Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Rozex 0.75% w/w Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 7.5mg metronidazole equivalent to metronidazole 0.75% w/w

Excipients with known effect

One gram of gel contains 30mg of propylene glycol.
Propyl parahydroxybenzoate (E216) 0.2 mg/g
Methyl parahydroxybenzoate (E218) 0.8 mg/g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel
Colourless to pale yellow homogenous gel which may turn to slightly brown colour over time.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of acute inflammatory exacerbations of rosacea.

4.2 Posology and method of administration

Posology
For topical administration only.

The average period of treatment is three to four months. The recommended duration of treatment should not be exceeded. However, if a clear benefit has been demonstrated, continued therapy for a further three to four months period may be considered by the prescribing physician depending on the severity of the condition. In clinical studies, topical metronidazole therapy for rosacea has been continued for up to 2 years. In the absence of a clear clinical improvement, therapy should be stopped.

Older people: The dosage recommended in the elderly is the same as that recommended in adults.

Paediatric population: Not recommended. Safety and efficacy have not been established.

Method of administration
A thin film of preparation is applied to the affected area twice daily. Areas to be treated should be washed with a mild cleanser before application. Patients may use non-comedogenic and non-astringent cosmetics after application of Rozex Gel.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

1. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use temporarily and to contact their physician concerning further use if necessary.
2. Contact with eyes and mucous membranes should be avoided. This product has been reported to cause tearing of the eyes.
3. Exposure of treated sites to ultraviolet or strong sunlight (sunbathing, solarium, sunlamp) should be avoided during use of metronidazole. Metronidazole transforms into inactive metabolite due to UV exposure, therefore its efficacy decreases significantly. Phototoxic side-effects haven't been reported in clinical trials in relation to metronidazole.
4. Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of, or history of, blood dyscrasias.
5. Unnecessary and prolonged use of this medication should be avoided.
6. Evidence suggests that metronidazole is carcinogenic in certain animal species. There is no evidence to date of a carcinogenic effect in human (see section 5.3).
7. Hepatotoxicity in Patients with Cockayne Syndrome: Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. Although systemic exposure after topical administration is expected to be low, caution should be taken if patients with Cockayne syndrome are treated with Rozex.
8. This product contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). This product contains 30mg propylene glycol in each gram which is equivalent to 3% w/w, it may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with systemic medication is unlikely because absorption of metronidazole following cutaneous application of Rozex Gel is low.

Nevertheless, it should be mentioned that disulfiram-like reactions has been reported in small number of patients taking metronidazole and alcohol concomitantly.

Oral metronidazole has been reported to potentiate the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known. However, very rare cases of modification of the INR values have been reported with concomitant use of Rozex and coumarin anticoagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence to date with the use of Rozex Gel in pregnant patients. In case of oral administration, metronidazole crosses the placenta barrier and rapidly enters the foetal circulation. No foetotoxicity was observed after oral metronidazole in rats or mice. However, because of animal reproduction studies are not always predictive of human response, and since oral metronidazole has been shown to be carcinogenic in some rodents, Rozex Gel should only be used in pregnancy if it is considered essential by the physician.

Breastfeeding

After oral administration, Metronidazole is excreted in breast milk in concentrations similar to those found in the plasma. Even though Metronidazole blood levels from topical administration are significantly lower than those achieved after oral administration, in nursing mothers, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following spontaneous adverse experiences have been reported, and within each system organ class, are ranked by frequency, using the following convention:

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system www.medicinesauthority.gov.mt/adrportal

Overdose

There is no human experience with overdosage of Rozex Gel. The acute oral toxicity of Rozex Gel was determined to be greater than 5g/kg (the highest dose given) in albino rats. No toxic effects were observed at this dose. This dose is equivalent to the intake of 12 30g tubes of Rozex 7.5 mg/g gel for an adult weighing 72 kg, and 2 tubes for a child weighing 12 kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Chemotherapeutics for external use
ATC code: D06BX01

Metronidazole is an antiprotozoal and antibacterial agent which is active against a wide range of pathogenic micro-organisms. The mechanisms of action of metronidazole in rosacea are unknown but available evidence suggests that the effects may be antibacterial and/or anti-inflammatory.

5.2 Pharmacokinetic properties

Metronidazole is rapidly and nearly totally absorbed after oral administration. The drug is not significantly bound to serum proteins and distributes well to all body compartments with the lowest concentration found in the fat. Metronidazole is excreted primarily in the urine as parent drug, oxidative metabolites and conjugates.

Bioavailability studies with Rozex Gel in rosacea patients treated with 7.5 mg metronidazole applied topically to the face resulted in maximum serum concentrations of 66 ng/ml which is approximately 100 times less than those attained after a single oral dose of 250 mg. In most patients at most time points after Rozex Gel application, serum concentrations of metronidazole were below the detectable limits of the assay (25 ng/ml).

5.3 Preclinical safety data

The toxicity studies conducted with Metronidazole 0.75% Topical Gel formulation demonstrate that the product is non-toxic in rats after acute oral administration of 5g /kg and produced no ocular irritation in rabbit eyes. The formulation produced no observable effects

in rabbits after dermal application of 13 mg/ kg for 90 days.

No compound-related dermal or systemic effects were observed in a 13-week cutaneous route toxicity study, in which Rozex Gel containing Metronidazole 0.75% w/w was applied daily to rabbits at doses ranging between 0.13 and 13mg/kg.

One study showed a significant enhancement of UV induced skin tumours in hairless mice treated with Metronidazole intraperitoneally (15μg per g body weight and per day for 28 weeks). Although the significance of these studies to man is not clear, patients should be advised to avoid or minimise exposure of metronidazole treated sites to sun.

Metronidazole has shown 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 injection and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200 to 1200mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 940
Disodium edetate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Propylene glycol
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Aluminium tubes with epoxy phenolic lining; pack sizes; 50 g, 40 g, 30 g and 5 g Physicians Sample.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Galderma International
Tour Europlaza
20 Avenue Andre Prothin
La Defense 4, 92927 La Defense Cedex
France

8. MARKETING AUTHORISATION NUMBER

MA 117/00602

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31st August 2007

10. DATE OF REVISION OF THE TEXT

June2026