

## PRODUCT INFORMATION

### **ROZEX GEL** (metronidazole)

**NAME OF THE MEDICINE** ROZEX GEL (metronidazole 7.5 mg/g)

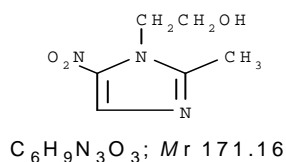
**Common name** Metronidazole

**Molecular formula** C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>

**Molecular weight** 171.2

**Chemical class** Antiprotozoal and antibacterial agent.

#### **Chemical structure**



#### **DESCRIPTION**

Metronidazole 7.5 mg/g in an aqueous gel containing methyl and propyl hydroxybenzoates, propylene glycol, carbomer 940, disodium edetate, sodium hydroxide and purified water.

Metronidazole is 1- (2 hydroxyethyl)-2-methyl-5-nitroimidazole. It is a white to brownish crystalline powder that is soluble in 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, but may include an antibacterial and / or anti-inflammatory effect.

*Pharmacokinetics.* 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.

#### **INDICATIONS**

Treatment of inflammatory papules, pustules and erythema of rosacea.

## **CONTRAINDICATIONS**

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

## **PRECAUTIONS**

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.

### **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 (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.

### **Use in children**

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.

### **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.

### **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**

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

### **ADVERSE 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$ ,  $< 1/10$ )

Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ )

Rare ( $\geq 1/10,000$ ,  $< 1/1,000$ )

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 (\*), seborrhea, 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.

**DOSAGE AND 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.

**OVERDOSAGE**

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 Poison Information Centre on 13 11 26 (Australia).

**PRESENTATION AND STORAGE CONDITIONS**

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

Store below 25°C

AUST R 15211

**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)**

08/02/93

**DATE OF MOST RECENT AMENDMENT**

20 March 2017