

VERMOX®

DATA SHEET

NAME OF THE MEDICINE

Mebendazole.

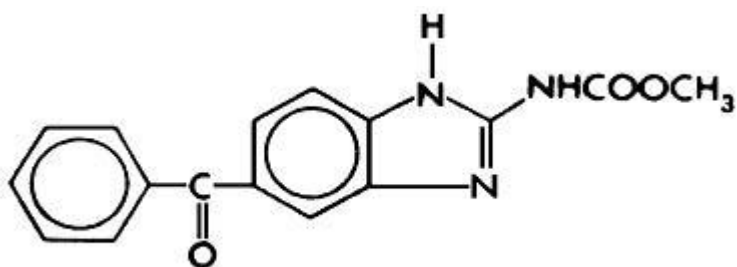
DESCRIPTION

Mebendazole is methyl 5-benzoyl-2-benzimidazole carbamate a synthetic benzimidazole derivative and is an off white to yellowish powder, insoluble in water and common organic solvents but freely soluble in formic acid.

VERMOX tablets contain mebendazole 100 mg - slightly orange, circular, flat, bevel-edged, half-scored tablet with orange flavour. The inactive ingredients in the tablets are cellulose - microcrystalline, sodium starch glycolate, purified talc, maize starch, sodium saccharin, hydrogenated cottonseed oil, magnesium stearate, orange flavour, anhydrous colloidal silica, sodium lauryl sulfate and sunset yellow SCF (orange yellow S (E110)).

VERMOX suspension contains mebendazole 2% w/v - a white banana flavoured suspension. Each spoonful contains mebendazole 100 mg. The inactive ingredients in the suspension are cellulose - microcrystalline cellulose, carmellose sodium (carboxymethylcellulose sodium), methylcellulose, sucrose, sodium lauryl sulfate, methyl hydroxybenzoate, propyl hydroxybenzoate, banana flavour 054330 A, citric acid monohydrate and water -purified.

VERMOX Choc Chews chewable tablets contain mebendazole 100 mg – lightly speckled chocolate brown, circular, flat, bevel-edged, half-scored tablet with chocolate flavour. The inactive ingredients in the tablets are fructose, cocoa powder, sucralose, chocolate powder AP0773-010, corn starch pregelatinised, macrogol 6000, magnesium stearate and talc – purified.



Molecular formula: C₁₆H₁₃N₃O₃.

MW: 295.30.

Action

Therapeutic Classification: Anthelmintic

Parasitology

In vitro and *in vivo* studies indicate that mebendazole inhibits *Trichuris trichiura* and hookworms (*Ancylostoma duodenale* and *Necator americanus*). *In vivo* efficacy has been demonstrated against

Trichuris, *Ascaris*, hookworm and *Enterobius*. The mechanism of action is probably a result of an inhibitory effect on the ability of the organism to utilise exogenous glucose. This interferes with the generation of phosphate bonds (ATP), ultimately leading to the death of the parasite.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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 to 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 (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.

Excretion

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. Approximately 95% of mebendazole is excreted in the faeces unchanged or as the primary metabolite (2-amino derivatives). Approximately 2 to 5% of mebendazole is excreted in the urine unchanged or as the primary metabolite.

Steady-State Pharmacokinetics

During chronic dosing (e.g. 40 mg/kg/day for 3 to 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.

Reproduction and Teratology Studies

The effect of mebendazole on reproduction was determined in various animal species. Included in these studies were determinations on potential embryotoxicity and teratogenicity in rats, rabbits, dogs, sheep and horses, and on male and female fertility in rats.

These studies showed that mebendazole is embryotoxic and teratogenic in rats at doses of 10 mg/kg and above but not in rabbits up to 40 mg/kg, or dogs and sheep up to 20 mg/kg. There was no significant effect on rat fertility when up to 40 mg/kg was given to males for 60 days before mating and to females at 20 mg/kg for 14 days before exposure to males.

Miscellaneous Studies

Mebendazole was tested for possible cardiovascular effects in dogs. It is concluded that single oral doses up to 160 mg/kg are devoid of electrocardiographic effects in dogs.

INDICATIONS

VERMOX tablets and suspension are indicated for the treatment of single or mixed helminthic infestations.

Clinical studies have shown mebendazole to be effective in the treatment of *Enterobius vermicularis* (threadworm), *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and of *Ancylostoma duodenale* and *Necator americanus* (hookworm).

Efficacy varies as a function of such factors as pre-existing diarrhoea, gastrointestinal transit time, degree of infection, and helminth strain.

CONTRAINDICATIONS

Mebendazole is contraindicated in persons who have shown hypersensitivity to the drug or other benzimidazole derivatives.

Paediatric Use

Mebendazole has not been studied in children under two years. Therefore, Vermox cannot be recommended in this age group pending the results of studies.

Convulsions in children, including infants below one year of age have been reported very rarely during post-marketing experience with Vermox.

PRECAUTIONS

Precautions Risk/ benefit analysis should be considered for the following.

Crohn's ileitis or ulcerative colitis:

May increase absorption and toxicity of mebendazole, especially in high dose therapy.

Use in Patients with Hepatic Function Impairment

Caution is advised for use in patients with hepatic impairment since this condition may prolong half-life and drug accumulation.

Use in Pregnancy

Category (B3)

The safety of use in pregnant women has not been established, although animal trials conducted in a wide range of species revealed an embryotoxic and teratogenic effect in the rat. Therefore, Vermox should not be administered during pregnancy, particularly in the first trimester, unless the potential benefit to the patient outweighs the possible risk to the foetus.

Use in Lactation

It is not known whether mebendazole passes into maternal milk and, thus, whether it is harmful to the newborn infant. The use of Vermox in breastfeeding mothers requires that anticipated benefits be weighed against possible risks. If use in the lactating mother is deemed essential by the treating clinician, alternative arrangements to feed the infant should be made.

INTERACTIONS WITH OTHER MEDICINES

Concurrent administration of cimetidine may inhibit the metabolism of mebendazole in the liver, producing increased plasma concentrations of the drug, especially during prolonged treatment. In the latter case, determination of plasma concentrations is recommended in order to allow dose adjustments.

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.

ADVERSE EFFECTS

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 (ADRS) occurred in $\geq 1\%$ 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 Disorders

Rash

Post-marketing Experience

Adverse drug reactions first identified during post-marketing experience with Vermox® (mebendazole) are included in Table 2. The frequencies are provided according to the following convention:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $\geq 1/1000$ and $< 1/100$

Rare $\geq 1/10,000$ and $< 1/1,000$

Very rare $< 1/10,000$ including isolated reports.

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

Table 2: Adverse Drug Reactions Identified During Post-marketing 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

Neutropenia

Immune System Disorders

Very rare

Hypersensitivity including anaphylactic reaction and anaphylactoid reaction

Nervous System Disorders

Very rare

Convulsions

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, urticarial, alopecia

DOSAGE AND ADMINISTRATION

Vermox is administered orally.

Vermox orange flavoured tablets may be swallowed whole, chewed or crushed into a teaspoon of food.

Vermox Choc Chews chewable tablets may be chewed or crushed into a teaspoon of food.

Shake the Vermox suspension well before use.

For control of *enterobiasis*

Adults and children 2-12 years:

1 Vermox tablet (100 mg) or 5 mL of suspension (100 mg) is given. Since reinfections by *Enterobius* are known to be very frequent, it is recommended that treatment be repeated after 2 to 4 weeks, especially in eradication programmes.

For control of *trichuriasis, ascariasis, ancylostomiasis* and mixed infections

Adults and children 2-12 years:

1 Vermox tablet (100 mg) or 5 mL of suspension (100mg) is administered in the morning and evening for three consecutive days.

If the patient is not cured three weeks after treatment, a second course of treatment is advised.

No special procedures such as fasting or the use of laxative are required.

OVERDOSAGE

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

Respiratory arrest and tachyarrhythmia associated with continuous convulsions have been reported in an 8-week old infant following accidental poisoning with mebendazole. Treatment by exchange transfusion and anticonvulsants was successful.

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

There is no specific antidote. Supportive and symptomatic therapy should be initiated in cases of overdosage. Activated charcoal may be given if considered appropriate

Contact the Poisons Information Centre in Australia on 131 126 or in New Zealand on 0800 POISON or 0800 764 766 for the latest advice on the treatment of oral poisoning.

PRESENTATION

Vermox orange flavoured tablets, 100 mg (slightly orange, circular, flat, bevel-edged, half-scored tablet with orange flavour), PVC/Aluminium blister pack: 2's, 4's, 6's, 12's*.

Vermox Choc Chews chewable tablets, 100 mg (lightly speckled chocolate brown, circular, flat, bevel-edged, half-scored tablet with chocolate flavour), PVC/Aluminium blister pack: 2's, 4's, 6's and 12's*.

Vermox Suspension, 100 mg/5 mL (2% w/v), (banana flavoured), glass bottle: 15 mL (with 5 mL spoon).

Storage Conditions

Store below 30 degrees Celsius

Keep out of reach of children.

POISON SCHEDULE

Pharmacy Medicine.

NAME AND ADDRESS OF THE SPONSOR

Valeant Pharmaceuticals New Zealand Ltd
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74 Westney Road
Airport Oaks
Auckland

DATE OF PREPARATION

28 July 2014

* Not marketed