

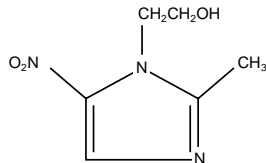
MetroLotion[®] Rx only
(metronidazole lotion)
Topical Lotion, 0.75%

FOR TOPICAL USE ONLY
(NOT FOR OPHTHALMIC USE)

DESCRIPTION

MetroLotion[®] (metronidazole lotion) Topical Lotion contains metronidazole, USP, at a concentration of 7.5 mg per gram (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide and/or lactic acid to adjust pH.

Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1H-imidazole-1-ethanol. The molecular formula is C₆H₉N₃O₃ and molecular weight is 171.16. Metronidazole is represented by the following structural formula:



CLINICAL PHARMACOLOGY

The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

Pharmacokinetics: Absorption of metronidazole after topical application of MetroLotion[®] Topical Lotion is less complete and more prolonged than after oral administration. Detectable plasma levels were found in all subjects following the administration of a 1 gram dose of MetroLotion[®] Topical Lotion (containing 7.5 mg of metronidazole) applied every morning and evening for 4 days to the faces of 8 patients. The highest concentration (96 ng/mL) seen following the morning dose on Day 5 was approximately 80 times lower than the peak concentrations produced by a single 250 mg tablet of metronidazole. The mean (± SD) AUC₀₋₂₄ after twice daily administration was 962 ± 373 ng.hr/mL.

INDICATIONS AND USAGE

MetroLotion[®] Topical Lotion is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CLINICAL STUDIES

A controlled clinical study was conducted in 144 patients with moderate to severe rosacea, in which MetroLotion[®] Topical Lotion was compared with its vehicle. Applications were made twice daily for 12 weeks during which patients were instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages, and caffeine. Patients were also provided samples of a soapless cleansing lotion and, if requested, a moisturizer. MetroLotion[®]

Topical Lotion was significantly more effective than its vehicle in mean percent reduction of inflammatory lesions associated with rosacea and in the investigators' global assessment of improvement. The results of the mean percent reduction in inflammatory lesion counts from baseline after 12 weeks of treatment and the investigators' global assessment of improvement at week 12 are presented in the following table:

| Efficacy Outcomes at Week 12 | | | | | | |
|---|-------|-----------|------------------------|----------------------|--------------------|-------|
| Mean Percent Reduction in Inflammatory Lesion Counts from Baseline | | | | | | |
| MetroLotion [®] Topical Lotion N=65 | | | Vehicle Lotion N=60 | | | |
| 55% | | | 20% | | | |
| Investigators' Global Assessment of Improvement (percent change from baseline) | | | | | | |
| | Worse | No Change | Minimal Improvement | Definite Improvement | Marked Improvement | Clear |
| MetroLotion [®] Topical Lotion N=65 | 5% | 12% | 11% | 32% | 32% | 8% |
| Vehicle Lotion N=60 | 15% | 27% | 23% | 15% | 20% | 0% |

The scale is based on the following definitions:

- Worse: Exacerbation of either erythema or quantitative assessment of papules and/or pustules.
- No Change: Condition remains the same.
- Minimal Improvement: Slight improvement in the quantitative assessment of papules and/or pustules, and/or slight improvement in erythema.
- Definite Improvement: More pronounced improvement in the quantitative assessment of papules and/or pustules, and/or more pronounced improvement in erythema.
- Marked Improvement: Obvious improvement in the quantitative assessment of papules and/or pustules, and/or obvious improvement in erythema.
- Clear: No papules or pustules and minimal residual or no erythema.

CONTRAINDICATIONS

MetroLotion[®] Topical Lotion is contraindicated in individuals with a history of hypersensitivity to metronidazole or to other ingredients of the formulation.

PRECAUTIONS

General: Topical metronidazole formulations have been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a

reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence or history of blood dyscrasia.

Information for Patients: Patients using MetroLotion® Topical Lotion should receive the following information and instructions:

1. This medication is to be used only as directed by the physician.
2. It is for external use only.
3. Avoid contact with the eyes.
4. Cleanse affected area(s) before applying this medication.
5. Patients should report any adverse reaction to their physician.

Drug Interactions: Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

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. Neither carcinogenicity nor photocarcinogenicity studies have been performed by the topical route with MetroLotion® Topical Lotion or any marketed metronidazole formulations.

In several long-term studies in mice, oral doses of approximately 198 mg/m²/day or greater (approximately 29 to 71 times the human topical dose on a mg/m² basis) were associated with an increase in lung tumors in male mice and lymphomas in female mice.

Several long-term studies by the oral route in rats have shown statistically significant increases in mammary and hepatic tumors in female rats and testicular tumors and pituitary adenomas in male rats at doses (in feed) of 1593 mg/m²/day or greater (approximately 230 to 573 times the human topical dose on a mg/m² basis). In another oral study (by gavage), mammary tumors in female rats were observed with a dose of 177 mg/m²/day (approximately 26 to 64 times the human topical dose on a mg/m² basis).

In a published study, the ultraviolet radiation-induced carcinogenesis was enhanced in albino hairless mice by intraperitoneal administration of 45 mg/m² metronidazole, as shown by a decreased latency period to the development of skin neoplasms. The concentration of metronidazole in the skin following the intraperitoneal administration was not determined. This study did not distinguish whether metronidazole must be present during the exposure to ultraviolet radiation in order to enhance tumor formation or whether metronidazole could promote tumor formation from preexisting ultraviolet radiation-initiated cells. The significance of these results in the topical use of metronidazole for the treatment of rosacea is unclear.

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

In rats, oral metronidazole at doses of 1770 mg/m²/day (approximately 255 to 637 times the human topical dose on a mg/m² basis) induced inhibition of spermatogenesis and severe testicular degeneration. In two strains of mice (ICR and CF1), conflicting results have been reported indicating either no effect or a similar effect to that reported in rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B: There are no ade-

quate and well-controlled studies with the use of MetroLotion® Topical Lotion 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. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with topically applied metronidazole than those achieved after oral administration of 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.

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

ADVERSE REACTIONS

In a controlled clinical trial, safety data from 141 patients who used MetroLotion® Topical Lotion (n=71), or the lotion vehicle (n=70), twice daily and experienced a local cutaneous adverse event which may or may not have been related to the treatments include: local allergic reaction, MetroLotion® Topical Lotion 2 (3%), lotion vehicle 0; contact dermatitis, MetroLotion® Topical Lotion 2 (3%), lotion vehicle 1 (1%); pruritus, MetroLotion® Topical Lotion 1 (1%), lotion vehicle 0; skin discomfort (burning and stinging), MetroLotion® Topical Lotion 1 (1%), lotion vehicle 2 (3%); erythema, MetroLotion® Topical Lotion 4 (6%), lotion vehicle 0; dry skin, MetroLotion® Topical Lotion 0, lotion vehicle 1 (1%); and worsening of rosacea, MetroLotion® Topical Lotion 1 (1%), lotion vehicle 7 (10%).

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.

DOSAGE AND ADMINISTRATION

Apply a thin layer to entire affected areas after washing. Use morning and evening or as directed by physician. Avoid application close to the eyes. Patients may use cosmetics after waiting for the MetroLotion® Topical Lotion to dry (not less than 5 minutes).

HOW SUPPLIED

MetroLotion® (metronidazole lotion) Topical Lotion, 0.75% is supplied in the following size:

2 fl. oz. (59 mL) plastic bottle – NDC 0299-3838-02

Storage: Store at controlled room temperature 68° to 77°F (20° - 25°C). Protect from freezing.

GALDERMA



Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA

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