PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVERMOX®

Mebendazole Tablets

Tablets, 100 mg, oral

House Std.

Anthelmintic

Janssen Inc.
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Toronto, Ontario
M3C 1L9
www.janssen.com/canada

Date of Initial Authorization:
July 8, 1975

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Aug 16, 2024

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General	08/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Vermox (mebendazole) is indicated for 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).

1.1 Pediatrics

Pediatrics (1 to <18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Vermox in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 7.1.3 Pediatrics).

2 CONTRAINDICATIONS

Vermox 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Adults and Children 2 Years and Older
Enterobiasis: 1 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 2 and 4 weeks, especially in eradication programs.

Trichuriasis, ascariasis, ankylostomiasis, strongyloidiasis, taeniasis and mixed infestations: 1 tablet (100 mg) two times a day in the morning and evening for 3 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 7.1.3 Pediatrics, Use in Children Under 2 Years.

4.4 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.

5 OVERDOSAGE

Agranulocytosis and glomerulonephritis are adverse reactions observed at high dosage and for prolonged periods of time. (see 8.5 Post-Market Adverse Reactions).

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

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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 100 mg	colloidal anhydrous silica, cottonseed oil hydrogenated, magnesium stearate, maize starch, microcrystalline cellulose, orange flavour, orange yellow S (E110), saccharin sodium, sodium lauryl sulphate, sodium starch glycolate, and talc

Vermox 100 mg tablets contain 100 mg mebendazole as the active medicinal ingredient.

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.

7 WARNINGS AND PRECAUTIONS

General
There have been reports of reversible liver function disturbances, hepatitis, and neutropenia described in patients who were treated with mebendazole at recommended dosages for indicated conditions. Agranulocytosis and glomerulonephritis have also been reported in patients treated with dosages substantially above those recommended and with treatment for prolonged periods of time (see 8.5 Post-Market Adverse Reactions).

Monitoring and Laboratory Tests
Patients should be carefully checked to detect any alteration in blood studies or hepatic or renal function tests following treatment with Vermox. Special attention should be given to patients with intestinal pathology (e.g., Crohn's ileitis, ulcerative colitis).

Skin
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 and metronidazole. Further data suggesting such a drug-drug interaction are not available. Therefore, concomitant use of Vermox and metronidazole should be avoided.

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 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 tablets are administered to nursing women.

7.1.3 Pediatrics

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 in infants, 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.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

At the recommended dose, Vermox 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.

8.5 Post-Market Adverse Reactions

Adverse drug reactions from spontaneous reports during post-marketing experience with Vermox are shown in Table 2 below.

Table 2 - Adverse Reactions Identified During Post-marketing Experience with Vermox

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	Agranulocytosis*, Neutropenia
Immune System Disorders	Hypersensitivity including anaphylactic reaction and anaphylactoid reaction
Nervous System Disorders	Convulsions, Dizziness

Gastrointestinal Disorders	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, Alopecia
Renal and Urinary Disorders	Glomerulonephritis*

* Observed in patients treated with higher and prolonged doses

9 DRUG INTERACTIONS

9.4 Drug-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 7 WARNINGS AND PRECAUTIONS, Skin).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

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.

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.

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.

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.

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.

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 ^{14}C-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.

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.

11 STORAGE, STABILITY AND DISPOSAL

Stability and Storage Recommendations
Store between 15 and 30°C. Protect from light.
Keep out of the sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

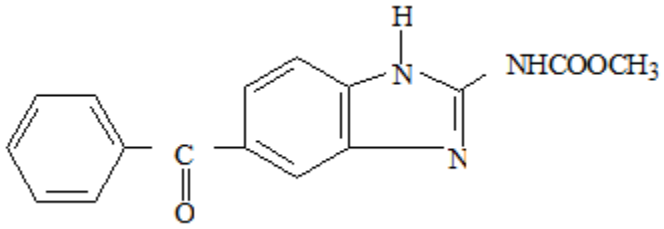
13 PHARMACEUTICAL INFORMATION

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The clinical trial data on which the indication was originally authorized is not available.

15 MICROBIOLOGY

In vitro and in vivo studies indicate that 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.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute

Acute oral toxicity of 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 LD_{50} 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.

Reproductive and Developmental Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVERMOX®
Mebendazole Tablets, House Std.

Read this carefully before you start taking **Vermox** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Vermox**.

What is Vermox used for?

Vermox is used to treat infestations of one or several of the following parasitic worms:
- pinworm;
- roundworm;
- whipworm;
- hookworm;
- threadworm;
- large tapeworm.

How does Vermox work?

Vermox stops parasitic worms from using sugar to live. This kills the worms.

What are the ingredients in Vermox?

Medicinal ingredient is: Mebendazole

Non-medicinal ingredients are: Colloidal anhydrous silica, cottonseed oil hydrogenated, magnesium stearate, maize starch, microcrystalline cellulose, orange flavour, orange yellow S (E110), saccharin sodium, sodium lauryl sulphate, sodium starch glycolate and talc.

Vermox comes in the following dosage forms:

Tablets, 100 mg

Do not use Vermox if:

- you are allergic to mebendazole
- you are allergic to any of the non-medicinal ingredients in Vermox

Vermox should not be given to children under the age of 1 years.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Vermox. Talk about any health conditions or problems you may have, including if you:

- have problems with your gut such as the conditions Crohn's disease or ulcerative colitis
- are pregnant, think you may be pregnant or are planning to become pregnant
- are breast-feeding or are planning to breastfeed

- are taking cimetidine, a medicine used to treat heartburn and other conditions that cause too much stomach acid
- are taking metronidazole, an antibiotic medicine used to treat various infections

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Vermox:

- Cimetidine, a medicine used to treat heartburn and other conditions that cause too much stomach acid. Your healthcare professional may need to change how much Vermox you take
- Metronidazole, an antibiotic medicine used to treat various infections. Vermox and metronidazole should not be taken together.

How to take Vermox:

- Always take Vermox exactly as your healthcare professional tells you to.
- Swallow tablets whole with water. Tablets may also be chewed.
- Tablets can be crushed before giving to children 1 to 6 years old who have trouble swallowing tablets.
- You can take Vermox with or without food.
- The amount of Vermox you take will depend on the type of worm that you are infested with.
- Check with your healthcare professional if you are not sure how to take Vermox.

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.

Infestation with roundworm, whipworm, hookworm, threadworm, large tapeworms and with several kinds of worms: Take 1 tablet two times a day (in the morning and in the evening) for 3 days in a row.

Overdose:

If you have taken too much Vermox you might get stomach cramps, nausea, vomiting and diarrhea.

If you think you, or a person you are caring for, have taken too much Vermox, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Vermox?

These are not all the possible side effects you may have when taking Vermox. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dizziness
- stomach aches and pains, gas, abdominal pain, diarrhea, nausea and vomiting
- skin rash
- hives
- hair loss, which in some cases may be permanent
- drowsiness
- itching
- headache

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE			
Liver Problems: upper abdominal pain, nausea or loss of appetite, extreme tiredness, fever, dark urine, skin and the white part of eyes to turn yellow		✓	
Neutropenia (decrease in white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms, sore throat, swollen lymph nodes, ulcers in mouth or around anus		✓	
Agranulocytosis (severe decrease in white blood cells): fever, tiredness, faster breathing, dizziness, increased heart rate, sore throat		✓	
Glomerulonephritis (kidney disease): swelling, blood in the urine, urinating less than usual, urinating at night, lack of appetite, nausea, vomiting, tiredness		✓	
Allergic reaction: swollen mouth, throat, extremities, difficulty breathing, shortness of breath, skin rash, itching, hives, flushing or fainting		✓	
Convulsions (seizures): uncontrollable jerking movements of the arms and legs, loss of consciousness, uncontrollable shaking		✓	
Toxic epidermal necrolysis (severe skin reaction): widespread skin pain, spreading rash, blisters and large areas of peeling skin		✓	
Stevens-Johnson syndrome (severe skin rash): redness, blistering and/or		✓	

peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			
Angioedema (swelling of tissues under the skin): swollen face, eyes, lips, tongue, throat or airway that may make it harder to breathe and talk, swollen hands or feet, dizziness, nausea, vomiting		✓	
UNKNOWN FREQUENCY			
Abnormal liver test results: extreme tiredness, dark urine, abdominal pain		✓	
Abnormal kidney function: extreme tiredness, swelling, changes in urination, skin and the white part of eyes to turn yellow		✓	
Hematuria (blood in urine): red or cola-colored urine, passing blood clots in urine, frequent or painful urination		✓	
Cylindruria (casts in urine): urine appears milky white, pain while urinating, pain in the loin region, weight loss		✓	

This is not a complete list of side effects. For any unexpected effects while taking Vermox, contact your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15 – 30°C). Protect from light.

Keep out of the sight and reach of children.

If you want more information about Vermox:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.janssen.com/canada/, or by calling 1-800-567-3331 or 1-800-387-8781.

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