# 1. TRADE NAME OF THE MEDICINAL PRODUCT

**VERMOX**

# 2. QUALITATIVE AND QUANTITATIVE 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.

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

# 4. CLINICAL PARTICULARS

## 4.1. Therapeutic indications

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.

## 4.2. 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 year, 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.

## 4.3. Contraindications

VERMOX is contraindicated in persons with a known hypersensitivity to the drug or its excipients.

## 4.4. Special warnings and special precautions for use

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

Convulsions in children, including in infants below one year of age: have been reported very-rarely during post-marketing experience with VERMOX (see section 4.8 adverse reactions). VERMOX is not recommended in children below 2 years of age.

VERMOX 100 mg should only be given to very young children if their worm infestation interferes significantly with their nutritional status and physical development

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.

Vermox oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption of sucrose-isomaltase insufficiency should not take this medicine.

## 4.5. Interaction 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, especially during prolonged treatment.

Concomitant use of mebendazole and metronidazole should be avoided (see section 4.4 special warnings and special precautions for use).

## 4.6. Pregnancy breast feeding and fertility

### Pregnancy

Teratogenic Effects
*Pregnancy category C*
Mebendazole has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg (approximately equal to the human dose, based on mg/m ). In view of these findings the use of mebendazole is not recommended in pregnant women. Although there are no adequate and well- controlled studies in pregnant women, a postmarketing survey has been done of a limited number of women who inadvertently had consumed mebendazole during the first trimester of pregnancy. The incidence of spontaneous abortion and malformation did not exceed that in the general population. In 170 deliveries on term, no teratogenic risk of mebendazole was identified.

### Breast feeding

It is not known whether mebendazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mebendazole is administered to a nursing woman.

### Fertility

Doses up to 40 mg/kg in mice (equal to the human dose,
based on mg/m ), given to males for 60 days and to females for 14 days prior to gestation, had no effect

upon fetuses and offspring, though there was slight maternal toxicity.

## 4.7. Effects on ability to drive and use machines

VERMOX does not affect the mental alertness or driving ability.

## 4.8. 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**<br><br>≥1/100 to <1/10 | **Uncommon**<br><br>≥1/1000 to <1/100 | **Rare**<br><br>≥1/10,000 to <1/1000 |
| **Blood and lymphatic system disorders** | | | Neutropoenia[b] |
| **Immune System Disorders** | | | Hypersensitivity including anaphylactic reaction and anaphylactoid reaction[b] |
| **Nervous System Disorders** | | | Convulsions[b]<br>Dizziness[a] |

| | | | |
|---|---|---|---|
| **Gastrointestinal Disorders** | Abdominal pain[a] | Abdominal discomfort[a]<br><br>Diarrhea[a]<br><br>Flatulence[a] | |
| **Hepatobiliary Disorders** | | | Hepatitis[b]<br><br>Abnormal liver function tests[b] |
| **Skin and Subcutaneous Tissue Disorders** | | | Rash[a]<br><br>Toxic epidermal necrolysis[b]<br><br>Stevens-Johnson syndrome[b]<br><br>Exanthema[b]<br><br>Angioedema[b]<br><br>Urticaria[b]<br><br>Alopecia[b] |

[a] ADR frequency data derived from Clinical Trials or Epidemiological Studies.

[b] ADRs not observed in clinical trials and frequency calculated using "Rule of 3", as detailed in SmPC guidelines 2009. 6276 patients exposed in clinical trials and epidemiological studies, divided by 3 (Frequency = 1/2092). Note: frequencies differ from those reported in Aug 2009 CCDS, as these were not calculated using the formula detailed in the SmPC guideline 2009.

## 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 rarely: alopecia, reversible liver function disturbances, hepatitis, agranulocytosis, neutropoenia, 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 Undesirable effects*)

*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.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

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

### Mechanism of action

In 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.

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 to extensive pre-systemic metabolism (first-pass effect). Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Dosing with a high fat meal leads to a modest increase in the bioavailability of mebendazole.

### 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 (amino and hydroxylated amino 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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

The inactive ingredients of the tablets are microcrystalline cellulose, sodium starch glycolate, talc, maize starch, sodium saccharin, magnesium stearate, Cottonseed seed oil hydrogenated, orange flavour, colloidal anhydrous silica, sodium lauryl sulphate and orange yellow S.

The inactive ingredients of the oral suspension are sucrose, microcrystalline cellulose, carboxymethylcellulose sodium, methylcellulose, 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

Do not store above 25°C

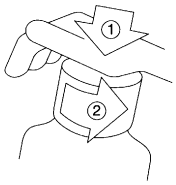
Keep out of sight and reach of children.

### 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 counter clockwise.




## 7. MANUFACTURER

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

Tablets: Janssen Cilag SpA , Latina , Italy

### LICENSE HOLDER

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