EMVERM® is indicated for the treatment of patients two years of age and older with gastrointestinal infections caused by:

- *Ancylostoma duodenale* (hookworm),
- *Ascaris lumbricoides* (roundworm),
- *Enteobius vermicularis* (pinworm),
- *Necator americanus* (hookworm), and
- *Trichuris trichiura* (whipworm),

(1)

**DOSE AND ADMINISTRATION**

<table>
<thead>
<tr>
<th>Pinworm (enterobiasis)</th>
<th>Whipworm (trichuriasis)</th>
<th>Roundworm (ascariasis)</th>
<th>Hookworm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 tablet once</td>
<td>1 tablet once</td>
<td>1 tablet once</td>
<td>1 tablet</td>
</tr>
<tr>
<td>morning and</td>
<td>morning and</td>
<td>morning and</td>
<td>once</td>
</tr>
<tr>
<td>for 3 consecutive days</td>
<td>for 3 consecutive days</td>
<td>for 3 consecutive days</td>
<td></td>
</tr>
<tr>
<td>evenings</td>
<td>evenings</td>
<td>evenings</td>
<td></td>
</tr>
</tbody>
</table>

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

**DOSE FORMS AND STRENGTHS**

Chewable tablet: 100 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).

To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories, Inc. at 1-877-994-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling. Revised: 06/2017

**FULL PRESCRIBING INFORMATION: CONTENTS**

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- DOSAGE AND ADMINISTRATION
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- ADVERSE REACTIONS

**DRUG INTERACTIONS**

Concomitant use of mebendazole, including EMVERM®, and metronidazole should be avoided (see Warnings and Precautions (5.3)).

**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 0.5-fold the total daily 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**

Diseases Associated with 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 trials, have reported an 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.

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 included body weight loss in one animal and maternal and fetal death in 11 of 20 animals, was seen at 40 mg/kg/day. At 10 mg/kg/day, increased embryo-fetal resorption (100%) were observed 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 0.5-fold the total daily MRHD, based on mg/m²).

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 0.2-fold the total daily MRHD, based on mg/m²) and higher, embryo-fetal resorption increased (100% at 40 mg/kg/day) and fetal weight was lower (50% at 10 mg/kg/day). 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].

**REFERENCES**

- Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses during organogenesis as low as 10 mg/kg (approximately 0.5-fold the total daily MRHD, based on mg/m²).

- *Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg chewable tablets*

- *Blood and Lymphatic System Disorders*
  - Agranulocytosis, Neutropenia
  - 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, Angina

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    - Exanthema, Angioedema,
    - Urticaria, Angina

- *Includes mebendazole formulations, dosages and treatment duration other than EMVERM® 100 mg chewable tablets*
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 (1.9-fold the total daily MRHD, based on mg/m²), 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 demonstrates 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 effects of milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of EMVERM® to a breastfed infant; therefore, developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EMVERM® and any potential adverse effects on the breastfed infant from EMVERM® or from the underlying maternal condition.

8.4 Pediatric 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.

10 OVERDOSAGE

In patients treated at dosages substantially higher than recommended or for periods of time longer than those recommended, 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

EMVERM® (mebendazole) is an orally administered, synthetic anthelmintic available as chewable tablets, each containing 100 mg of mebendazole. Inactive ingredients are: microcrystalline cellulose, corn starch, stearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6.

Chemically, mebendazole is methyl 5-benzoylbenzimidazole-2-carboxamide with a molecular formula of C 16H13N3O3 and the following structural formula:

\[
\text{CH}_3\text{O} = \text{N} - \text{C}_6\text{H}_4\text{COCH}_3
\]

Mebendazole is a white or slightly yellow powder with a molecular weight of 295.29. It is less than 0.05% soluble in water, dilute mineral acid solutions, alcohol, ether and chloroform, but is soluble in formic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

Following oral administration of mebendazole, the majority of the dose remains in the gastrointestinal tract where it exerts an anthelmintic effect locally. Following administration of 100 mg twice daily for three consecutive days, plasma concentrations of EMVERM® (mebendazole) and its primary metabolite, the 2-amino-hydroxylated metabolite, do not exceed 0.03 mcg/mL and 0.09 mcg/mL, respectively. Doses of Emverm® high fat meal increases the bioavailability of mebendazole, although the overall effect of food on the amount of drug remaining in the gastrointestinal tract is not expected to be substantial.

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 (hydroxylated and reduced forms of mebendazole) are higher than those of mebendazole. All metabolites are devoid of anthelmintic activity. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma concentrations of mebendazole.

Excretion

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.

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 uptake, digestion and reproductive functions are disrupted, leading to immobilization, inhibition of egg production and death of the helminth.

Antimicrobial Activity

Mebendazole is active against: Anisakis andniformis Ascariasis lumbricoides Enterobius vermicularis Necator americanus 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 (one to two times the human dose, based on mg/m²) 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 (2 times the total daily human dose, based on mg/m²), given to males for 60 days and to females for 14 days prior to gestation, had no effect on fetal survival or growth.

14 CLINICAL STUDIES

Efficacy rates derived from various studies are shown in Table 4 below:

<table>
<thead>
<tr>
<th>Table 4: Mean Cure Rates and Egg Reduction from Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinworm (enterobiasis)</td>
</tr>
<tr>
<td>Cure rate (mean)</td>
</tr>
<tr>
<td>Egg reduction (mean)</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

EMVERM® (mebendazole) is available as a 100 mg, round, light peach-colored chewable tablet, unscored, debossed “ap” above “1900” on one side and plain on the other side. As per the following:

Blister package of 1 tablet NDC 64896-669-30 Store at 68° to 77°F (20° to 25°C) (See USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients that:

• Taking EMVERM® and metronidazole together may cause diarrhea.

Advise patients to:

• Tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

• If you take too much Emverm, you might have symptoms that include stomach cramps, nausea, vomiting or diarrhea.

What should I avoid while taking EMVERM?

Do not take Emverm with metronidazole (a medicine used to treat bacterial and protozoan infections) as serious skin reactions called Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can happen.

What should I avoid while taking EMVERM?

• Low white blood cell count (neutropenia), Neutropenia can cause you to get other infections. Your healthcare provider will check your blood count regularly during your treatment with EMVERM. Tell your healthcare provider right away if you have a fever or any signs of infection while taking EMVERM.

• Severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrosis). EMVERM may cause rare, but serious skin reactions when taken with metronidazole and other medicines that contain mebendazole. These severe allergic reactions are most likely to occur within the first 6 months of taking EMVERM and if you continue taking EMVERM after developing a reaction while taking EMVERM.

The most common side effects of EMVERM include:

• loss of appetite (anorexia)
• nausea
• stomach pain
• diarrhea
• passing gas

Tell your healthcare provider if you have any side effect that bothers you or if it does not go away.

These are not all the possible side effects of EMVERM. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EMVERM?

Store at room temperature between 68°F to 77°F (20°C to 25°C)

• Safely throw away medicine that is out of date or no longer needed.

Keep EMVERM and all medicines out of the reach of children.

General information about the safe and effective use of EMVERM is available at the following:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EMVERM for a condition for which it was not prescribed. Do not give EMVERM to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EMVERM that is written for health professionals.

What are the ingredients in EMVERM?

Active Ingredient: mebendazole

Inactive ingredients: microcrystalline cellulose, corn starch, anhydrous lactose NF, sodium starch glycolate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium saccharin, and FD&C Yellow #6.

Manufactured by: Impax Specialty Pharma
Distributed by: Impax Laboratories, Inc. at 1-877-99-IMPAX (1-877-994-6729).

This Patient Information has been approved by the U.S. Food and Drug Administration.

1901-02 Rev. 06/2017