PRODUCT INFORMATION

# ROZEX CREAM
*(metronidazole)*

**NAME OFTHE MEDICINE:** ROZEX cream (metronidazole 7.5 mg/g)

**AAN:** Metronidazole

**Chemical Name:** 2-methyl-5-nitroimidazole-1-ethanol

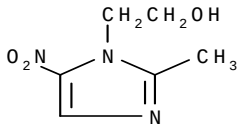
**Molecular formula:** $C_6H_9N_3O_3$

**CAS Registry Number:** 443-48-1

**Molecular weight:** 171.16

**Chemical class:** Antiprotozoal and antibacterial agent.

**Chemical Structure:**




$C_6H_9N_3O_3$; *M*r 171.16

## DESCRIPTION
Contains 0.75% w/w metronidazole as the active ingredient in an oil-in-water cream base containing benzyl alcohol, isopropyl palmitate, glycerol, sorbitol 70% (non-crystallising), emulsifying wax, lactic acid or sodium hydroxide solutions to adjust pH and purified water.

## PHARMACOLOGY
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.

*Pharmacokinetics*.
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).

**CLINICAL TRIALS**
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<br>Vehicle | 71<br>72 | 13.0<br>12.0 | n.s. |
| Week 12 | Metronidazole cream<br>Vehicle | 63<br>65 | 4.0<br>7.0 | p=0.015 |
| Endpoint<br>(last observed visit) | Metronidazole cream<br>Vehicle | 69<br>69 | 4.0<br>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.

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

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

**PRECAUTIONS**
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 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.

**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 (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.

**Use in children**
Rozex (metronidazole 0.75%) 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

**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.

**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.

**INTERACTIONS WITH OTHER MEDICINES**
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.

## ADVERSE 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 **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** | | | |
| 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.

**DOSAGE AND 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 should not be used in or close to the eyes.

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

**OVERDOSAGE**

There is no human experience with overdosage of Rozex cream.

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

**PRESENTATION AND STORAGE CONDITIONS**

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

Store below 25°C. Do not refrigerate.

AUST R 72393

**NAME AND ADDRESS OF SPONSOR**

Galderma Australia
13b Narabang Way
Belrose NSW 2085
Call 1800 800 765 (Australia)
0800 174 104 (New Zealand)

**POISONS SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

27th February 2002.

**DATE OF MOST RECENT AMENDMENT**

20 March 2017