1. NAME OF THE MEDICINAL PRODUCT

Rozex Gel.

2. COMPOSITION

Rozex Gel contains metronidazole (INN) at a concentration of 7.5 mg per gram (0.75%) in a gel vehicle consisting of Carbomer 940, propylene glycol, disodium edetate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium hydroxide and purified water.

3. PHARMACEUTICAL FORM

Rozex Gel is an aqueous gel for cutaneous use only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rozex Gel is indicated for cutaneous application in the treatment of rosacea.

4.2 Dosage and method of administration

Rozex Gel 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 Gel**. The dosage does not need to be adjusted for elderly patients. Safety and effectiveness in pediatric patients have not been established.

The average period of treatment is three to four months. 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. In clinical studies, topical metronidazole therapy for rosacea has been continued for up to 2 years. In the absence of a clear clinical improvement, therapy should be stopped.

4.3 Contra-indications

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

4.4 Special Warnings and Special Precautions for Use

Contact with eyes and mucous membranes should be avoided. If irritation does occur the patient should be advised to use **Rozex Gel** less frequently or to stop usage temporarily and to seek medical advice if necessary.

Metronidazole is a nitro imidazole and should be used with caution in patients with an evidence of, or history of blood dyscrasia.

Unnecessary and prolonged use of this medication should be avoided. Evidence suggests that metronidazole is carcinogenic in certain animal species. There is no evidence to date of a carcinogenic effect in humans (**see Section Preclinical Safety Data**).

4.5 Interaction with other medications and other forms of interaction

Interaction with systemic medication is unlikely because absorption of metronidazole following cutaneous application of **Rozex Gel** 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 Pregnancy and Lactation

There has been no experience to date with the use of **Rozex Gel** in pregnant patients. Metronidazole crosses the placental barrier and enters foetal circulation rapidly. No foetotoxicity was observed after oral metronidazole in either rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with cutaneous application of **Rozex Gel** than those achieved after oral metronidazole, in nursing mothers, a decision should be made whether 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

Based upon the pharmacodynamic profile and clinical experience, performance related to driving and using machines should not to be affected.

4.8 Undesirable effects

Only local and mild adverse events have been detected with the topical use of **Rozex Gel**. They mainly consisted of skin discomfort (burning and stinging), erythema, skin irritation, pruritus and worsening of rosacea. All individual events occured in less than 3% of patients.

4.9 Overdose

No data exists about overdosage in humans. Acute oral toxicity studies with a topical formulation containing 0.75% w/w metronidazole in rats have shown no toxic action with doses of up to 5 g of finished product per kilogram body weight, the highest dose used. This dose is equivalent to the oral intake of 12 tubes of **Rozex Gel** for an adult weighing 72 kg, and 2 tubes for a child weighing 12 kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metronidazole has an antibacterial and antiprotozoal effect against a large number of pathogenic micro-organisms. The mechanism of action of metronidazole in rosacea is not known but pharmacological data available suggests that the activity is based on an antibacterial and / or anti-inflammatory action.

5.2 Pharmacokinetic properties

Following a single, topical 1 gram application of **Rozex Gel** to the face of twelve normal human subjects, a mean maximum serum metronidazole concentration of 29.1 $ng.ml^{-1}$ was reported (range: 19.1 to 42.7 $ng.ml^{-1}$). This is less than 0.5% of the mean maximum serum metronidazole concentration reported in the same subjects administered a single, oral 250 mg tablet of metronidazole (mean Cmax = 7248 $ng.ml^{-1}$, range: 4270 to 13970 $ng.ml^{-1}$). The Tlag and Tmax for metronidazole after topical administration the gel formulation were significantly ($p < 0.05$) prolonged as compared with oral administration. In relation to the oral tablet, the mean Tmax occurred 7.0 hours (95% confidence interval: 2.7 to 11.3 hours) later with the gel formulation.

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 Gel** 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 gel ranged from below the quantifiable limit to 17.6 $ng.ml^{-1}$.

The extent of exposure [(area under the curve (A.U.C.)] from a 1 gram application of metronidazole administered topically (**Rozex Gel**) was 1.2% of the A.U.C. of a single oral 250 mg metronidazole dose (mean = 912.7 ng.hr . ml^{-1} and approximately 67207 $ng.hr.ml^{-1}$ 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 Gel** 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 tumors in mice and possibly other tumors, including liver tumors, 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 beadvised to avoid or minimise exposure to metronidazole lotion treated sites to excessive sunlight or artificial sources of UV irradiation such as sunbeds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rozex Gel is an aqueous gel vehicle consisting of Carbomer 940, propylene glycol, disodium edetate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, odium hydroxide and purified water

6.2 Incompatibilities

None known.

6.3 Shelf-life

Three years.

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C.
Keep out of reach of children. Ovoid freezing during transport and storage.

6.5 Nature and contents of container

Rozex Gel is packaged in 30 g collapsible aluminium tubes coated internally with an epoxy-phenolic resin and fitted with white polypropylene screw caps.

6.6 Instructions for use/handling

Squeeze the tube gently at its base to place a quantity of gel on the fingertips sufficient to cover the affected areas. Replace the cap tightly after use. **Rozex Gel** is not for oral use.