Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rozex 7.5 mg/g Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole 0.75% w/w (7.5 mg/g)

Excipients with known effect:

Each gram of cream contains 22 mg of benzyl alcohol (E1519) and 100 mg of cetastearyl alcohol.

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Cream.
White to slightly beige shiny cream.

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 areas of skin, twice daily, morning and evening. 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 7.5 mg/g cream.

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. Contact with eyes and mucous membranes should be avoided.
2. If a reaction suggesting local irritation occurs patients should be directed to use the medication less frequently, discontinue use temporarily and to seek medical advice if necessary.

3. Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of, or history of, blood dyscrasia.
4. Unnecessary and prolonged use of this medication should be avoided.
5. 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.
6. The excipient cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis). This medicine also contains 22mg benzyl alcohol (E1519) in each gram which is equivalent to 2.2%w/w, it may cause allergic reactions and mild local irritation.
7. 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)

4.5 Interaction with other medicinal products and other forms of interactions

Interaction with systemic medication is unlikely because absorption of metronidazole following cutaneous application of Rozex 7.5 mg/g cream 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 experience to date with the use of Rozex 7.5 mg/g cream inpregnant patients. In case of oral administration, metronidazole crosses the placental barrier and rapidly enters the foetal circulation. No foetotoxicity was observed after oral 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 carcinogenic in some rodents, Rozex 7.5 mg/g cream 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 cream 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 HPRA Pharmacovigilance; Website: www.hpra.ie

4.9 Overdose

There is no human experience with overdosage of Rozex 7.5 mg/g cream. The acute oral toxicity of a gel formulation 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 cream 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.

Following a single topical 1 gram application of Rozex Cream to the face, the mean maximum serum metronidazole concentration is 32.9 ng/ml. This is less than 1% of the mean maximum serum metronidazole concentration after a single oral 250mg tablet of metronidazole.

5.3 Preclinical safety data

No evidence for a primary dermal irritation was observed in rabbits following a single 24-hour cutaneous application of Rozex 7.5 mg/g cream to abraded and non-abraded skin, under occlusion.

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

No further pre-clinical study was performed with Rozex 7.5 mg/g cream since pharmacokinetic data in humans demonstrated that the bioavailability of metronidazole following cutaneous application was similar for both the gel and cream formulations.

Oral administration of metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic oral administration in mice and rats but not in hamsters.

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

Emulsifying wax (cetostearyl alcohol and Polysorbate-60)
Benzyl alcohol (E1519)
Isopropyl palmitate
Glycerol
Sorbitol 70% (non-crystallising)
Lactic Acid and/or 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 refrigerate.

6.5 Nature and contents of container

Aluminium tubes with epoxy phenolic lining, fitted with white polypropylene screw caps; pack sizes: 30g, 40g and 50g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Replace cap tightly after use.
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 André Prothin,La Défense 4,92927 Paris,La Défense,CEDEX,France

8 MARKETING AUTHORISATION NUMBER

PA22743/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 6th March 2008

10 DATE OF REVISION OF THE TEXT

May 2022