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 PARTICULARS4.1 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 orx 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 orx 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 yearsee 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

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

Risk Summary

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 [see Data]. There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy [see Clinical Considerations].
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 0.5-fold the total daily maximum recommended human dose [MRHD]). Maternal toxicity was present at the highest of these doses [see Data].
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risks

Untreated soil transmitted helminth infections in pregnancy are associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

Data

Human Data

Several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association between mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific pattern or frequency of major birth defects with mebendazole use. However, these studies cannot definitely establish the absence of any mebendazole-associated risk because of methodological limitations, ® ® including recall bias, confounding factors and, in some cases, small sample size or exclusion of first trimester mebendazole exposures.

Animal Data

Embryo-fetal developmental toxicity studies in rats revealed no adverse effects on dams or their progeny at doses up to 2.5 mg/kg/day on gestation days 6–15 (the period of organogenesis). Dosing at ≥10 mg/kg/day resulted in a lowered body weight gain and a decreased pregnancy rate. Maternal toxicity, including body weight loss in one animal and maternal death in 11 of 20 animals, was seen at 40 mg/kg/day. At 10 mg/kg/day, increased embryo-fetal resorption (100% were resorbed at 40 mg/kg/day), decreased pup weight and increased incidence of malformations (primarily skeletal) were observed. Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses during organogenesis as low as 10 mg/kg (approximately 0.5-fold the total daily MRHD, based on mg/m).
In embryo-fetal developmental toxicity studies in mice dosed on gestation days 6–15, doses of 10 mg/kg/day and higher resulted in decreased body weight gain at 10 and 40 mg/kg/day and a higher mortality rate at 40 mg/kg/day. At doses of 10 mg/kg/day (approximately 0.2-fold the total daily MRHD, based on mg/m) and higher, embryo-fetal resorption increased (100% at 40 mg/kg) and fetal malformations, including skeletal, cranial, and soft tissue anomalies, were present. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at doses up to 40 mg/kg/day (1.6 to 3.9-fold the total daily MRHD, based on mg/m).
In a peri- and post-natal toxicity study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (1.9-fold the total daily MRHD, based on mg/m), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found on gross and radiographic examination of pups at birth.

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 ≥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 (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥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

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

[a] ADR frequency data derived from Clinical Trials or Epidemiological Studies
[b] 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, embryolethality) 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^2), given to

males for 60 days and to females for 14 days prior to gestation, had no effect upon foetuses 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^2).

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:

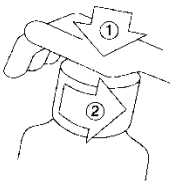
Shelf life after first opening: 28 days

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

REGISTRATION HOLDER

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