

Enclosure

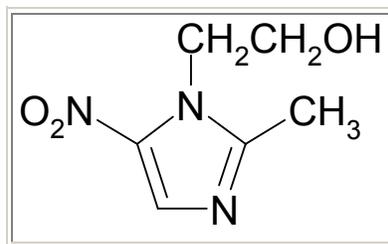
METROGEL[®]

(metronidazole gel), 1%

For topical use only. Not for oral, ophthalmic or intravaginal use.

DESCRIPTION

METROGEL[®] (metronidazole gel), 1 % contains metronidazole, USP. Chemically, metronidazole is 2-methyl-5-nitro-1 *H*-imidazole-1-ethanol. The molecular formula for metronidazole is C₆H₉N₃O₃. It has the following structural formula:



Metronidazole has a molecular weight of 171.16. It is a white to pale yellow crystalline powder. It is slightly soluble in alcohol and has a solubility in water of 10 mg/mL at 20°C. METROGEL[®] (metronidazole gel), 1% is a member of the imidazole class of anti-bacterial agents and is classified as an antiprotozoal and anti-bacterial agent.

METROGEL[®] (metronidazole gel), 1% is an aqueous gel; each gram contains 10 mg of metronidazole in a base of betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide phenoxyethanol, propylene glycol, propylparaben and purified water.

CLINICAL PHARMACOLOGY

The contribution to efficacy of individual components of the vehicle has not been established.

Pharmacokinetics: Topical administration of a one gram dose of METROGEL[®] (metronidazole gel) 1% to the face of 13 patients with moderate to severe rosacea once daily for 7 days resulted in a mean \pm SD C_{max} of metronidazole of 32 \pm 9 ng/mL. The mean \pm SD AUC₍₀₋₂₄₎ was 595 \pm 154 ng*hr/mL. The mean C_{max} and AUC₍₀₋₂₄₎ are less than 1% of the value reported for a single 250 mg oral dose of metronidazole. The time to maximum plasma concentration (T_{max}) was 6-10 hours after topical application.

Pharmacodynamics: The mechanisms by which metronidazole acts are unknown.

CLINICAL STUDIES

Clinical Studies: Safety and efficacy of METROGEL[®] (metronidazole gel), 1% has been demonstrated in a 10-week, randomized, vehicle-controlled trial in 746 patients with rosacea. Patients were treated once daily for ten weeks with METROGEL[®] (metronidazole gel), 1% or with gel vehicle. Most patients had “moderate” rosacea at baseline. Efficacy was determined by recording reduction in

inflammatory lesion counts and success rate in the Investigator Global Assessment (percentage of subjects “clear” and “almost clear” of rosacea at the end of the study). The scale is based on the following definitions:

| Investigator Global Assessment Scale | | |
|--------------------------------------|----------|--|
| Score | Grade | Definition |
| 0 | Clear | No signs or symptoms present; at most, mild erythema |
| 1 | Almost | Very mild erythema present. Very few small papules/pustules |
| 2 | Mild | Mild erythema. Several small papules/pustules |
| 3 | Moderate | Moderate erythema. Several small or large papules/pustules, and up to 2 nodules |
| 4 | Severe | Severe erythema. Numerous small and/or large papules/pustules, up to several nodules |

The results are shown in the following table:

| Inflammatory Lesion Counts and Global Scores in a Clinical Trial for Rosacea | | | | | |
|--|-----|--------------|-----|---------------|---------|
| | | Metrogel 1% | | Vehicle | p-value |
| | N | Result N (%) | N | Results N (%) | |
| Inflammatory lesions | 557 | | | | |
| Baseline, mean count | | 18.3 | | 18.4 | |
| Week-10, mean count | | 8.9 | | 12.8 | |
| Reduction | | 50.7% | | 32.6% | <0.0001 |
| Investigator Global Assessment | 557 | | 189 | | |
| Subjects clear or almost clear | | 214 (38.42) | | 52 (27.51) | 0.0060 |
| Subjects with no change | | 159 (28.5) | | 77 (40.7) | |

Patients treated with METROGEL[®] (metronidazole gel), 1% experienced a mean reduction of 9.4 inflammatory lesions in the Week-10 LOCF group, compared to a reduction of 5.6 for those treated with vehicle, or a difference in means of 3.8 lesions.

Safety Studies: Studies of cumulative irritation (n=35), contact sensitization-repeat insult patch test (n=230), phototoxicity (n=29), and photoallergy (n=30) of METROGEL[®] (metronidazole gel), 1% were conducted. No significant evidence of irritation, sensitization, phototoxicity or photoallergy was found in these studies.

INDICATIONS AND USAGE

METROGEL[®] (metronidazole gel), 1% is indicated for the topical treatment of inflammatory lesions of rosacea.

CONTRAINDICATIONS

METROGEL[®] (metronidazole gel), 1% is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation.

PRECAUTIONS

General: Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local skin irritation occurs, patients should be directed to use the medication less often or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.

Information for Patients: Patients using METROGEL[®] (metronidazole gel) 1% should receive the following information and instructions:

1. This medication is to be used as directed.
2. It is for external use only.
3. Avoid contact with the eyes.
4. Cleanse affected area(s) before applying METROGEL[®] (metronidazole gel) 1%.
5. This medication should not be used for any other condition than that for which it is prescribed.
6. Patients should report any adverse reaction to their physician.

Drug Interaction: Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when METROGEL[®] (metronidazole gel), 1% is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but not in studies involving hamsters.

In several long-term studies in mice, oral doses of approximately 225 mg/m²/day or greater (approximately 37 times the human topical dose on a mg/m² basis) were associated with an increase in pulmonary tumors and lymphomas. Several long-term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m²/day (144 times the topical human dose).

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months.

In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m²/day (approximately 7 times the human topical dose on a mg/m² basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with METROGEL[®] (metronidazole gel), 1% or any marketed metronidazole formulations.

Pregnancy: Teratogenic Effects: Pregnancy Category B. There are no adequate and well-controlled studies with the use of METROGEL[®] (metronidazole gel), 1% in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole in rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has shown carcinogenic activity in rodents.

Because animal reproduction studies are not always predictive of human response, METROGEL[®] (metronidazole gel), 1% should be used during pregnancy only if clearly needed.

Nursing Mothers: After oral administration, metronidazole is secreted in breast milk in concentration similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole, 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 and the risk to the infant.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: While specific clinical trials in the geriatric population have not been conducted, sixty-six patients aged 65 years and older treated METROGEL[®] (metronidazole gel), 1% over ten weeks showed comparable safety and efficacy as compared to the general study population.

ADVERSE REACTIONS

In a controlled clinical trial, 557 patients used METROGEL[®] (metronidazole gel), 1% and 189 patients used the gel vehicle once daily. The following table summarizes the treatment-related:

| System Organ Class/ Preferred Term | Metronidazole Gel, 1% | Gel Vehicle |
|--|-----------------------|------------------|
| | N=557 | N=189 |
| Patients with at least one AE Number (%) of Patients | 186 (33.4) | 51 (27.0) |
| Infections and infestations | 76 (13.6) | 28 (14.8) |
| Bronchitis | 6 (1.1) | 3 (1.6) |
| Influenza | 8 (1.4) | 1 (0.5) |
| Nasopharyngitis | 17 (3.1) | 8 (4.2) |
| Sinusitis | 8 (1.4) | 3 (1.6) |
| Upper respiratory tract infection | 14 (2.5) | 4 (2.1) |
| Urinary tract infection | 6 (1.1) | 1 (0.5) |
| Vaginal mycosis | 1 (0.2) | 2 (1.1) |
| Musculoskeletal and connective tissue disorders | 19 (3.4) | 5 (2.6) |
| Back pain | 3 (0.5) | 2 (1.1) |
| Neoplasms^b | 4 (0.7) | 2 (1.1) |
| Basal cell carcinoma | 1 (0.2) | 2 (1.1) |
| Nervous system disorders | 18 (3.2) | 3 (1.6) |
| Headache | 12 (2.2%) | 1 (0.5%) |
| Respiratory, thoracic and mediastinal disorders | 22 (3.9) | 5 (2.6) |
| Nasal congestion | 6 (1.1%) | 3 (1.6) |
| Skin and subcutaneous tissue disorders | 36 (6.5) | 12 (6.3) |
| Contact dermatitis | 7 (1.3) | 1 (0.5) |
| Dry skin | 6 (1.1) | 3 (1.6) |
| Vascular disorders | 8 (1.4) | 1 (0.5) |
| Hypertension | 6 (1.1) | 1 (0.5) |

The following table summarizes the highest scores of local cutaneous signs and symptoms of irritation that were worse than baseline:

| | Metronidazole Gel, 1% | Gel Vehicle |
|-------------------------|------------------------------|--------------------|
| Sign/Symptom | N=544 | N=184 |
| Dryness | 138 (25.4) | 63 (34.2) |
| Mild | 93 (17.1) | 41 (22.3) |
| Moderate | 42 (7.7) | 20 (10.9) |
| Severe | 3 (0.6) | 2 (1.1) |
| Scaling | 134 (24.6) | 60 (32.6) |
| Mild | 88 (16.2) | 32 (17.4) |
| Moderate | 43 (7.9) | 27 (14.7) |
| Severe | 3 (0.6) | 1 (0.5) |
| Pruritus | 86 (15.8) | 35 (19.0) |
| Mild | 53 (9.7) | 21 (11.4) |
| Moderate | 27 (5.0) | 13 (7.1) |
| Severe | 6 (1.1) | 1 (0.5) |
| Stinging/burning | 56 (10.3) | 28 (15.2) |
| Mild | 39 (7.2) | 18 (9.8) |
| Moderate | 7 (1.3) | 9 (4.9) |
| Severe | 10 (1.8) | 1 (0.5) |

The following additional adverse experiences have been reported with the topical use of metronidazole: skin irritation, transient redness, metallic taste, tingling or numbness of extremities, and nausea.

OVERDOSAGE

There are no reported human experiences with overdose of METROGEL[®] (metronidazole gel), 1%. Topically applied metronidazole can be absorbed in sufficient amount to produce systemic effects.

DOSAGE AND ADMINISTRATION

Areas to be treated should be cleansed before application of METROGEL[®] (metronidazole gel), 1%. Apply and rub in a thin film of METROGEL[®] (metronidazole gel), 1% once daily to entire affected area(s). Patients may use cosmetics after application of METROGEL[®] (metronidazole gel), 1%.

HOW SUPPLIED

METROGEL[®] (metronidazole gel), 1% is available in a 45 gram tube.

45 gram tube.....NDC XXXX

Keep out of the reach of children.

Storage Conditions: Store at controlled room temperature: 20° to 25°C (68° to 77°F), excursions permitted between 59° and 86°F (15° to 30°C).

Prescribing Information as of XXXXX.

Rx Only

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NDA 21-789

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