HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VERMOX™ CHEWABLE safely and effectively. See full prescribing information for VERMOX™ CHEWABLE.

VERMOX™ CHEWABLE (mebendazole chewable tablets), for oral use
Initial U.S. Approval: 1974

----------RECENT MAJOR CHANGES ----------

Dosing and Administration (2) 9/2021

----------INDICATIONS AND USAGE----------

VERMOX™ CHEWABLE is an anthelmintic indicated for the treatment of patients one year of age and older with gastrointestinal infections caused by:

- *Ascaris lumbricoides* (roundworm) and
- *Trichuris trichiura* (whipworm) (1).

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage in patients one year of age and older is one single tablet of VERMOX™ CHEWABLE 500 mg taken as a single dose, chewed completely before swallowing (2).
- See Full Prescribing Information for administration instructions for patients who have difficulty chewing the tablets (2)

----------DOSAGE FORMS AND STRENGTHS----------

Chewable Tablet: 500 mg (3)

----------CONTRAINDICATIONS----------

- Patients with a known hypersensitivity to the drug or its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Convulsions: Convulsions in infants below the age of 1 year have been reported (5.1)
- Hematologic Effects: Neutropenia and agranulocytosis have been reported in patients receiving mebendazole at higher doses and for prolonged duration. Monitor blood counts in these patients (5.2)
- Metronidazole and Serious Skin Reactions: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole. Avoid concomitant use of mebendazole and metronidazole (5.3)

----------ADVERSE REACTIONS----------

Adverse reactions reported in clinical trials were anorexia, abdominal pain, diarrhea, flatulence, nausea, vomiting and rash. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VERMOX™ CHEWABLE is indicated for the treatment of patients one year of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm).

2 DOSAGE AND ADMINISTRATION

The recommended dosage in patients one year of age and older is one VERMOX™ CHEWABLE 500 mg tablet taken as a single dose.

Chew VERMOX™ CHEWABLE 500 mg tablet completely before swallowing. Do not swallow the tablet whole.

For patients who have difficulty chewing the tablet, approximately 2 mL to 3 mL of drinking water can be added to a suitably sized spoon and the VERMOX™ CHEWABLE 500 mg tablet placed into the water. Within 2 minutes, the tablet absorbs the water and turns into a soft mass with semi-solid consistency, which can then be swallowed.

VERMOX™ CHEWABLE 500 mg tablet can be taken without regard to food intake *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Chewable Tablet: 500 mg round, flat radius-edged white to yellowish chewable tablet that is debossed with “M/500” on one side and “J” on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Convulsions

Convulsions have been reported in infants below the age of 1 year during post-marketing experience with mebendazole *[see Adverse Reactions (6.2)]*.

5.2 Hematologic Effects

Agranulocytosis and neutropenia have been reported with mebendazole use at higher doses and for more prolonged durations than is recommended for the treatment of soil-transmitted helminth infections. Monitor blood counts if VERMOX™ CHEWABLE is used at higher doses or for prolonged duration.

5.3 Metronidazole Drug Interaction and Serious Skin Reactions

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported with the concomitant use of mebendazole and metronidazole. Avoid concomitant use of mebendazole and metronidazole.

6 ADVERSE REACTIONS

6.1 Clinical Studies

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 practice.

The safety of mebendazole was evaluated in 6276 adult and pediatric subjects one year of age and older who participated in 39 clinical trials for treatment of single or mixed parasitic infections of the gastrointestinal tract. In these trials, the formulations, dosages and duration of mebendazole treatment varied. Adverse reactions reported in mebendazole-treated subjects from the 39 clinical trials are shown in Table 1 below.

Table 1: Adverse Reactions Reported in Mebendazole-Treated Subjects from 39 Clinical Trials*

Adverse Reaction(s)
Gastrointestinal Disorders
Anorexia
Abdominal Pain
Diarrhea
Flatulence
Nausea
Vomiting
Skin and Subcutaneous Tissue Disorders
Rash

* Includes mebendazole formulations, dosages and treatment duration other than VERMOX™ CHEWABLE 500 mg tablet

Clinical Studies with Mebendazole Chewable 500 mg Tablet

The safety profile of mebendazole chewable 500 mg tablets administered as a single dose was evaluated in 677 pediatric subjects aged 1 to 16 years and in 34 adults. The safety profile was consistent with the known safety profile of mebendazole.

6.2 Postmarketing Experience

The following adverse reactions have been identified in adult and pediatric patients postmarketing with mebendazole formulations and dosages other than the VERMOX™ CHEWABLE 500 mg tablet. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 2: Adverse Reactions Identified During Postmarketing Experience with Mebendazole*

	Adverse Reaction(s)
Blood and Lymphatic System Disorders	Agranulocytosis, Neutropenia
Immune System Disorders	Hypersensitivity including anaphylactic reactions
Nervous System Disorders	Convulsions, Dizziness
Hepatobiliary Disorders	Hepatitis, Abnormal liver tests
Renal and Urinary Disorders	Glomerulonephritis
Skin and Subcutaneous Tissue Disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Exanthema, Angioedema, Urticaria, Alopecia

* Includes mebendazole formulations, dosages and treatment durations other than VERMOX™ CHEWABLE 500 mg tablet

7 DRUG INTERACTIONS

Concomitant use of mebendazole and metronidazole should be avoided *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available published literature on mebendazole use in pregnant women has not reported a clear association between mebendazole and a potential risk of major birth defects or miscarriages *[see Data]*. There are risks to the mother and fetus associated with untreated helminthic infection during pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, soft tissue malformations, decreased pup weight, embryolethality) were observed when mebendazole was administered to pregnant rats during the period of organogenesis at single oral doses as low as 10 mg/kg (approximately 0.2-fold the maximum recommended human dose (MRHD)). Maternal toxicity was present at the highest of these doses *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risks

Untreated soil-transmitted helminth infections in pregnancy are associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

Data

Human Data

Several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association between mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific pattern or frequency of major birth defects with mebendazole use. However, these studies cannot definitely establish the absence of any mebendazole-associated risk because of methodological limitations, including recall bias, confounding factors and, in some cases, small sample size or exclusion of first trimester mebendazole exposures.

Animal Data

Embryo-fetal developmental toxicity studies in rats revealed no adverse effects on dams or their progeny at doses up to 2.5 mg/kg/day on gestation days 6-15 (the period of organogenesis). Dosing at ≥10 mg/kg/day resulted in a lowered body weight gain and a decreased pregnancy rate. Maternal toxicity, including body weight loss in one animal and maternal death in 11 of 20 animals, was seen at 40 mg/kg/day. At 10 mg/kg/day, increased embryo-fetal resorption (100% were resorbed at 40 mg/kg/day), decreased pup weight and increased incidence of malformations (primarily skeletal) were observed. Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses during organogenesis as low as 10 mg/kg (approximately 0.2-fold the MRHD, based on mg/m^2).

In embryo-fetal developmental toxicity studies in mice dosed on gestation days 6-15, doses of 10 mg/kg/day and higher resulted in decreased body weight gain at 10 and 40 mg/kg/day and a higher mortality rate at 40 mg/kg/day. At doses of 10 mg/kg/day (approximately 0.1-fold the MRHD, based on mg/m^2) and higher, embryo-fetal resorption increased (100% at 40 mg/kg) and fetal malformations, including skeletal, cranial, and soft tissue anomalies, were present. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at doses up to 40 mg/kg/day (0.6 to 1.6-fold the MRHD, based on mg/m^2).

In a peri- and post-natal toxicity study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (0.8-fold the MRHD, based on mg/m^2), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found on gross and radiographic examination of pups at birth.

8.2 Lactation

Risk Summary

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant, and the limited reports on the effects on milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of VERMOX™ CHEWABLE to a breastfed infant; therefore, developmental and

health benefits of breastfeeding should be considered along with the mother's clinical need for VERMOX™ CHEWABLE and any potential adverse effects on the breastfed infant from VERMOX™ CHEWABLE or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of VERMOX™ CHEWABLE 500 mg tablets have been established in pediatric patients 1 to 16 years of age. Use of VERMOX™ CHEWABLE 500 mg tablets in children is supported by evidence from adequate and well-controlled studies of VERMOX™ CHEWABLE 500 mg tablets *[see Clinical Studies (14)]*.

The safety and effectiveness of mebendazole, including VERMOX™ CHEWABLE have not been established in pediatric patients less than one year of age. Convulsions have been reported with mebendazole use in this age group *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.

8.5 Geriatric Use

Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Adult Use

The safety and effectiveness of VERMOX™ CHEWABLE 500 mg tablets have been established in adults for the treatment of gastrointestinal infections by *T. trichiura* and *A. lumbricoides*. Use of VERMOX™ CHEWABLE 500 mg tablets in adults for these indications is supported by evidence from an adequate and well-controlled trial in pediatric patients ages 1 to 16 years *[see Clinical Studies (14.1)]*, safety data in adults *[see Adverse Reactions (6.1)]*, pharmacokinetic data in adults *[see Clinical Pharmacology (12.3)]*, and the evidence from published literature.

10 OVERDOSAGE

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported: alopecia, reversible transaminase elevations, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis.

Symptoms and signs

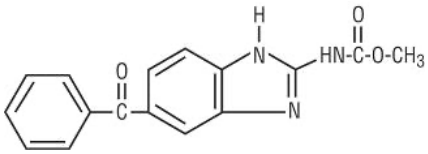
In the event of accidental overdose, gastrointestinal signs/symptoms may occur.

Treatment

There is no specific antidote.

11 DESCRIPTION

VERMOX™ CHEWABLE (mebendazole chewable tablets) is an orally administered anthelmintic. Chemically, it is methyl 5-benzoylbenzimidazole-2-carbamate. Its molecular formula is $C_{16}H_{13}N_3O_3$. Its molecular weight is 295.30. It has the following chemical structure:



Mebendazole exhibits polymorphism. The polymorph used in VERMOX™ CHEWABLE is polymorph form C. Mebendazole is a white to almost white powder. It is practically insoluble in water, in ethanol (96%) and in methylene chloride.

Each round, flat radius-edged white to yellowish chewable tablet contains 500 mg of mebendazole and is debossed with "M/500" on one side and "J" on the other side.

Inactive ingredients consist of: crospovidone, magnesium stearate, microcrystalline cellulose, povidone, purified water, strawberry flavor and sucralose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mebendazole, a benzimidazole, is an anthelmintic *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Absorption

Following oral administration of VERMOX™ CHEWABLE 500 mg tablet, the majority of the dose remains in the gastrointestinal tract where it exerts an anthelmintic effect locally. Dosing the VERMOX™ CHEWABLE 500 mg tablet with a high fat meal increases the bioavailability of mebendazole. In the clinical studies conducted in pediatric patients with soil transmitted helminth infections, the majority of these patients were administered VERMOX™ CHEWABLE 500 mg tablets with food.

Mean plasma pharmacokinetic parameters of mebendazole in healthy adult subjects under fasted and fed conditions are summarized in Table 3.

Table 3: Mean (SD) Plasma Pharmacokinetic Parameters After a Single VERMOX™ CHEWABLE 500 mg Dose in Healthy Adult Subjects (n=16) Under Fasted and Fed (High-fat Meal) Conditions

Parameter	Fasted	Fed
C_{max} (ng/mL)	14.0 (9.17)	56.2 (35.8)
T_{max} (h)*	1.5 (0.5-3.0)	4.0 (2.0-6.0)
AUC_{last} (ng.h/mL)	175 (129)	456 (249)

* median (range)

Distribution

The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that absorbed mebendazole penetrates areas outside the vascular space.

Metabolism

Orally administered mebendazole is extensively metabolized primarily by the liver. Plasma concentrations of its major metabolites (hydrolyzed and reduced forms of mebendazole) are 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. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients. Less than 2% of orally administered mebendazole is excreted in urine and the remainder in the feces as unchanged drug or its metabolites.

Specific Populations

Pediatric

Based on a limited number of blood samples, the pharmacokinetic results following single-dose administration of a 500 mg mebendazole chewable tablet to pediatric patients (age 1 to 16 years) with single or mixed infections of *T. trichiura* and/or *A. lumbricoides* indicated that children aged 1 to 3 years have higher systemic exposure than adults.

12.4 Microbiology

Mechanism of Action

Mebendazole interferes with cellular tubulin formation in the helminth and causes ultrastructural degenerative changes in its intestine. As a result, its glucose uptake and the digestive and reproductive functions are disrupted, leading to immobilization, inhibition of egg production and death of the helminth.

Antimicrobial Activity

Mebendazole is active against:

Ascaris lumbricoides

Trichuris trichiura

Resistance

There is a potential for development of resistance to mebendazole. The mechanism of resistance to mebendazole is likely due to changes of beta-tubulin protein, which reduces binding of mebendazole to beta-tubulin; however, the clinical significance of this is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity tests of mebendazole in mice and rats, no carcinogenic effects were seen at doses as high as 40 mg/kg (0.4 to 0.8-fold the MRHD, based on mg/m^2) given daily over two years. No mutagenic activity was observed with mebendazole in a bacterial reverse gene mutation test. Mebendazole was mutagenic in the absence of S-9 when tested using a continuous (24 hour) treatment incubation period in the mouse lymphoma thymidine kinase assay. Mebendazole was aneugenic *in vitro* in mammalian somatic cells. In the *in vivo* mouse micronucleus assay, orally administered mebendazole induced an increased frequency of micronucleated polychromatic erythrocytes with evidence suggestive of aneugenicity. Doses up to 40 mg/kg in rats (0.8-fold the MRHD, based on mg/m^2), given to males for 60 days and to females for 14 days prior to gestation, had no effect upon fetuses and offspring.

14 CLINICAL STUDIES

The efficacy of VERMOX™ CHEWABLE 500 mg tablets was evaluated in a double-blind, randomized, placebo controlled trial conducted in Africa in 295 pediatric patients between the ages of 1 year to 16 years of age with *A. lumbricoides* and/or *T. trichiura* infections. Patients were stratified by worm type and randomized to receive either VERMOX™ CHEWABLE 500 mg tablet (N=149) or placebo (N=146) at the baseline visit (double-blind period). After the 19 day double-blind period, all subjects received a single VERMOX™ CHEWABLE 500 mg tablet (open-label period).

Clinical cure was defined as zero egg count (*A. lumbricoides* and/or *T. trichiura*) at the end of the double-blind period (Day 19) in patients with positive egg count for the respective worm(s) at baseline. Patients with missing stool sample at Day 19 were considered not cured (Table 4).

Table 4: Clinical Response at the End of the Double-Blind Period (Day 19) for *A. lumbricoides* and *T. trichiura*

Infection Type	VERMOX™ CHEWABLE 500 mg All Patients=149*	Placebo All Patients=146*	Difference[1] (95% CI)
A. lumbricoides	**N=86 n (%)**	**N=81 n (%)**	
Cure	72 (83.7)	9 (11.1)	**72.6 (62.3, 82.7)[2]**
Failure[3]	9 (10.5)	67 (82.7)	
Missing[4]	5 (5.8)	5 (6.2)	
T. trichiura	**N=124 n (%)**	**N=119 n (%)**	
Cure	42 (33.9)	9 (7.6)	**26.2 (16.7, 35.6)[2]**
Failure[3]	76 (61.3)	103 (86.6)	
Missing[4]	6 (4.8)	7 (5.8)	

[1] Difference in cure rates, expressed in percentages, and based on Mantel Haenszel methods to account for stratification by site.
[2] P-value <0.001 based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
[3] Failures include patients who tested positive for the worm at Visit 3 (Day 19, i.e. test-of-cure).
[4] Patients with missing stool sample at Day 19.
* Some patients had mixed infection.

In patients treated with VERMOX™ CHEWABLE 500 mg, egg count reduction rate at the end of the double-blind period (Day 19) in patients with *A. lumbricoides* and/or *T. trichiura* was statistically significant ($p<0.001$) compared to placebo, 100% compared to 30.0% for *A. lumbricoides*, respectively, and 81.2% compared to 27.4% for *T. trichiura*, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

VERMOX™ CHEWABLE tablets are supplied as 500 mg, round, flat radius-edged white to yellowish chewable tablets that are debossed with "M/500" on one side and "J" on the other side. They are supplied as follows:

Bottles of 200 tablets NDC 50458-675-20

Store below 30°C. Keep container tightly closed. Unused tablets should be discarded 1 month after the bottle is first opened. When the bottle is first opened this Discard After date should be written on the bottle label in the place provided.

17 PATIENT COUNSELING INFORMATION

Advise patients that:

- VERMOX™ CHEWABLE tablet must be chewed completely before swallowing. For patients who have difficulty chewing the tablet, VERMOX™ CHEWABLE tablet can be turned into a soft mass with semi-solid consistency by adding 2 mL to 3 mL of drinking water to a spoon then placing the tablet into the water, which can then be swallowed. *[see Dosage and Administration (2)]*
- VERMOX™ CHEWABLE tablet must not be swallowed whole. *[see Dosage and Administration (2)]*
- VERMOX™ CHEWABLE tablet can be taken with or without food. *[see Dosage and Administration (2)]*
- Taking VERMOX™ CHEWABLE tablet and metronidazole together may cause serious skin reactions and should be avoided. *[see Warnings and Precautions (5.3)]*

Product of China

Manufactured by:
Lusomedicamenta
Lisbon, Portugal

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

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