METRONIDAZOLE- metronidazole gel
Taro Pharmaceuticals U.S.A., Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METRONIDAZOLE GEL safely and effectively. See full prescribing information for METRONIDAZOLE GEL.

METRONIDAZOLE gel, for topical use
Initial U.S. Approval: 1963

INDICATIONS AND USAGE

Metronidazole gel 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 metronidazole. (2)
- Apply and rub in a thin film of metronidazole once daily to affected area(s). (2)
- Cosmetics may be applied after the application of metronidazole. (2)

DOSAGE FORMS AND STRENGTHS

Gel, 1%. (3)

CONTRAINDICATIONS

Metronidazole gel 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 metronidazole therapy. (5.1)
- Blood Dyscrasias: Metronidazole 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 Taro Pharmaceuticals U.S.A., Inc. at 1-866-923-4914 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 metronidazole gel 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 and FDA-approved patient labeling.
Revised: 1/2023

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 USP, 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 metronidazole gel.

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

Cosmetics may be applied after the application of metronidazole gel.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Metronidazole gel 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 metronidazole 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 with metronidazole gel. 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 metronidazole gel 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	Metronidazole 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 Symptoms of Irritation That Were Worse Than Baseline

	Metronidazole 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: 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 metronidazole 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 metronidazole.

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 to 4% and

15 to 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 metronidazole gel.

8.4 Pediatric Use

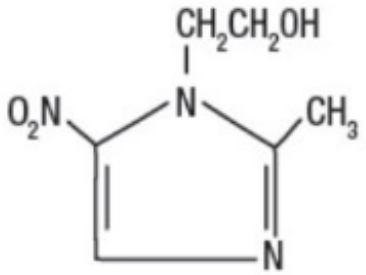
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Sixty-six subjects aged 65 years and older were treated with metronidazole gel 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

Metronidazole Gel USP, 1% 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.

Metronidazole is a colorless to slightly yellow gel; each gram contains 10 mg of metronidazole in a base of alcohol (9.3% w/w), edetate disodium, hydroxyethylcellulose, polyethylene glycol 400, propylene glycol, sorbic acid, 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 metronidazole on the QTc interval has not been adequately characterized.

12.3 Pharmacokinetics

Topical administration of a one-gram dose of metronidazole gel 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 to 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 metronidazole gel 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

	Metronidazole Gel		**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 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

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

45 gram tube - (NDC 51672-4215-6)

60 gram tube - (NDC 51672-4215-3)

55 gram pump - (NDC 51672-4215-9)

16.2 Storage and Handling

Storage Conditions: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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 metronidazole gel.

Advise patients to report any adverse reaction to their healthcare providers.

Lactation

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

Rx Only
Mfd. by: Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 2624761
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
Revised: December 2022

5201281-1222-01

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PATIENT INFORMATION
Metronidazole
(me troe ni da zole)
Gel, 1%

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

What is metronidazole gel?
Metronidazole gel 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 metronidazole gel is safe and effective in children.

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

Before using metronidazole gel, 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 metronidazole gel will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if metronidazole gel passes into your breast milk. Do not breastfeed during treatment with metronidazole gel. Talk to your healthcare provider about the best way to feed your baby during treatment with metronidazole gel.

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 metronidazole gel?

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

What are the possible side effects of metronidazole gel?
Metronidazole gel 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 metronidazole gel.
- **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 metronidazole gel.
- **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 metronidazole gel.

The most common side effects of metronidazole gel include:

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

Tell your healthcare provider if you get any side effects during treatment with metronidazole gel.
These are not all of the possible side effects of metronidazole gel.
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 Taro Pharmaceuticals U.S.A., Inc. at 1-866-923-4914.

How should I store metronidazole gel?

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

Keep metronidazole gel and all medicines out of the reach of children.

General information about the safe and effective use of metronidazole gel.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use metronidazole gel for a condition for which it was not prescribed. Do not give metronidazole gel 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 metronidazole gel that is written for health professionals.

What are the ingredients in metronidazole gel?
Active ingredient: metronidazole
Inactive ingredients: alcohol (9.3% w/w), edetate disodium, hydroxyethylcellulose, polyethylene glycol 400, propylene glycol, sorbic acid, and purified water.
Mfd. by: Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 2624761
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
For more information, call 1-866-923-4914

This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: December 2022

5201281-1222-01

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PRINCIPAL DISPLAY PANEL - 60 g Tube Carton

NDC 51672-4215-3

Metronidazole
Gel USP, 1%

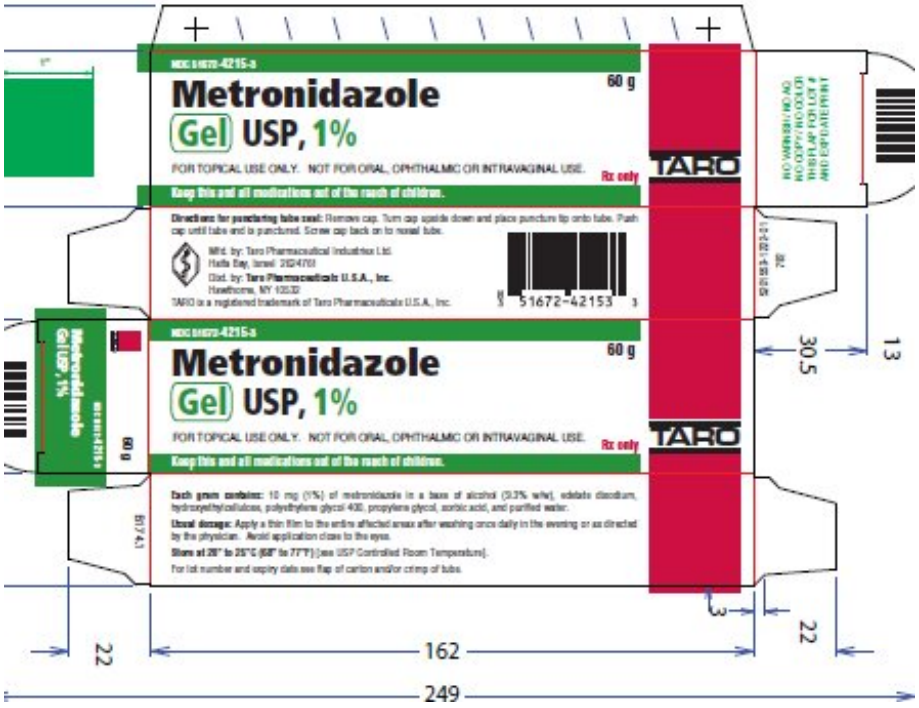
60 g

FOR TOPICAL USE ONLY. NOT FOR ORAL, OPHTHALMIC OR INTRAVAGINAL USE.

Rx only

Keep this and all medications out of the reach of children.

TARO



METRONIDAZOLE

metronidazole gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51672-4215
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Metronidazole (UNII: 140QMO216E) (Metronidazole - UNII:140QMO216E)	Metronidazole	10 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
alcohol (UNII: 3K9958V90M)	
edetate disodium (UNII: 7FLD91C86K)	
polyethylene glycol 400 (UNII: B697894SGQ)	
propylene glycol (UNII: 6DC9Q167V3)	
water (UNII: 059QF0KO0R)	
sorbic acid (UNII: X045WJ989B)	

Product Characteristics			
Color	YELLOW (clear to yellow)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51672-4215-6	1 in 1 CARTON	04/09/2019	
1		45 g in 1 TUBE; Type 0: Not a Combination Product		
2	NDC:51672-4215-3	1 in 1 CARTON	04/09/2019	
2		60 g in 1 TUBE; Type 0: Not a Combination Product		
3	NDC:51672-4215-9	1 in 1 CARTON	04/09/2019	
3		55 g in 1 BOTTLE, PUMP; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204651	04/09/2019	

Labeler - Taro Pharmaceuticals U.S.A., Inc. (145186370)

Establishment

Name	Address	ID/FEI	Business Operations
Taro Pharmaceutical Industries Ltd.		600072078	MANUFACTURE(51672-4215)

Revised: 1/2023 Taro Pharmaceuticals U.S.A., Inc.