New Zealand Datasheet

1 PRODUCT NAME
ROZEX GEL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Metronidazole 7.5 mg/g

3 PHARMACEUTICAL FORM
Colourless to pale yellow homogeneous gel, which may turn to slightly brown colour over time.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of inflammatory papules, pustules and erythema of rosacea.

4.2 Dosage 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 GEL 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 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 Children
ROZEX GEL has not been studied in children. Rosacea is a skin disorder which principally affects adults. ROZEX GEL 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
Drug interactions are less likely with topical administration but should be kept in mind when ROZEX GEL 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
(Category B2)
There is no experience to date with the use of ROZEX GEL 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.

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 GEL, based on body surface area.

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

4.8 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 GEL. Adverse reactions reported with ROZEX GEL 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 (*), seborrhea, skin infection, sunburn, urticarial

Nervous System disorders:
Uncommon: hypoesthesia, paraesthesia, dysgeusia (metallic taste), dizziness

Gastrointestinal disorders:
Uncommon: nausea, gastritis

Respiratory System disorders:
Uncommon: bronchitis, rhintis

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 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://nzphvc.otago.ac.nz/reporting/.

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

For 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 GEL acts in reducing inflammatory lesions of rosacea are unknown, but may include an antibacterial and / or anti-inflammatory effect.

5.2 Pharmacokinetic properties

The absorption of metronidazole following topical administration is negligible. Studies on the topical administration of 1 gram of ROZEX GEL (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

No evidence for a primary dermal irritation was observed in rabbits following a single 24-hour cutaneous application of Rozex to abraded and non-abraded skin, under occlusion. Metronidazole has shown mutagenic activity in several in vitro bacterial assay systems. In vivo, metronidazole did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of mice treated either intraperitoneally or orally at doses up to 1500 and 2000 mg.kg-1 respectively, treatments at which clear signs of clinical toxicity were apparent. In the induction of chromosome aberrations study in cultured human peripheral blood lymphocytes, metronidazole did not induce aberrations in cultured human peripheral blood lymphocytes when tested to a maximum concentration of 10 mM in the absence and presence of metabolic activation. The carcinogenicity of metronidazole by the oral route of administration has been evaluated in rats, mice and hamsters. These studies showed that oral metronidazole causes an increased incidence of pulmonary tumours in mice and possibly other tumours, including liver tumours, in the rat. Conversely, two lifetime carcinogenicity 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). The significance of these results to the cutaneous use of metronidazole for the treatment of rosacea is unclear and after several decades of systemic use no evidence has been published to suggest that metronidazole is associated with a carcinogenic potential in humans. Although the significance of this to man is not clear, patients should be advised to avoid or minimise exposure to metronidazole lotion / cream/ gel treated sites to excessive sunlight or artificial sources of UV irradiation such as sunbeds.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 940, propylene glycol, disodium edetate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium hydroxide 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)

6.5 Nature and contents of container
Gel: Aluminium tubes of 3 g, 5 g, 15 g, 30 g, 50 g. Not all pack sizes may be marketed.

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

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9 DATE OF FIRST APPROVAL
25 July 1991

10 DATE OF REVISION OF THE TEXT
19 November 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8.0	Correction of sponsor details