New Zealand Datasheet

1 PRODUCT NAME
ROZEX® CREAM

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Metronidazole 7.5 mg/g

3 PHARMACEUTICAL FORM
Contains 0.75% w/w metronidazole as the active ingredient in an oil-in-water cream base containing

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
ROZEX CREAM is indicated for the treatment inflammatory papules and pustules of rosacea.

4.2 Dosage 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 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
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 hepatoxicity/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 CREAM 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 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 Children
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.

4.5 Interaction with other medicines and other forms of interaction
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
Use in 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 metonidazole 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.

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.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects

Table: Adverse events with incidence >1%, reported by patients treated with ROZEX (*Metronidazole 0.75%)* CREAM, ROZEX CREAM vehicle and ROZEX (*Metronidazole 0.75%)* GEL during controlled clinical trials. With the exception of the safety studies, these adverse events were not necessarily drug related.

	ROZEX (*Metronidazole 0.75%)* **CREAM** (n= 118)	ROZEX CREAM **vehicle** (n= 72)	ROZEX (*Metronidazole 0.75%)* **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%	-

	ROZEX (Metronidazole 0.75%) **CREAM** (n= 118)	ROZEX CREAM **vehicle** (n= 72)	ROZEX (Metronidazole 0.75%) **GEL** (n=53)
Skin & Appendage			
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, 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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/ .

4.9 Overdose
There is no human experience with overdosage of ROZEX CREAM.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Chemotherapeutics for external use - ATC code: D06BX01

Metronidazole is an antiprotozoal (trichomoniasis, amoebiasis, giardiasis) and anaerobic antibacterial agent. However, the mechanisms by which ROZEX CREAM acts in reducing inflammatory lesions of rosacea are unknown.

Clinical Studies

One multicentre randomised, double-blind, placebo-controlled clinical study was conducted to evaluate ROZEX CREAM for the treatment of rosacea. All of 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 1: 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

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).

The hydroxymetabolite (2-hydroxymethylmetronidazole) C_{max} after the 250 mg oral dose ranged from 626 to 1788 ng. ml^{-1} and peaked betweem 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}.

The extent of exposure [area under the curve (AUC.)] from a 1gram application of metronidazole administered topically was 1.2% of the AUC.of a single oral 250mg

metronidazole dose (mean = 912.7 ng.hr ml^{-1} and approximately 67207 ng.hr ml^{-1} and respectively).

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 Cream to abraded and non-abraded skin, under occlusion.

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 1200 mg/day of oral metronidazole for 1 to 24 months. However, the preponderance of evidence from these studies suggests that although metronidazole has a potential for producing mutations, this should not occur in well oxygenated mammalian cells, i.e., under normal aerobic conditions.

The carcinogenicity of metronidazole by the oral route of administration has been evaluated in rats, mice and hamsters. These studies showed that oral metronidazole caused an increased incidence of pulmonary tumours in mice and possibly other tumours, including liver tumours, in the rat. Conversely, two lifetime studies in hamsters produced negative results. Moreover, one study showed a significant enhancement of UV-induced skin tumours in hairless mice treated with metronidazole intraperitoneally (15 µg per g body weight and per day for 28 weeks).

Although the significance of these results to the cutaneous use of metronidazole for the treatment of rosacea is unclear, patients should be advised to avoid or minimise exposure of metronidazole cream-treated sites to sun. After several decades of systemic use, no evidence has been published to suggest that metronidazole is associated with carcinogenic potential in humans.

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

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C (room temperature). Do not refrigerate.

6.5 Nature and contents of container

Cream: Aluminium tubes of 5 g, 30 g.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Sponsor and distributor in New Zealand
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph (09) 918 5100
Fax (09) 918 5101

For:
Galderma Australia Pty Ltd
Suite 4, 13B Narabang Way,
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9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION OF THE TEXT

19 December 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Addition of Cockayne syndrome in Contraindiations
4.8 & 4.9	Update ADR information to align with the current New Zealand data sheet template