NAME OF THE MEDICINAL PRODUCT
VERMOX® (PANTELMIN)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg mebendazole.
The oral suspension contains 20 mg mebendazole per ml.

PHARMACEUTICAL FORM
VERMOX® 100 mg tablet: slightly orange, circular, flat, bevel-edged, half-scored tablet.
VERMOX® 20 mg/ml oral suspension: white homogeneous suspension.

CLINICAL PARTICULARS
Therapeutic indications
VERMOX® is indicated for the treatment of single or mixed gastrointestinal infestations by *Enterobius vermicularis* (pinworm); *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); *Ancylostoma duodenale*, *Necator americanus* (hookworm); *Strongyloides stercoralis* (threadworm); *Taenia spp.* (tapeworm).

Posology and method of administration
1) Enterobiasis:
Adults and children
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 programes.
2) Ascariasis, trichuriasis, hookworm and mixed infestations:
Adults and children
1 tablet b.i.d. or 5 ml oral suspension in the morning and in the evening for 3 consecutive days.
3) Taeniasis and strongyloidiasis:
Adults:
Although favorable results have been obtained with lower dosages, it is suggested that 2 tablets b.i.d. or 10 ml oral suspension be prescribed in the morning and the evening for 3 consecutive days, to obtain complete cure. Even at this higher dosage undesirable effects are rare.
Children
1 tablet b.i.d. or 5 ml oral suspension b.i.d. for 3 consecutive days. No special procedures, such as diet or use of laxatives, are required. For infants < 1 year, see Special warnings and special precautions for use.
[For infants < 1 year, see section Special warnings and special precautions for use.]

Contraindications
VERMOX® is contraindicated in persons with a known hypersensitivity to the drug or its components.

Special warnings and special precautions for use
Convulsions in children, including in infants below one year of age , have been reported very, rarely during post-marketing experience with VERMOX® (see Undesirable effects). VERMOX® 100 mg (Pantelmen) 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.

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. In the latter case, determination of plasma concentrations are recommended in order to allow dose adjustments.

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

Pregnancy and lactation

Mebendazole has shown embryotoxic and teratogenic activity in rats and in mice at single oral doses. No harmful effects on reproduction were noted in other animal species tested. (see Preclinical safety data) The possible risks associated with prescribing VERMOX® during pregnancy, particularly during the first trimester, should be weighed against the expected therapeutic benefits.

Mebendazole is only absorbed to a small extent. It is not known whether mebendazole is excreted in human breast milk. Therefore, caution should be exercised when VERMOX® is administered to nursing women.

Effects on ability to drive and use machines

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

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.

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 drug reactions (ADRs) occurred in ≥1% of VERMOX®-treated subjects. ADRs occurring in <1% of VERMOX®-treated subjects are shown in Table 1.

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

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

Postmarketing Experience

Adverse drug reactions first identified during post-marketing experience with VERMOX® (mebendazole) are included in Table 2. In the table the frequency categories are provided 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

In Table 2, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 2: Adverse Drug 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	Neutropoenia
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
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

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 Postmarketing Experience)

Symptoms

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

Treatment

There is no specific antidote. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In therapeutic indications (section 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. There is no evidence that VERMOX® is effective in the treatment of cysticercosis.

Pharmacokinetic properties

Absorption

Following oral administration, approximately 20% 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.

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. 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. 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.

PHARMACEUTICAL PARTICULARS

List of excipients

The inactive ingredients of the tablets are microcrystalline cellulose, sodium starch glycolate, talc, maize starch, sodium saccharin, magnesium stearate, cottonseed 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, sodium carmellose, methylcellulose, methyl parahydroxybenzoate, sodium lauryl sulphate, propyl parahydroxybenzoate, banana flavor 1, citric acid monohydrate and purified water.

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

Special precautions for storage

Store between 15° and 30°C.

Keep out of reach of children.

Nature and contents of container

VERMOX® tablets (each containing 100 mg mebendazole) is supplied in packs of 6 tablets.

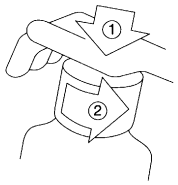
VERMOX® drinkable suspension is supplied in bottles of 30 ml with a measuring cap of 5 ml.

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.



MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

September 2010