AUSTRALIAN PRODUCT INFORMATION – ROZEX (METRONIDAZOLE) CREAM

1 NAME OF THE MEDICINE

Metronidazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rozex cream contains 0.75% w/w metronidazole as the active ingredient in an oil-in-water cream base.

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

3 PHARMACEUTICAL FORM

White to beige shiny cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rozex cream is indicated for the treatment inflammatory papules and pustules of rosacea.

4.2 DOSE AND METHOD OF ADMINISTRATION

Rozex cream should be applied in a thin layer to the affected areas of the 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 cream. The dosage does not need to be adjusted for elderly patients. Safety and effectiveness in paediatric patients have not been established. Rozex cream is not recommended for use in children.

The average period of treatment is three to four months. The recommended duration of treatment should not be exceeded. 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 upon the severity of the condition. Clinical experience with Rozex cream over prolonged periods is limited at present. Patients should be monitored to ensure that clinical benefit continues and that no local or systemic events occur. In the absence of a clear clinical improvement therapy should be stopped.

Rozex cream should not be used in or close to the eyes.

The use of a sunscreen is recommended when exposure to sunlight cannot be avoided.

4.3 CONTRAINDICATIONS

Rozex cream is contraindicated in individuals with a history of hypersensitivity to metronidazole or other ingredients of the formulation.

Metronidazole must not be used 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rozex has been reported to irritate the eyes (watering), therefore contact with the eyes should be avoided, as well as with mucous membranes. 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 transforms into inactive metabolite due to UV exposure, therefore its efficacy decreases significantly. Phototoxic side-effects haven't been reported in clinical trial in relation to metronidazole.

Metronidazole is a nitroimidazole compound and should be used with care in patients with evidence or a history of blood dyscrasia. Patients should be advised to avoid or minimise exposure of areas treated with topical metronidazole to sunlight or other sources of UV light (see Section 5.3 Preclinical safety data: Genotoxicity and Carcinogenicity; and Section 4.6: Effects on 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 cream has not been studied in children. Rosacea is a skin disorder which principally affects adults.

Rozex cream 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

Interaction with systemic medication is unlikely because absorption of metronidazole following cutaneous application of Rozex cream is low. Nevertheless, it should be mentioned that a disulfiram-like reaction has been reported in a small number of patients taking oral metronidazole and alcohol concomitantly. Oral metronidazole has also been reported to potentiate the effect of warfarin and other coumarin anticoagulants resulting in a prolongation of prothrombin time. However, 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 cream, based on body surface area.

Use in pregnancy – Pregnancy Category B2

The potential adverse effects of Rozex cream on pregnancy have not been determined however oral metronidazole is known to cross the placental barrier and enter the foetal circulation rapidly. There is no conclusive evidence of fetotoxicity or teratogenicity in animal studies with

metronidazole nor has clinical experience to date with the use of metronidazole in pregnant women revealed evidence of a fetotoxic or teratogenic effect of the drug. Because there are no well controlled studies of therapy with Rozex cream in pregnant women, Rozex cream 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)

Table 1. Adverse events with incidence >1%, reported by patients treated with Rozex cream, Rozex cream vehicle and Rozex gel during controlled clinical trials. With the exception of the safety studies, these adverse events were not necessarily drug related.

	Rozex **cream** (n= 118)	Rozex cream **vehicle** (n= 72)	Rozex **gel** (n=53)
Body as a whole			
Abdominal pain	-	1.4%	-
Abscess	-	-	1.8%
Accidental Injury	-	1.4%	1.8%
Back pain	-	2.8%	-
Flu syndrome	11.0%	18.6%	7.4%
Headache	2.5%	2.8%	-
Infection	-	-	1.8%
Pain	-	1.4%	-
Surgic./medic/proc.	2.5%	-	-
Cardiovascular			
Angina pectoris	-	1.4%	-
Myocardial infarction	-	1.4%	-
Digestive system			
Constipation	-	1.4%	-
Gastritis	-	-	1.8%
Gingivitis	-	1.4%	-
Tooth disorder	2.5%	1.4%	-
Endocrine disorders			
Hypothyroidism	-	-	1.4%
Musculoskeletal			
Bursitis	-	-	1.8%
Myalgia	-	-	1.8%
Osteoporosis	-	-	1.8%
Central Nervous System			
Dizziness	-	-	1.8%
Hypertension	-	1.4%	-
Hypertonia	-	-	1.8%
Insomnia	-	1.4%	-
Respiratory System			
Bronchitis	1.7%	4.2%	1.8%
Increased cough	-	1.4%	-
Pharyngitis	2.5%	-	-
Rhinitis	3.4%	2.8%	3.7%
Sinusitis	4.2%	1.4%	-
Skin & Appendage			

	Rozex **cream** (n= 118)	Rozex cream **vehicle** (n= 72)	Rozex **gel** (n=53)
Contact dermatitis	2.8%	-	-
Erythema	-	1.4%	-
Psoriasis	-	-	1.8%
Rosacea worsening	3.4%	2.8%	9.4%
Seborrhoea	-	-	3.7%
Skin carcinoma	1.4%	-	-
Skin discomfort	1.7%	-	-
Skin infection	1.69%	-	3.7%
Skin irritation	1.7%	-	3.7%
Sunburn	-	-	1.8%
Urticaria	-	-	1.8%
Safety studies			
burning	8.4%	13.0%	6.1%
dryness	20.3%	23.2%	28.5%
itching	9.3%	20.2%	16.3%
stinging	11.0%	8.6%	8.2%
Special Senses			
Conjunctivitis	-	1.4%	1.4%
Urogenital System			
Urinary Tract Infection		1.4%	
Vaginitis		1.4%	

The total number of adverse effects occurred in less than 3% of patients. Of the eleven patients who discontinued a study prematurely because of a dermatologic adverse event, 2.5% were in the cream treatment group and 6.7% in the gel treatment group.

Post-marketing experience

The following non-serious adverse experiences have been reported since Rozex cream was first marketed in 1995: contact dermatitis/allergic reaction; skin exfoliation, swelling face, local irritation, erythema, pruritus, 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 cream.

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.

Clinical trials

One multicentre randomised, double-blind, placebo-controlled clinical study was conducted to evaluate Rozex Cream for the treatment of rosacea. All the patients included in the trial had moderate to severe (Stage 2) rosacea. The prescribed therapy was applied daily for 12 weeks with follow up at weeks 3, 6, 9 and 12. The results are tabulated below.

Table 2. Inflammatory lesion counts in the ITT population at baseline and endpoint.

Visit	Treatment Group	No. patients	Median lesion count	p=value
Baseline	Metronidazole cream Vehicle	71 72	13.0 12.0	n.s.
Week 12	Metronidazole cream Vehicle	63 65	4.0 7.0	p=0.015
Endpoint (last observed visit)	Metronidazole cream Vehicle	69 69	4.0 8.0	p=0.009

There were no significant differences between the treatment groups in the reduction of erythema or telangiectasis. For a subgroup within the Rozex cream group who had dry skin there was a significant reduction in erythema (59.6% vs 30.4%, p=0.05).

In another randomised single-blind multicentre study (n=100) in which the gel and cream formulations were compared, there were no significant differences in lesion counts or global assessment of improvement at weeks 4, 8 and 12. All patients recruited to the study had moderate to severe stage 2 rosacea. The percent reduction in mean lesion count from baseline to week 12 was 61.3% (MZ cream) vs 63.5% (MZ gel), p= n.s.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single topical 1-gram application of Rozex cream to the face of twelve normal human subjects, a mean maximum serum metronidazole concentration of 32.9ng.ml^{-1} was reported (range: 14.8 to 54.4 ng.ml^{-1}). This is less than 0.5% of the mean maximum metronidazole concentration reported in the same subjects administered a single oral 250 mg tablet of metronidazole (mean C_{max} = 7248 ng.ml^{-1}, range:4270 to 13970 ng.ml^{-1}). The T_{lag} and T_{max} for metronidazole after topical administration of the cream formulation were significantly ($p<0.05$) prolonged when compared with oral administration. In comparison to the oral tablet the mean T_{max} for the topical formulation occurred 7.0 hours later (95% confidence interval: 2.7 to 11.3 hours).

Distribution

The extent of exposure (area under the curve (AUC.)) from a 1-gram application of metronidazole administered topically was 1.2% of the AUC of a single oral 250 mg metronidazole dose (mean = 912.7 ng.hr ml^{-1} and approximately 67207 ng.hr ml^{-1} and respectively).

Metabolism

The hydroxymetabolite (2-hydroxymethylmetronidazole) C_{max} after the 250 mg oral dose ranged from 626 to 1788 ng. ml^{-1} and peaked between 4 and 12 hours. Following topical application of Rozex cream the hydroxymetabolite serum concentrations were below the quantifiable limit of the assay (<9.6 ng. ml^{-1}) at the majority of time points. The hydroxymetabolite C_{max} after topical administration of the cream ranged from below the quantifiable limit to 17.6 $ng.ml^{-1}$.

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 cream and to avoid or to minimise exposure of sites treated with Rozex cream to the sun.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

benzyl alcohol, isopropyl palmitate, glycerol, sorbitol 70% (non-crystallising), emulsifying wax, lactic acid or sodium hydroxide solutions to adjust pH 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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

3g, 5g, 15g, 30g and 50g tubes. Not all pack sizes may be marketed.

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6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

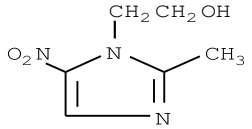
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name

2-methyl-5-nitroimidazole-1-ethanol

Chemical structure



$C_6H_9N_3O_3$; *Mr* 171.16

Molecular formula

$C_6H_9N_3O_3$

Molecular weight

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

27 February 2002

10 DATE OF REVISION

07 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat to TGA format
8	Update to the Sponsor address due to office move.
4.3	Addition of Cockayne syndrome in Contraindications