack of sufficient safety data, Vermox should not be used in children below the age of 1 year.

Vermox should only be given to very young children if their worm infestation interferes significantly with their nutritional status and physical development.

## **4.4 Vermox oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this with other medicinal products and other forms of interaction**

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

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

## **4.5 Fertility, Pregnancy and lactation**

### Pregnancy

Since Vermox is contraindicated in pregnancy, patients who think they are or may be pregnant should not take this preparation.

### 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 is administered to breast-feeding women.

## **4.6 Effects on ability to drive and use machines**

Vermox has no influence on the ability to drive and use machines.

## **4.7 Undesirable effects**

Throughout this section adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of Vermox based on the comprehensive assessment of the available adverse event information. A causal relationship with Vermox 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.

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 drug reactions (ADRs) occurred in  $\geq 1\%$  of Vermox-treated subjects.

ADRs identified from clinical trials and post-marketing experience with Vermox are included in Table 1. The displayed frequency categories use the following convention:

Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1000$ ); Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions Reported in Clinical Trials and Post-marketing Experience for Vermox

	Adverse Drug Reactions		
System Organ Class	Frequency Category		
	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥1/10,000 to <1/1000)
<b>Blood and Lymphatic System Disorders</b>			Neutropenia <sup>b</sup> Agranulocytosis <sup>b</sup> *
<b>Immune System Disorders</b>			Hypersensitivity including anaphylactic reaction and anaphylactoid reaction <sup>b</sup>
<b>Nervous System Disorders</b>			Convulsions <sup>b</sup> Dizziness <sup>a</sup>
<b>Gastrointestinal Disorders</b>	Abdominal pain <sup>a</sup>	Abdominal discomfort <sup>a</sup> ; Diarrhoea <sup>a</sup> ; Flatulence <sup>a</sup> Nausea <sup>a</sup> , Vomiting <sup>a</sup>	
<b>Hepatobiliary Disorders</b>			Hepatitis; <sup>b</sup> Abnormal liver function tests <sup>b</sup>
<b>Skin and Subcutaneous Tissue Disorders</b>			Rash <sup>a</sup> Toxic epidermal necrolysis <sup>b</sup> ; Stevens-Johnson syndrome <sup>b</sup> ; Exanthema <sup>b</sup> ; Angioedema <sup>b</sup> ; Urticaria <sup>b</sup> ; Alopecia <sup>b</sup>
<b>Renal and Urinary Disorders</b>			Glomerulonephritis <sup>b</sup> *

<sup>a</sup> ADR frequency data derived from Clinical Trials or Epidemiological Studies

<sup>b</sup> ADRs not observed in clinical trials and frequency calculated based on 6276 patients exposed in clinical trials and epidemiological studies, divided by 3 (Frequency = 1/2092).

\* Observed in higher and prolonged doses

#### 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

#### 4.8 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 section 4.8).

#### *Signs and symptoms*

In the event of accidental overdosage, abdominal cramps, nausea, vomiting and diarrhoea may occur.

#### *Treatment*

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

## 5. PHARMACOLOGICAL PROPERTIES **5.1 Pharmacodynamic properties**

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

*In vitro* and *in vivo* work suggests that mebendazole blocks the uptake of glucose by adult and larval forms of helminths, in a selective and irreversible manner. Inhibition of glucose uptake appears to lead to endogenous depletion of glycogen stores within the helminth. Lack of glycogen leads to decreased formation of ATP and ultrastructural changes in the cells.

There is no evidence that Vermox is effective in the treatment of cysticercosis.

## **5.2 Pharmacokinetic properties**

### *Absorption*

Following oral administration, < 10% of the dose reaches the systemic circulation, due to incomplete absorption and 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. Administration with a high fat meal increases the bioavailability of mebendazole, but 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 metabolised primarily by the liver. Plasma concentrations of its major metabolites (hydrolysed and reduced forms of mebendazole) are substantially 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.

## **5.3 Preclinical safety data**

In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, soft tissue malformations, decreased pup weight, embryoletality) were observed when mebendazole was administered to pregnant rats and mice throughout the period of organogenesis or as a single oral dose as low as 10 mg/kg in rats (approximately 0.2-fold the maximum recommended human dose (MRHD)). Maternal toxicity was present at the highest of these doses. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity. Doses up to 40 mg/kg in rats (0.8-fold the MRHD, based on mg/m<sup>2</sup>), given to

males for 60 days and to females for 14 days prior to gestation, had no effect upon fetuses and offspring.

No mutagenic activity was observed with mebendazole in bacterial reverse mutation tests. Mebendazole was mutagenic when tested in the mouse lymphoma thymidine kinase assay and 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.

Mebendazole had no carcinogenic effects at doses as high as 40 mg/kg/day when administered daily in the diet over 2 years in carcinogenicity tests in mice and rats (0.4 to 0.8-fold the MRHD, based on mg/m<sup>2</sup>).

## **PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

The inactive ingredients of the tablets are microcrystalline cellulose, sodium starch glycolate (Sodium carboxymethylamilate), talc, maize starch, sodium saccharin, magnesium stearate, Cottonseed oil hydrogenated, orange flavor, colloidal anhydrous silica, sodium lauryl sulphate, orange yellow S (E110), purified water, Isopropyl alcohol (does not appear in final product)

The inactive ingredients of the oral suspension are sucrose, microcrystalline cellulose & carboxymethylcellulose sodium, methylcellulose 15 mPa.s, methyl parahydroxybenzoate, sodium lauryl sulphate, propyl parahydroxybenzoate, banana flavor 1, citric acid, monohydrate and purified water.

Each 5ml suspension contains 500mg of sucrose.

### **6.2 Special precautions for storage**

Tablets:

Do not store above 25°C

Keep out of reach and sight of children.

Suspension:

Do not store above 25°C

Keep out of reach and sight of children.

### **Shelf life**

The expiry date of the product is indicated on the packaging materials

Vermox suspension:

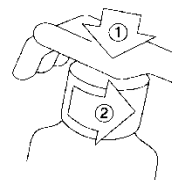
Shelf life after first opening: 28 days

### **6.3 Instructions for use/handling**

The suspension should be shaken before use.

The bottle comes with a child-proof cap, and should be opened as follows:

Push the plastic screw cap down, while turning it counterclockwise.



## 7. MANUFACTURER

Suspension: Janssen Pharmaceutica N.V., Beerse, Belgium

Tablets: Lusomedicamenta Sociedade Tecnica Farmaceutica, S.A, Portugal

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Kibbutz Shefayim 6099000

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