AUSTRALIAN PRODUCT INFORMATION – ROZEX (METRONIDAZOLE) GEL

1 NAME OF THE MEDICINE

metronidazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROZEX Gel contains metronidazole 7.5 mg/g in an aqueous gel.

Excipients with known effect: Contains hydroxybenzoates**.**

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ROZEX Gel is a colourless to pale yellow viscous and homogeneous gel with no foreign matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of inflammatory papules, pustules and erythema of rosacea.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Apply and rub in a thin film of gel twice daily, morning and evening, to entire affected areas of the skin after washing.

Elderly

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

Children

Not recommended.

Areas to be treated should be cleansed before application of gel. Patients may use cosmetics after application of the product.

Significant therapeutic results should be noted within three weeks. Clinical studies have demonstrated continuing improvement over nine weeks of therapy. In the absence of a clear clinical improvement, therapy should be stopped.

The average period of treatment is usually of three to four months. The recommended duration of treatment should not be exceeded.

4.3 CONTRAINDICATIONS

Contraindicated in individuals with a history of hypersensitivity to metronidazole, hydroxybenzoates or other ingredients of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rozex has been reported to irritate the eyes (watering), therefore contact with the eyes and mucous membranes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently, discontinue use temporarily or discontinue use until further instructions. Metronidazole is a nitroimidazole compound and should be used with care in patients with evidence or a history of blood dyscrasia.

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.

Patients should be advised to avoid or minimize exposure of areas treated with topical metronidazole to sunlight or other sources of UV light (see section: carcinogenicity, mutagenicity and impairment of fertility). Unnecessary or prolonged use of this medication should be avoided, as the long-term safety of topical metronidazole is unknown.

Use in the elderly

No data available.

Paediatric use

Rozex (metronidazole 0.75%) gel has not been studied in children. Rosacea is a skin disorder which principally affects adults. Rozex is not recommended for use in children due to a lack of data on safety and efficacy.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug interactions are less likely with topical administration but should be kept in mind when Rozex is prescribed for patients who are receiving anticoagulent treatment. 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 anticoagulent effect of coumarin and warfarin resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin is not known.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral metronidazole caused hypospermatogenesis, infertility and abnormal spermatozoa in mice and rats with a NOEL in rats being about 200 times the estimated human metronidazole dose contained in the Rozex gel, based on body surface area.

Use in pregnancy – Pregnancy Category B2

There is no experience to date with the use of Rozex in pregnancy. In case of oral administration, metronidazole crosses the placental barrier and rapidly enters the foetal circulation. There is inadequate evidence of the safety of metronidazole in human pregnancy. In animal studies metronidazole was not teratogenic or embryotoxic unless administered at extremely high doses. Because there are no well-controlled studies of therapy with Rozex gel in pregnant women, Rozex gel should not be used during pregnancy.

Use in lactation.

After oral administration metronidazole is excreted in breast milk in concentrations similar to those found in the plasma. Metronidazole blood levels from topical application are significantly lower than those achieved after oral metronidazole. 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

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (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 Rozex. Adverse reactions reported with Rozex include eye irritation (watering) if the gel is applied too closely to this area, transient redness, mild dryness, burning and skin irritation. None of the side effects exceeded an incidence of 2% of patients.

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

Very common (≥1/10)
Common (≥1/100, < 1/10)
Uncommon (≥ 1/ 1,000, < 1/100)
Rare (≥1/10,000, < 1/1,000)
Very rare (<1/10,000), including isolated reports

Skin and subcutaneous tissue disorders

Common: dry skin, erythema, pruritus, skin discomfort (burning, pain of skin/stinging), skin irritation, worsening of rosacea.

Unknown frequency: contact dermatitis, skin exfoliation, swelling face (*), seborrhoea, skin infection, sunburn, urticaria

Nervous System disorders:

Uncommon: hypoesthesia, paraesthesia, dysgeusia (metallic taste), dizziness

Gastrointestinal disorders:

Uncommon: nausea, gastritis

Respiratory System disorders:

Uncommon: bronchitis, rhinitis

Endocrine disorders:

Rare: hypothyroidism

Musculoskeletal:

Rare: bursitis, myalgia, osteoporosis.

Special senses:

Rare: conjunctivitis

Body as a whole:

Uncommon: abscess, accidental injury, flu symptom, infection

Post-marketing experience

The following non-serious adverse experiences have been reported since 1995: contact dermatitis/allergic reaction; skin exfoliation, swelling face, local irritation, erythema, pruritis, burning, dryness, tightness, discomfort, rash; hyperpigmentation, pigmentation disorders, hypertrichosis; facial oedema; eyelid oedema; treatment failure (worsening of rosacea); watery eyes; metallic taste; tingling or numbness in the extremities; nausea; other (zoster lesion, pustules on the nose and vesicular bullous eruptions). The causal relationship with topical metronidazole has not been unequivocally established for these adverse experiences.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no human experience with overdosage of Rozex. The acute oral toxicity of the Rozex formulation was determined to be greater than 5g/kg (the highest dose given) in albino rats.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Metronidazole is an antiprotozoal (trichomoniasis, amoebiasis, giardiasis) and anaerobic antibacterial agent. However, the mechanisms by which Rozex acts in reducing inflammatory lesions of rosacea are unknown, but may include an antibacterial and / or anti-inflammatory effect.

Clinical trials

5.2 PHARMACOKINETIC PROPERTIES

The absorption of metronidazole following topical administration is negligible. Studies on the topical administration of 1 gram of Rozex (7.5 mg of metronidazole) to the face of 10 rosacea patients showed a maximum serum concentration of 66 nanogram/mL in one patient. This concentration is approximately 100 times less than concentrations afforded by a single 250 mg tablet. The serum metronidazole concentrations were below the detectable limits of the assay at the majority of time points in all patients. Three of the patients had no detectable serum concentrations of metronidazole at any time point. The mean dose of gel applied during clinical studies was 600 mg, which represents 4.5 mg of metronidazole per application. Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Metronidazole has shown evidence of mutagenic activity in several bacterial 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 has been found in human lymphocyte cultures. The benefit/risk ratio should therefore be carefully assessed in each case particularly in relation to the severity of the disease and the age of the patient.

Carcinogenicity

Animal studies with oral metronidazole showed increased incidences of tumour in the lung, liver, testes, reticulum, mammary gland and pituitary gland in certain rodent species. Evidence of photocarcinogenicity of metronidazole has also been reported in mice. Although there is no evidence to date of a carcinogenic effect in humans it is prudent to avoid unnecessary and prolonged use of Rozex gel and to avoid or to minimise exposure of sites treated with Rozex gel to the sun.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Methyl and propyl hydroxybenzoates, propylene glycol, carbomer 940, disodium edetate, sodium hydroxide and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. [optional]

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

Gel : 2g, 5g, 15g, 30g and 50g tubes. Not all pack sized may be marketed.

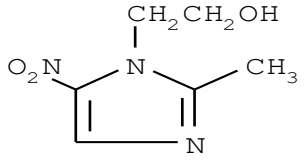
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Metronidazole is 1- (2 hydroxyethyl)-2-methyl-5-nitroimidazole. It is a white to brownish crystalline powder that is soluble in water.

Chemical structure



$C_6H_9N_3O_3$; *Mr* 171.16

CAS number

443-48-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Galderma Australia Pty Ltd
Level 18, 1 Denison Street
North Sydney NSW 2060

Call 1800 800 765 (Australia)

0800 174 104 (New Zealand)

9 DATE OF FIRST APPROVAL

08 February 1993

10 DATE OF REVISION

29 August 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Re-format into the TGA preferred format.
8	Change in Australian sponsor address due to office move.