HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Metronidazole Gel, 1%.
For topical use.
Initial U.S. Approval: 1963

-------INDICATIONS AND USAGE------
Metronidazole Gel, 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)
- Apply and rub in a thin film of Metronidazole Gel, 1% once daily to affected area(s). (2)
- Treated areas should be cleansed before the application of Metronidazole Gel, 1%. (2)
- Cosmetics may be applied after the application of Metronidazole Gel, 1%. (2)

-DOSAGE FORMS AND STRENGTHS-
Gel, 1%.

----------CONTRAINDICATIONS--------
Metronidazole Gel, 1% is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation. (4)

--WARNINGS AND PRECAUTIONS--
- Peripheral neuropathy, characterized by numbness or paresthesia of an extremity has been reported in patients treated with systemic metronidazole. Although not evident in clinical trials for topical metronidazole, peripheral neuropathy has been reported with the post approval use. The appearance of abnormal neurologic signs should prompt immediate reevaluation of Metronidazole Gel, 1% therapy. (5.1)
- Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia. (5.2)
- If dermatitis occurs, patients may need to discontinue use. (5.3)
- Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. (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 Prasco Laboratories, at 1-866-525-0688 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. Drug interactions should be kept in mind when 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. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Metronidazole Gel, 1% is indicated for the topical treatment of inflammatory lesions of rosacea.

2 DOSAGE AND ADMINISTRATION
Apply and rub in a thin film of Metronidazole Gel, 1% once daily to affected area(s).
A gentle cleanser should be used before the application of Metronidazole Gel, 1%.
Cosmetics may be applied after the application of Metronidazole Gel, 1%.
Not for oral, ophthalmic or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS
Gel, 1%. Metronidazole Gel is a clear, colorless to pale yellow gel. Each gram of Metronidazole Gel, 1% contains 10 mg (1%) of metronidazole.

4 CONTRAINDICATIONS
Metronidazole Gel, 1% 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. Although not evident in clinical trials for topical metronidazole, peripheral neuropathy has been reported with the post approval use. The appearance of abnormal neurologic signs should prompt immediate reevaluation of Metronidazole Gel, 1% therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

5.2 Blood Dyscrasias
Metronidazole 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. 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 patients used metronidazole gel, 1% and 189 patients 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	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	**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 Symtoms 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.

6.2 Post Marketing Experience
The following adverse reaction has been identified during post approval use

of topical metronidazole: peripheral neuropathy. 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.

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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B.

There are no adequate and well-controlled studies with the use of 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, Metronidazole Gel, 1% should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

After oral administration, metronidazole is secreted in breast milk in concentrations 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

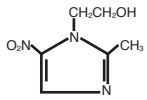
Sixty-six subjects aged 65 years and older were treated with metronidazole gel, 1% in the clinical study. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

There are no reported human experiences with overdosage of Metronidazole Gel, 1%. Topically applied metronidazole can be absorbed in sufficient amount to produce systemic effects.

11 DESCRIPTION

Metronidazole Gel, 1% contains metronidazole, USP. 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.

Metronidazole Gel, 1% 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.

12.3 Pharmacokinetics

Topical administration of a one gram dose of Metronidazole Gel, 1% to the face of 13 patients 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 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/m^2/day or greater (approximately 37 times the human topical dose on a mg/m^2 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/m^2/day (144 times the 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/m^2/day (approximately 7 times the human topical dose on a mg/m^2 basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with Metronidazole Gel, 1% or any marketed metronidazole formulations.

14 CLINICAL STUDIES

In a randomized, vehicle-controlled trial, 746 subjects with rosacea were treated with metronidazole gel, 1% or gel vehicle once daily for 10 weeks. Most subjects 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:

Table 3: Investigator Global Assessment Scale

Score	Grade	Definition
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	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 papuples/pustules, up to several nodules

The results are shown in the following table:

Table 4: Inflammatory Lesion Counts and Global Scores in a Clinical Trial of Rosacea

	Metronidazole Gel, 1%		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 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.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Metronidazole Gel, 1% is clear, colorless to pale yellow in color, and supplied as follows:

60 gram tube – **NDC** 66993-936-61

55 gram pump – **NDC** 66993-936-58

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

Patients using 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 Metronidazole Gel, 1%.
5. This medication should not be used for any condition other than that for which it is prescribed.
6. Keep out of reach of children.
7. Patients should report any adverse reaction to their physicians.

Rx Only

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

Manufactured by:
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Baie d'Urfé, QC, H9X 3S4 Canada
Made in Canada.

Marketed by:
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