HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METROGEL, 1% safely and effectively. See full prescribing information for METROGEL, 1%.

METROGEL® (metronidazole) gel for topical use.
Initial U.S. Approval: 1963

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

METROGEL, 1% is a nitroimidazole indicated for the topical treatment of inflammatory lesions of rosacea. (1)

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

- Not for oral, ophthalmic, or intravaginal use. (2)
- Cleanse treated areas before the application of METROGEL. (2)
- Apply and rub in a thin film of METROGEL once daily to affected area(s). (2)
- Cosmetics may be applied after the application of METROGEL. (2)

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

Gel, 1%.

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

METROGEL is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation. (4)

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

- Neurologic Disease: Peripheral neuropathy, characterized by numbness or paresthesia of an extremity has been reported in patients treated with systemic metronidazole. Peripheral neuropathy has been reported with the post approval use of topical metronidazole. The appearance of abnormal neurologic signs should prompt immediate reevaluation of METROGEL therapy. (5.1)
- Blood Dyscrasias: METROGEL is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia. (5.2)
- Contact Dermatitis: If dermatitis occurs, patients may need to discontinue use. (5.3)
- Eye Irritation: Topical metronidazole has been reported to cause tearing of the eyes. Therefore, avoid contact with the eyes. (5.4)

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

Most common adverse reactions (incidence > 2%) are nasopharyngitis, upper respiratory tract infection, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Use caution when administering METROGEL concomitantly to patients who are receiving anticoagulant treatment. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

METROGEL, 1% is indicated for the topical treatment of inflammatory lesions of rosacea.

2 DOSAGE AND ADMINISTRATION

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

Cleanse treated areas before the application of METROGEL.

Apply and rub in a thin film of METROGEL once daily to affected area(s).

Cosmetics may be applied after the application of METROGEL.

3 DOSAGE FORMS AND STRENGTHS

Gel, 1%. METROGEL is a clear, colorless to pale yellow gel. Each gram of METROGEL contains 10 mg (1%) of metronidazole.

4 CONTRAINDICATIONS

METROGEL is contraindicated in patients with a history of hypersensitivity to metronidazole or to any other ingredient in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Neurologic Disease

Peripheral neuropathy, characterized by numbness or paresthesia of an extremity, has been reported in patients treated with systemic metronidazole. Peripheral neuropathy has been reported with the post approval use of topical metronidazole. The appearance of abnormal neurologic signs should prompt immediate reevaluation of METROGEL therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

5.2 Blood Dyscrasias

METROGEL is a nitroimidazole; use with care in patients with evidence of, or history of, blood dyscrasia.

5.3 Contact Dermatitis

Irritant and allergic contact dermatitis have been reported with METROGEL. If dermatitis occurs, patients may need to discontinue use.

5.4 Eye Irritation

Topical metronidazole has been reported to cause tearing of the eyes. Avoid contact with the eyes.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

In a controlled clinical trial, 557 subjects used METROGEL and 189 subjects used the gel vehicle once daily for up to 10 weeks. The following table summarizes selected adverse reactions that occurred at a rate of ≥1%:

Table 1: Adverse Reactions That Occurred at a Rate of ≥1%

System Organ Class/Preferred Term	METROGEL	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	**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)

Table 2: Local Cutaneous Signs and Symptoms of Irritation That Were Worse Than Baseline

	METROGEL	**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: transient redness, metallic taste, tingling or numbness of extremities, and nausea.

6.2 Post Marketing Experience

The following adverse reaction has been identified during post- approval use of topical metronidazole. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Nervous System Disorders: Peripheral neuropathy *[see Warnings and Precautions (5.1)]*

7 DRUG INTERACTIONS

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 is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data have not established an association with metronidazole use during pregnancy and major birth defects, miscarriage or other adverse maternal or fetal outcomes. No fetotoxicity was observed after oral administration of metronidazole in pregnant rats or mice. The available data do not allow the calculation of relevant comparisons between the systemic exposures of metronidazole observed in animal studies to the systemic exposures that would be expected in humans after topical use of METROGEL.

The background risk of major birth defects and miscarriage for the indicated population 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.

8.2 Lactation

Risk Summary

It is not known whether metronidazole is present in human milk after topical administration. Published literature reports the presence of metronidazole in human milk after oral administration. There are reports of diarrhea and candida infection in breastfed infants of mothers receiving oral treatment with metronidazole. There are no data on the effects of metronidazole on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with METROGEL.

8.4 Pediatric Use

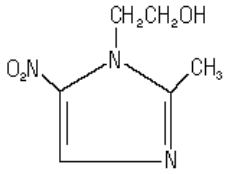
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Sixty-six subjects aged 65 years and older were treated with METROGEL in the clinical study. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

METROGEL contains metronidazole, USP. It is intended for topical use. Chemically, metronidazole is 2-methyl-5-nitro-1 *H*-imidazole-1-ethanol. The molecular formula for metronidazole is $C_6H_9N_3O_3$. 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 solubility in water of 10 mg/mL at 20˚C. Metronidazole belongs to the nitroimidazole class of compounds.

METROGEL is a clear, colorless to pale yellow, 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of metronidazole in the treatment of rosacea is unknown**.**

12.2 Pharmacodynamics

The pharmacodynamics of metronidazole in association with the treatment of rosacea are unknown.
Cardiac Electrophysiology: The effect of METROGEL on the QTc interval has not been adequately characterized.

12.3 Pharmacokinetics

Topical administration of a one-gram dose of METROGEL to the face of 13 subjects with moderate to severe rosacea once daily for 7 days resulted in a mean ± SD C_{max} of metronidazole of 32 ± 9 ng/mL. The mean ± SD $AUC_{(0-24)}$ was 595 ± 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole has shown evidence of carcinogenic activity in 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/m^2/day or greater 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/m^2/day.

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.

14 CLINICAL STUDIES

In a randomized, vehicle-controlled trial, 746 subjects with rosacea were treated with METROGEL or vehicle once daily for 10 weeks. Most subjects had a disease severity score of 3 ("moderate") on the 5-point Investigator Global Assessment (IGA) scale, with 8 to 50 inflammatory lesions and no more than two nodules at baseline. The co-primary efficacy endpoints were the percent reduction in inflammatory lesion counts and percentage of subjects with success on IGA, defined as an IGA score of 0 ("clear") or 1 ("almost clear") at Week 10.
The efficacy results are shown in the following table:

Table 3: Inflammatory Lesion Counts and Global Scores in a Clinical Trial of Rosacea

	METROGEL		Vehicle	
	N	Results N (%)	N	Results N (%)
Inflammatory lesions	557		189	
Baseline, mean count		18.3		18.4
Week-10, mean count		8.9		12.8
Reduction		9.4 (50.7)		5.6 (32.6)
Investigator Global Assessment	557		189	
Subject clear or almost clear		214 (38.42)		52 (27.51)
Subject with no change		159 (28.5)		77 (40.7)

Subjects treated with METROGEL 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.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

METROGEL® is clear, colorless to pale yellow in color, and supplied as follows:
60 gram tube – NDC 0299-3820-60
55 gram pump – NDC 0299-3820-01

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions
Use as directed. Avoid contact with the eyes.
Cleanse treated areas before the application of METROGEL
Advise patients to report any adverse reaction to their healthcare providers.

Lactation
Advise women not to breastfeed during treatment with METROGEL *[see Use in Specific Populations (8.2)]*.

Rx Only
US Patent No. 6,881,726 and 7,348,317

Marketed by:
Galderma Laboratories, L.P.
Fort Worth, Texas 76177 USA
P5XXXX-X

Made in Canada

PATIENT INFORMATION
METROGEL® (MET-TRO-GEL)
(metronidazole)
Gel

Important: METROGEL is for use on the skin only (topical use). Do not use METROGEL in your mouth, eyes, or vagina.

What is METROGEL?

METROGEL is a prescription medicine used on the skin (topical) to treat pimples and bumps (inflammatory lesions) caused by a condition called rosacea.

It is not known if METROGEL is safe and effective in children.

Do not use METROGEL if you are allergic to metronidazole or any of the ingredients in METROGEL. See the end of this leaflet for a complete list of ingredients in METROGEL.

Before using METROGEL, tell your healthcare provider about all your medical conditions, including if you:

- have tingling or numbness in your hands or feet
- have or have had a blood disorder or disease
- are pregnant or plan to become pregnant. It is not known if METROGEL will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if METROGEL passes into your breast milk. Do not breastfeed during treatment with METROGEL. Talk to your healthcare provider about the best way to feed your baby during treatment with METROGEL.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use METROGEL?

- Use METROGEL exactly as your healthcare provider tells you to.
- Cleanse the treated area before applying METROGEL.
- Apply and rub in a thin film of METROGEL 1 time a day to the affected area(s).
- You can apply cosmetics after applying METROGEL.
- Avoid contact of METROGEL with your eyes.

What are the possible side effects of METROGEL?

METROGEL may cause serious side effects, including:

- **Peripheral neuropathy.** Tingling, burning, pain or numbness in the hands or feet (peripheral neuropathy) have happened in people treated with metronidazole used on the skin. Tell your healthcare provider if you experience tingling, burning, pain or numbness in your hands or feet during treatment with METROGEL.
- **Skin reactions,** including allergic reactions. Tell your healthcare provider if you develop any skin reactions, including rash, itching, redness, swelling, or blisters during treatment with METROGEL.
- **Eye irritation.** Tearing from eye irritation has happened in people treated with metronidazole used on the skin. Tell your healthcare provider if you experience tearing, redness or discomfort of the eyes during treatment with METROGEL.

The most common side effects of METROGEL include:

- sore throat and nasal congestion
- upper respiratory tract infections
- headache

Tell your healthcare provider if you get any side effects during treatment with METROGEL.
These are not all of the possible side effects of METROGEL.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Galderma Laboratories, L.P. at 1-866-735-4137.

How should I store METROGEL?

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

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

General information about the safe and effective use of METROGEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use METROGEL for a condition for which it was not prescribed. Do not give METROGEL 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 METROGEL that is written for health professionals.

What are the ingredients in METROGEL?
Active ingredient: metronidazole
Inactive ingredients: betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide, phenoxyethanol, propylene glycol, propylparaben and purified water

Marketed by: Galderma Laboratories, L.P., Fort Worth, Texas 76177 USA
P5XXXX-X
Made in Canada
US Patent No. 6,881,726 and 7,348,317
For more information, call 1-866-735-4137.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 03/2022