Summary of Product Characteristics

1. Name of the medicinal product
METROGYL GEL
(Metronidazole Gel USP)

2. Qualitative and quantitative composition
Each gram of gel contains:
Metronidazole USP……..10 mg
Water soluble gel base……...q.s.

3. Pharmaceutical form
Gel

4. Clinical particulars

4.1 Therapeutic indications
METROGYL, 1% is indicated for the topical treatment of inflammatory lesions of rosacea.

4.2 Posology and method of administration
For topical use only, not for oral, ophthalmic, or intravaginal use.
Cleanse treated areas before the application of METROGYL.
Apply and rub in a thin film of METROGYL once daily to affected area(s).
Cosmetics may be applied after the application of METROGYL.
Safety and effectiveness in pediatric patients have not been established.

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

4.4 Special warnings and precautions for use
Avoid contact with the eyes.
Acyclovir is intended for cutaneous use only.
Safety in pregnancy has not been established.
Resistance has been reported with varicella zoster virus.
Not recommended for application to mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction
<u>Neurologic Disease</u>
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 METROGYL therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

<u>Blood Dyscrasias</u>
METROGYL is a nitroimidazole; use with care in patients with evidence of, or history of, blood dyscrasia.

Contact Dermatitis

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

Eye Irritation

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

4.6 Pregnancy and lactation

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 METROGYL.

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.

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 METROGYL.

4.7 Effects on ability to drive and use machines

METROGYL has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Because of the minimal absorption of metronidazole and consequently its insignificant plasma concentration after topical administration, the adverse experiences reported with the oral form of the drug have not been reported with Metronidazole gel. Adverse reactions reported with Metronidazole gel have been only local and mild.

System Organ Class	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Common (≥1/100, < 1/10)	Dry skin, erythema, pruritus, skin discomfort (burning, pain of skin/stinging), skin irritation, worsening of rosacea
	Unknown frequency	Contact dermatitis, swelling

		face, skin exfoliation
Nervous system disorders	Uncommon (≥ 1/ 1,000, < 1/100)	Hypothesia, paraesthesia, dysgeusia (metallic taste)
Gastrointestinal disorders	Uncommon(≥ 1/ 1,000, < 1/100)	Nausea

Watery eyes have been reported if applied too closely to this area.

4.9 Overdose
No data exists about over dosage in humans.

5. Pharmaceutical properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Chemotherapeutics for external use
ATC code: D06BX01
The etiology of rosacea is unknown although a variety of hypotheses have been reported.

5.2 Pharmacokinetic properties
Topical administration of a one-gram dose of Metonidazole 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.

5.3 Preclinical safety data
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.

6. Pharmaceutical particulars

6.1 List of excipients
Propyl Hydroxybenzoate BP
Propylene Glycol BP
Carbomer 940 NF

Edetate Disodium BP
Sodium Hydroxide BP
Methyl Hydroxybenzoate BP
Purified Water BP

6.2. Incompatibilities
Not Applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C. Do not freeze.

6.5 Nature and contents of container
- 30 g Laminated tube packed in a carton along with leaflet.
- 30 g Aluminium tube packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing Authorization Holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Division of J.B. Chemicals & Pharmaceuticals Ltd.)
Neelam center, B Wing, 4th floor, Hind cycle road,
Worli, Mumbai 400 030, INDIA

8. Marketing Authorization Number
04672/07156/NMR/2019

9. Date of First Authorization/Renewal of the Authorization
Date of First Authorization: 10/10/2019

10. Date of revision of the text
27/07/2023