

PRODUCT MONOGRAPH

PrVERMOX®

Mebendazole Tablets, House Std.

100 mg

Anthelmintic

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Date of Preparation:
July 8, 1975

Date of Revision:
March 20, 2019

Submission Control No.: 215898

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CLINICAL PHARMACOLOGY

VERMOX[®] mebendazole induces in vitro and in vivo inhibition of the glucose uptake by parasitic helminths; this is associated with glycogen depletion and a decrease in the generation of ATP, leading to inhibition of larval development.

There is no evidence that VERMOX[®] is effective in the treatment of cysticercosis.

Absorption: Following oral administration, < 10% of the dose reaches the systemic circulation, due to incomplete absorption and 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 three-fold higher exposure to steady-state compared to single dosing.

INDICATIONS AND CLINICAL USE

VERMOX[®] mebendazole has a broad spectrum of anthelmintic activity and is effective in the treatment of single or mixed helminthic infestations. Clinical studies have shown it to be effective in the treatment of *Enterobius vermicularis* (pinworm); *Ascaris lumbricoides* (roundworm); *Trichuris trichiura* (whipworm); *Ancylostoma duodenale* and *Necator americanus* (hookworm). It has also been used to treat infestations due to *Strongyloides stercoralis* (threadworm) and *Taenia solium* (large tapeworms).

CONTRAINDICATIONS

VERMOX[®] mebendazole is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Composition** section of the Product Monograph.

WARNINGS

There have been reports of reversible liver function disturbances, hepatitis, and neutropenia described in patients who were treated with mebendazole at standard dosages for indicated conditions. 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 (see **ADVERSE REACTIONS – Post-marketing Experience**).

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 VERMOX[®] mebendazole and metronidazole. Further data suggesting such a drug-drug interaction are not available. Therefore, concomitant use of VERMOX[®] and metronidazole should be avoided.

Use in Pregnancy: Animal trials conducted in a wide range of species revealed an embryotoxic and teratogenic effect in the rat. Also, the safety of use in pregnant women has not been established. 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 fetus.

PRECAUTIONS

Patients should be carefully checked to detect any alteration in blood studies or hepatic or renal function tests following treatment with VERMOX[®] mebendazole. Special attention should be given to patients with intestinal pathology (e.g., Crohn's ileitis, ulcerative colitis).

Use in Nursing Mothers: 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[®] tablets are administered to nursing women.

Use in Children Under 2 Years: Since VERMOX[®] has not been extensively studied in infants under 2 years of age, its use in such individuals should only be implemented in cases where the potential therapeutic effects outweigh the possible hazard to the patient.

Convulsions in children, including infants less than 1 year old, have been reported during post-marketing experience with VERMOX[®]. VERMOX[®] should only be given to very young children if their worm infestation interferes significantly with their nutritional status and physical development.

Drug Interactions

Concomitant treatment with cimetidine may inhibit the metabolism of VERMOX[®] in the liver, resulting in increased plasma concentrations of the drug, especially during prolonged treatment.

Concomitant use of VERMOX[®] and metronidazole should be avoided (see **WARNINGS**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

At the recommended dose, VERMOX[®] mebendazole is generally well tolerated. However, patients with high parasitic burdens have manifested diarrhea, vomiting, and/or abdominal pain when treated with VERMOX[®]. Other adverse reactions reported were drowsiness, itching, headache, flatulence, dizziness, increased SGOT, SGPT, alkaline phosphatase, and BUN. Eosinophilia and decreased hemoglobin and/or white cell count, hematuria, and cylindruria have been reported.

Post-marketing Experience

Adverse drug reactions from spontaneous reports during post-marketing experience with VERMOX[®] are included below.

System Organ Class

Blood and the lymphatic system disorders

neutropenia
agranulocytosis*

Immune system disorders

hypersensitivity including anaphylactic and anaphylactoid reactions

Nervous system disorders

convulsions, dizziness

Gastrointestinal disorders

abdominal discomfort, abdominal pain, nausea, vomiting

Hepatobiliary disorders

hepatitis, abnormal liver function tests

Skin and subcutaneous tissue disorders

toxic epidermal necrolysis, Stevens-Johnson syndrome, exanthema, angioedema, urticaria, rash, alopecia

Renal and Urinary Disorders

glomerulonephritis*

* Observed in higher and prolonged doses

SYMPTOMS AND TREATMENT OF OVERDOSE

In patients treated at dosages substantially higher than recommended and/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 VERMOX[®] mebendazole at standard dosages.

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 administered to aid in the removal of unabsorbed drug if considered appropriate. General supportive measures are recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Adults and Children 2 Years and Older

Enterobiasis: One tablet (100 mg) given as a single dose. Since reinfections by *Enterobius* are known to be very frequent, it is recommended that treatment be repeated after two and four weeks, especially in eradication programs.

Trichuriasis, ascariasis, ankylostomiasis, strongyloidiasis, taeniasis and mixed infestations:

One tablet (100 mg) two times a day in the morning and evening for three consecutive days.

No special procedures such as fasting or purgation are required.

Children Under 2 Years

VERMOX[®] 100 mg tablets should not be used in children below the age of 1 year. For use in children between 1 and 2 years of age, see **PRECAUTIONS, Use in Children Under 2 Years**.

Administration

VERMOX[®] tablets may be chewed or swallowed whole. For children 1 to 6 years old who have difficulty in swallowing tablets, crush the tablet before administering.

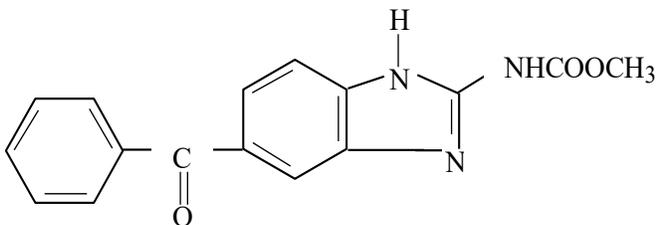
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: mebendazole

Chemical Name: Methyl 5-benzoyl-2-benzimidazolecarbamate

Structural Formula:



Molecular Formula: $C_{16}H_{13}N_3O_3$

Molecular Weight: 295.30

Description: Mebendazole is an off-white to slightly yellow powder which is insoluble in water and common organic solvents but is freely soluble in formic acid. The melting point of mebendazole is 288.5°C.

Composition

VERMOX[®] 100 mg tablets contain 100 mg mebendazole as the active medicinal ingredient. Non-medicinal ingredients include microcrystalline cellulose, sodium starch glycolate, talc, corn starch, saccharin sodium, magnesium stearate, cotton seed oil hydrogenated, orange flavour, colloidal anhydrous silica, sodium lauryl sulphate and FD&C Yellow #6 (orange yellow S).

Stability and Storage Recommendations

Store between 15 and 30°C. Protect from light.

Keep out of the sight and reach of children.

AVAILABILITY OF DOSAGE FORMS

VERMOX[®] is available as a faintly orange, flat-faced, round tablet inscribed with “JANSSEN” on one side and “Me/100” (scored) on the other and contains 100 mg of mebendazole.

VERMOX[®] tablets are supplied in cartons with 1 blister card containing 6 tablets.

PARASITOLOGY

In vitro and in vivo studies indicate that VERMOX® mebendazole inhibits larval development for the eggs of *Trichuris trichiura* and hookworms. In vivo efficacy has been demonstrated against *Trichuris*, *Ascaris*, hookworm, *Enterobius*, *Strongyloides*, *Taenia*, and *Lymenolipos*.

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.

PHARMACOLOGY

VERMOX® mebendazole at 40 mg/kg in mice and 160 mg/kg in rats is devoid of parasympatholytic, parasympathomimetic, CNS-stimulating, CNS-depressing, hypnotic, morphine-like, acetylsalicylic acid-like, anticonvulsive, and toxic effects.

Mebendazole has also been tested in rats for its anti-inflammatory effects in the *Mycobacterium butyricum* arthritis test and was found devoid of effect.

The metabolism of mebendazole appears to be similar in humans and animals. In rats and dogs, the drug is mainly excreted with the feces (about 90%), in its unchanged form. Only 1% (dogs) and 5 to 10% (rats) of the dose was eliminated with the urine up to four days after drug administration. The urine samples of these treated animals contained mainly metabolic breakdown products. Tissue levels were low and comprised mainly metabolites.

In the pig, 30 to 50% of the dose was eliminated with the urine within three days of drug administration. Metabolites were found mainly in the urine. Excretion in the feces was also considerable, consisting of 45 to 65% of the administered dose.

In a study where three male subjects were administered 0.1 mg/kg of ¹⁴C-VERMOX® mebendazole, plasma levels were low, peaking two to four hours after treatment. Approximately 10% of the administered dose was excreted in the urine in less than eight hours. The major metabolite detectable in the urine was 2-amino-5(6)-benzimidazolyl phenyl ketone.

Animal and human studies indicate that mebendazole is slightly to moderately absorbed. It is excreted mainly in the feces and partially in the urine. The metabolites identified in the urine are common to all species tested, indicating a similar metabolic pathway.

TOXICOLOGY

Acute

Acute oral toxicity of VERMOX[®] mebendazole has been investigated in 12 animal species. The single-dose toxicity evaluations in multiple species revealed that mebendazole was well tolerated and has a large margin of safety. The only side effects observed were transient softening of the feces and, occasionally, diarrhea. In LD₅₀ studies, single oral doses up to 1280 mg/kg in mice, rats, guinea pigs, and pheasants; 1000 mg/kg in chickens and cats; 640 mg/kg in rabbits and dogs; 400 mg/kg in horses; 320 mg/kg in sheep; 80 mg/kg in cattle; and 20 mg/kg in pigs produced no deaths.

Chronic

The chronic oral toxicity of mebendazole has been investigated in horses, sheep, chickens, guinea fowl, rats, dogs, pigs, and pheasants. In these studies, the oral administration of mebendazole to dogs at doses up to 40 mg/kg once daily for 13 weeks; to horses at doses up to 6 g/250 lb once daily for 15 days; to sheep at doses of 60 mg/kg once daily for 5 days; to pheasants at doses of 125 ppm for 63 days; and to guinea fowl at doses up to 120 ppm for 10 days did not cause any significant side effects as observed by clinical examination, clinical pathology, gross pathology, or histopathology. However, in dogs the liver weight was increased for all treated animals and some showed hyaline degeneration.

Doses ranging from 23 mg/kg once daily for 74 days to 51 mg/kg once daily for 66 days to horses failed to produce any overt clinical effects or significant changes in the hematological and biochemical parameters examined. In the pig, doses of 63 ppm once daily in food for 92 days produced diarrhea but no other drug-related changes. In chickens, 125 ppm for one month was considered the upper level of safe medication: higher doses markedly reduced both rate of lay and hatchability. In the rat, histological studies revealed a chronic stimulation of the hepatocytes at 160 mg/kg given once daily for 13 weeks. At 160 mg/kg, the testes of the rat had deficient tubules and impaired spermatogenesis. The upper limits of safe treatment of rats appeared to be 40 mg/kg for at least nine months and 160 mg/kg for six weeks.

In controlled safety studies, humans have received from 100 to 1200 mg of mebendazole daily for up to 14 days with no reported side effects.

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.

Teratogenicity and Reproduction

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

These studies show that mebendazole is embryotoxic and teratogenic in rats at 40 mg/kg given daily from Days 6 to 15 of pregnancy or at 10 mg/kg given on the tenth day of pregnancy. Effects observed with other species were inconclusive regarding teratogenicity and embryotoxicity.

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PART III: CONSUMER INFORMATION

PrVERMOX®

Mebendazole Tablets, House Std.

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VERMOX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

VERMOX® is a drug used to treat infestations of the intestine with one or several of the following parasitic worms:

- pinworm (*Enterobius vermicularis*);
- roundworm (*Ascaris lumbricoides*);
- whipworm (*Trichuris trichiura*);
- hookworm (*Ancylostoma duodenale*; *Necator americanus*);
- threadworm (*Strongyloides stercoralis*);
- tapeworm (*Taenia solium*).

What it does:

VERMOX® is believed to disrupt the intestinal function of the parasitic worms, which helps end the worm infestation.

When it should not be used:

You should not take VERMOX® if you are allergic to mebendazole, or to any of the non-medicinal ingredients in the product (see **What the non-medicinal ingredients are**).

What the medicinal ingredient is:

Mebendazole

What the non-medicinal ingredients are:

Colloidal anhydrous silica, cotton seed oil hydrogenated, corn starch, FD&C Yellow #6 (orange yellow S), magnesium stearate, microcrystalline cellulose, orange flavour, saccharin sodium, sodium lauryl sulphate, sodium starch glycolate and talc.

What dosage forms it comes in:

100 mg tablets

WARNINGS AND PRECAUTIONS

BEFORE you use VERMOX® talk to your doctor or pharmacist if:

- you are pregnant, or think you may be;
- you are breast-feeding or planning to breastfeed;
- you are taking cimetidine (medicine used for acid in the stomach);
- you are taking metronidazole (medicine used to treat bacterial and protozoan infections);

- you are taking any other medications, including prescription, over-the-counter, herbal or natural health products (See **INTERACTIONS WITH THIS MEDICATION**).

INTERACTIONS WITH THIS MEDICATION

Inform your doctor if you are taking cimetidine (medicine used for acid in the stomach). If so, your VERMOX® dosage might have to be adapted. The use of VERMOX® with metronidazole (medicine used to treat bacterial and protozoan infections) should be avoided.

PROPER USE OF THIS MEDICATION

Take the tablets with some liquid. You do not have to take VERMOX® with food. You do not have to follow a special diet or take products which stimulate the stools. The amount of VERMOX® you have to take will depend on the type of worm you are infected with. If in doubt, consult your doctor or pharmacist.

Tablets may be chewed or swallowed whole. For children 1 to 6 years old who have difficulty in swallowing tablets, crush the tablet before giving. Always supervise a child while they are taking this medicine.

Usual dose: Adults and Children over 2 years of age

Infestation with pinworm: Take 1 tablet as a single dose.

After 2 and 4 weeks, take 1 tablet again. This is necessary to completely get rid of the infestation. The first treatment killed off the worms, but not their eggs. Those eggs might cause another infestation.

Infestation with whipworm, roundworm, hookworm,

threadworm, tapeworm or with several worm species: Take 1 tablet in the morning and in the evening, for 3 days in a row.

If infestation continues after 3 weeks, contact your doctor.

Overdose:

If amounts higher than recommended are taken, blood, kidney, and liver disorders, some of which may be serious, may occur. Hair loss, which in some cases may be permanent, may also occur.

If you have taken too much VERMOX®, you might suffer from stomach cramps, nausea, vomiting and diarrhea. If this is the case, you should consult your doctor.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following undesired effects have been reported and may occur during treatment with VERMOX®:

- dizziness;
- stomach aches and pains, intestinal gas, diarrhea, nausea and vomiting;
- skin rash;
- hives;
- hair loss, which in some cases may be permanent;
- blood and liver disorders;
- Inflammatory kidney disease and severely decreased number of white blood cells can occur with prolonged use of VERMOX® at doses substantially higher than recommended (much more than normally prescribed).

If any of the following symptoms occur, **contact your doctor immediately**:

- A severe skin disorder consisting of skin rashes, blisters on the skin and sores in the mouth, or on the eyes, anus or genitals region, along with fever;
- A severe hypersensitivity (allergic) reaction occurs after administration with symptoms such as swollen mouth, throat, extremities, difficulty breathing, shortness of breath, skin rash, itching, hives, flushing or fainting.
- Convulsions (seizures) have been reported, including in infants.

This is not a complete list of side effects. For any unexpected effects while taking VERMOX®, contact your doctor or pharmacist.

HOW TO STORE IT

VERMOX® tablets should be stored at room temperature (15–30°C) and protected from light.

Keep out of the sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada website at: www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada
NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.janssen.com/canada> or by contacting the sponsor, Janssen Inc. at: 1-800-567-3331 or 1-800-387-8781.

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Last revised: March 20, 2019