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RESEARCH**

APPLICATION NUMBER:

21-806

LABELING

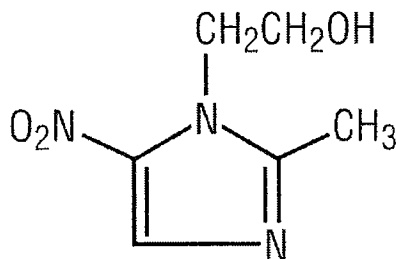
METRONIDAZOLE VAGINAL GEL, 0.75%

6111

**FOR INTRAVAGINAL USE ONLY
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE**

Rx only**DESCRIPTION**

Metronidazole vaginal gel is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole USP at a concentration of 0.75%. Metronidazole is a member of the imidazole class of antibacterial agents. Chemically, metronidazole is a 2-methyl-5-nitroimidazole-1-ethanol.



C₆H₉N₃O₃ M.W. 171.16

Metronidazole vaginal gel is a colorless to yellow gel, containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel also contains edetate disodium, hypromellose, methylparaben, propylene glycol, propylparaben, sodium hydroxide and purified water.

Each applicator full of 5 grams of vaginal gel contains approximately 37.5 mg of metronidazole.

CLINICAL PHARMACOLOGY

Following a single, intravaginal 5 gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole) to 38 healthy female volunteers, a mean maximum serum metronidazole concentration of 281ng/mL was reported (range: 134 to 464 ng/mL). The average time to achieve this C_{max} was 9.5 hours (range: 4 to 17 hours) after dosing with metronidazole vaginal gel. This C_{max} is approximately 2% of the mean maximum serum concentration reported in healthy subjects administered a single, oral 500 mg dose of metronidazole (mean C_{max} = 12,785 ng/mL).

The extent of exposure [area under the curve (AUC)] of metronidazole, when administered as a single intravaginal 5 gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole), was 5,989 ng•hr/mL (range: 2,797 to 10,515 ng•hr/mL). This AUC_{0-∞} is

approximately 5% of the reported AUC of metronidazole following a single oral 500 mg dose of metronidazole approximately 125,000 ng•hr/mL.

Patients with Bacterial Vaginosis

Following single and multiple 5 gram doses of a similar metronidazole vaginal gel product to 4 patients with bacterial vaginosis, a mean maximum serum metronidazole concentration of 214 ng/mL on day one and 294 ng/mL (range: 228 to 349 ng/mL) on day five were reported. Steady state metronidazole serum concentrations following oral dosages of 400 to 500 mg BID have been reported to range from 6,000 to 20,000 ng/mL.

Microbiology

The intracellular targets of action of metronidazole on anaerobes are largely unknown. The 5-nitro group of metronidazole is reduced by metabolically active anaerobes, and studies have demonstrated that the reduced form of the drug interacts with bacterial DNA. However, it is not clear whether interaction with DNA alone is an important component in the bactericidal action of metronidazole on anaerobic organisms.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. (See **INDICATIONS AND USAGE**.)

Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis*, *Mobiluncus* spp., and *Mycoplasma hominis*, has not been defined. Nonetheless, metronidazole is an antimicrobial agent active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.
Gardnerella vaginalis
Mobiluncus spp.
Peptostreptococcus spp.

INDICATIONS AND USAGE

Metronidazole vaginal gel, is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis) in non-pregnant women. There are no adequate and well-controlled studies of metronidazole vaginal gel in pregnant women.

NOTE: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a “fishy” amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram’s stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus should be ruled out.

CONTRAINDICATIONS

Metronidazole vaginal gel is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS**Convulsive Seizures and Peripheral Neuropathy**

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or intravenous metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with central nervous system diseases.

Psychotic Reactions

Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last two weeks.

PRECAUTIONS

Metronidazole vaginal gel results in minimal peak serum levels and systemic exposure (AUCs) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions, cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

General

Patients with severe hepatic disease metabolize metronidazole slowly. This results in the accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously.

Known or previously unrecognized vaginal candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel. Approximately 10% of patients treated with metronidazole vaginal gel developed symptomatic *Candida* vaginitis during or immediately after therapy.

Disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded.

Metronidazole vaginal gel contains ingredients that may cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

Information for the Patient

The patient should be cautioned about drinking alcohol while being treated with metronidazole vaginal gel. While blood levels are significantly lower with metronidazole vaginal gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.

The patient should be instructed not to engage in vaginal intercourse, or use other vaginal products (such as tampons or douches) during treatment with this product.

Metronidazole vaginal gel, 0.75% is supplied with 5 vaginal applicators. For once daily dosing, one applicator should be used per dose. For twice-daily dosing, the applicator should be washed, rinsed, and dried following the morning application, and re-used for the evening dose. After the evening dose, the applicator should be discarded and a new applicator used for the next day's dose. See DIRECTIONS FOR USE for complete instructions on how to use the product and the vaginal applicator.

Drug Interactions

The intravaginal administration of metronidazole vaginal gel, results in relatively lower systemic metronidazole concentrations compared to that following a 500 mg metronidazole oral dose (see **CLINICAL PHARMACOLOGY**). The following drug interactions were reported for oral metronidazole.

Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole vaginal gel is prescribed for patients on this type of anticoagulant therapy.

In patients stabilized on relatively high doses of lithium, short-term oral metronidazole therapy has been associated with elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.

Use of cimetidine with oral metronidazole may prolong the half-life and decrease plasma clearance of metronidazole.

Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminostransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide-adenine dinucleotides (NAD + NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole has shown evidence of carcinogenic activity after chronic oral administration in mice and rats. Pulmonary tumors and lymphomas were reported in several oral mouse studies in which mice were dosed at 75 mg/kg and above (about 5 times the clinical human dose based on

body surface area comparison). Malignant liver tumors were reported in male mice dosed at doses equivalent to a human dose of 41 mg/kg/day (33 times the recommended clinical dose based on body surface area comparisons). Chronic oral dosing of metronidazole in rats at doses above 150 mg/kg (about 120 times the clinical human dose based on body surface area comparison) has resulted in mammary and hepatic tumors. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative. No life-time studies were performed to evaluate the carcinogenic potential of metronidazole vaginal gel, 0.75%.

Metronidazole has shown mutagenic activity in a number of *in vitro* assay systems. In addition, a dose dependent increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosome aberrations has been reported in one study of patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in a second study, no increase in chromosome aberrations was reported in patients with Crohn's disease who were treated with metronidazole for 8 months.

Fertility studies have been performed in mice up to six times the recommended human oral dose (based on mg/m²) and have revealed no evidence of impaired fertility.

Pregnancy

Teratogenic Effects

Pregnancy category B

There is no data available regarding the use of metronidazole vaginal gel in pregnant women and therefore, no adequate and well-controlled studies in pregnant women. Oral reproductive toxicity studies have been performed in mice at doses up to six times the recommended human dose based on body surface area comparisons and have revealed no evidence of impaired fertility or harm to the fetus. However, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed.

Animal studies have shown that metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Because animal reproduction studies are not always predictive of human response, and because metronidazole crosses the placental barrier and is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole.

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of metronidazole vaginal gel in the treatment of bacterial vaginosis in post-menarchal females have been established on the extrapolation of clinical trial data from

adult women. The safety and efficacy of metronidazole vaginal gel in pre-menarchal females have not been established.

Geriatric Use

Clinical studies with metronidazole vaginal gel did not include sufficient numbers of subjects 65 years of age or older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

ADVERSE EVENTS

Clinical Trials

There were no deaths or serious adverse events related to drug therapy in a clinical trial involving 220 non-pregnant women who received metronidazole vaginal gel once daily at bedtime for 5 days. Metronidazole vaginal gel was discontinued in 5 patients (2.3%) due to adverse events. Adverse events judged definitely or probably related to drug occurred in 25 patients (11.4%).

The incidence of all adverse events was 42% (92/220). Events occurring in $\geq 1\%$ of patients were: fungal infection (12%), headache (7%), pruritus (6%), abdominal pain (5%), nausea (3%), dysmenorrhea (3%), pharyngitis (2%), rash (1%), infection (1%), diarrhea (1%), breast pain (1%), and metrorrhagia (1%).

Adverse events judged to be definitely related or probably related to study medication occurring in $\geq 1\%$ of patients were: fungal infection (9.1%).

Additional uncommon events, not necessarily related to metronidazole vaginal gel, but reported by $< 1\%$ of those women treated included:

<i>General:</i>	allergic reaction, back pain, flu syndrome, mucous membrane disorder, pain
<i>Cardiovascular:</i>	anorexia, constipation, dyspepsia, flatulence, gingivitis, vomiting
<i>Nervous System:</i>	depression, dizziness, insomnia
<i>Respiratory System:</i>	asthma, rhinitis
<i>Skin and Appendages:</i>	acne, sweating, urticaria
<i>Urogenital System:</i>	breast enlargement, dysuria, female lactation, labial edema, leucorrhea, menorrhagia, pyelonephritis, salpingitis, urinary frequency, urinary tract infection, vaginitis, vulvovaginal disorder

Other Metronidazole Formulations

Other Vaginal Formulations

Other effects that have been reported in association with the use of other formulations of metronidazole vaginal gel include: unusual taste and decreased appetite.

Topical (dermal) Formulations

Other effects that have been reported in association with the use of topical (dermal) formulations of metronidazole include skin irritation, transient skin erythema, and mild skin dryness and burning. None of these adverse events exceeded an incidence of 2% of patients.

Oral and Parenteral Formulations

Metronidazole vaginal gel results in minimal peak serum levels and systemic exposure (AUC) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

The following adverse reactions and altered laboratory tests have been reported with the oral or parenteral use of metronidazole:

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: (See **WARNINGS**.) Headache, dizziness, syncope, ataxia, confusion, convulsive seizures, peripheral neuropathy, vertigo, incoordination, irritability, depression, weakness, insomnia.

Gastrointestinal: Abdominal discomfort, nausea, vomiting, diarrhea, an unpleasant metallic taste, anorexia, epigastric distress, abdominal cramping, constipation, "furry" tongue, glossitis, stomatitis, pancreatitis, and modification of taste of alcoholic beverages.

Genitourinary: Overgrowth of *Candida* in the vagina, dyspareunia, decreased libido, proctitis.

Hematopoietic: Reversible neutropenia, reversible thrombocytopenia.

Hypersensitivity Reactions: Urticaria; erythematous rash; flushing; nasal congestion; dryness of the mouth, vagina, or vulva; fever; pruritus; fleeting joint pains.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, darkened urine.

OVERDOSAGE

There is no human experience with overdosage of metronidazole vaginal gel. Vaginally applied metronidazole gel, 0.75% could be absorbed in sufficient amounts to produce systemic effects. (See **WARNINGS**.)

DOSAGE AND ADMINISTRATION

The recommended dose is one applicator full of metronidazole vaginal gel, (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days. For once a day dosing, metronidazole vaginal gel should be administered at bedtime.

HOW SUPPLIED

Metronidazole vaginal gel, 0.75% is supplied in a 70 gram tube and packaged with 5 vaginal applicators.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing.

METRONIDAZOLE VAGINAL GEL, 0.75%

DIRECTIONS FOR USE

1. Filling the applicator

- Remove cap and puncture metal seal on tube with the pointed tip of cap. (See Figure 1)
- Screw end of applicator onto tube. (See Figure 2)
- Slowly squeeze gel out of tube and into applicator. Plunger will stop when the applicator is full. (See Figure 3)
- Unscrew applicator and replace cap on tube.

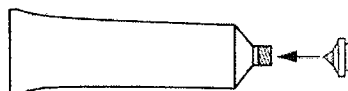


Figure 1

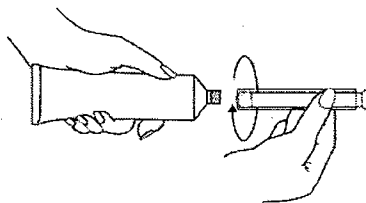


Figure 2

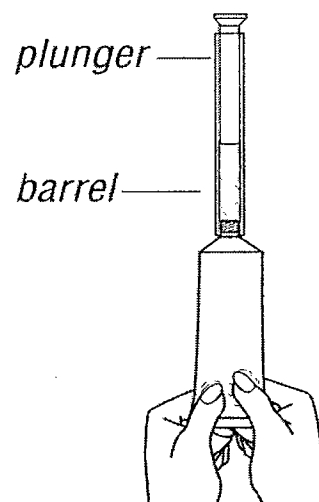


Figure 3

2. Inserting the applicator

- The applicator may be inserted while lying on your back with your knees bent or in any comfortable position.
- Hold filled applicator by barrel, and gently insert into vagina as far as it will comfortably go. (See Figure 4)
- Slowly press the plunger until it stops to deposit gel into vagina and then withdraw the applicator.

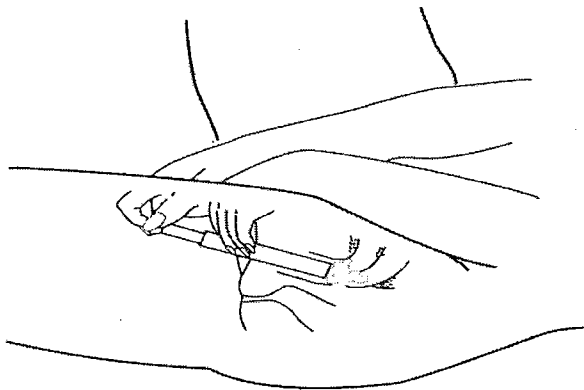


Figure 4

3. Care of the applicator

If physician prescribes once-a-day dosing:

- After use, the applicator may be discarded

If physician prescribes twice-a-day dosing:

- After the morning dose, pull the plunger out of the barrel. (See Figure 5)
- Wash both plunger and barrel in warm soapy water and rinse thoroughly and dry.
- For the evening dose, the applicator can be reassembled by gently pushing the plunger back into barrel.

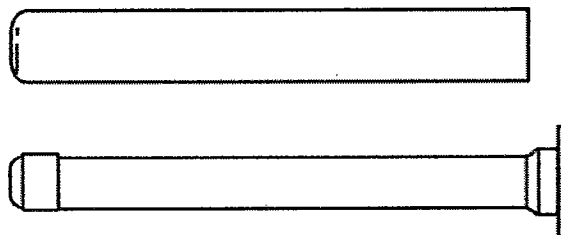


Figure 5

IMPORTANT:

This product is supplied with 5 vaginal applicators.

For once-a-day dosing:

- apply one applicator full at bedtime. After using the applicator, discard it and use a new applicator for the next day's dose.

For twice-a-day dosing:

- apply one applicator full each morning and evening for five days. Following the morning application, wash, rinse, and dry the applicator (as instructed above). The applicator may be reassembled for the evening dose. After the evening dose, discard the applicator and use a new applicator for the next day's dose.

WARNINGS:

- If significant irritation develops from the use of this medication, discontinue use and consult your physician.
- Do not use during pregnancy except under the supervision of a physician.
- Keep this and all medications out of reach of children.
- For vaginal use only. Not for use in the eyes, on the skin or in the mouth.

Store at room temperature. Avoid exposure to extreme heat or cold. See end of carton and bottom of tube for lot number and expiration date.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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/s/

Renata Albrecht
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