Rozex®
metronidazole
TOPICAL GEL

COMPOSITION
ROZEX Gel contains metronidazole 0.75% as the active ingredient in a single phase, colourless to pale yellow, viscous and homogenous gel containing purified water, methylparaben, propylparaben, propylene glycol, carbomer 940, disodium edetate and sodium hydroxide.

PHARMACEUTICAL FORM
Colourless to pale yellow homogeneous gel, which may turn to slightly brown colour over time.
ROZEX Gel is for cutaneous use only.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics: 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 suggest that the activity is based on an antibacterial and / or anti-inflammatory action.
Pharmacokinetics: Following a single, topical 7.5mg application of ROZEX Gel to the face of ten rosacea patients (aged 36 to 70 years), the maximum metronidazole serum concentration (C_{max}) ranged from below detectable limits (n =3) to 66 ng/mL, with a mean in the seven patients with quantifiable serum concentrations of 40.6 ng/mL. The mean C_{max} following 30 mg oral dose of a 5 mg/mL metronidazole solution administered in the same patients was 850 ng/mL. When corrected for the dose difference between formulations, the estimated C_{max} for the oral solution is 212 ng/mL. The difference in C_{max} between the two formulations was significant ($p < 0.01$). The time of the maximum serum concentration (T_{max}) was also found to be significantly ($p < 0.01$) different between the two formulations. The median Tmax was 5.98 hours with the topical gel as compared to 0.97 hours with the oral solution. An accurate estimation of the area under the curve (AUC) following the topical 0.75% gel was not possible because of undetectable serum concentrations at the majority time points. The mean (%CV) AUC following the oral solution was 7476.1 (35.8%) ng.hr/mL. Serum metronidazole and the hydroxymethyl metabolite (2-hydroxymethylmetronidazole) were below the detectable limits of the assay (< 25 ng/mL) at the majority of time points in all patients after topical administration.
Carcinogenesis: Tumorigenicity in Rodents. Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. These studies have not been conducted with 0.75% metronidazole gel which would result in significantly lower systemic blood levels than oral formulations.
Mutagenicity Studies: Although metronidazole has shown mutagenic activity in a number of in vitro bacterial assay systems, studies in mammals (in vivo) have failed to demonstrate a potential for genetic damage.

INDICATIONS AND USAGE
ROZEX Gel is indicated for topical application in the treatment of inflammatory papules, pustules and erythema of rosacea.

CONTRA-INDICATIONS
Rozex Gel is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other Ingredients of the formulation.

UNDESIRABLE EFFECTS
When 0.75% metronidazole gel was administered to rosacea patients during the clinical trials only infrequent, irritant-type local adverse events were attributable to the drug. No correlations were made between these events and patient-demographic, drug-disease, or drug-drug interactions. No systemic adverse events or abnormal clinical laboratory data were attributable to metronidazole gel. Since topically applied 0.75% metronidazole gel was shown to be minimally absorbed, systemic events are minimised. The adverse event occurrence rates were of 1.8% for irritation, dryness or redness effect and of 0.9% for watery (tearing) eyes or burning effect. All individual events occurred in less than 2% of patients. Additionally, results from patch testing in humans showed no evidence of irritancy, sensitisation, phototoxicity or photoallergic reactions when topical metronidazole was applied to non-facial areas of normal volunteers.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
General: ROZEX has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritations occurs, patients should be directed to use the medication less frequently, discontinue use temporarily or discontinue use until further Instructions. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.
Pediatric use: The use of ROZEX is not recommended in children.

PREGNANCY AND LACTATION
Pregnancy: There has been no experience to date with the use of ROZEX in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was oberved after oral metronidazole in 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.

Galderma Laboratories

Product code: MOCK UP
Product description: ROZEX GEL
Market: EX2
Article: Leaflet
Flat size: 180x315
Fold size: 180x26,25
Font size: 11 pt
Pharmacode: TBD

GRAPHIC DESIGNER: Bérangère BLANCO
INDUSTRIALIZATION DEPARTMENT
LABORATOIRES GALDERMA - Z.I. Galderma - 74540 ALBY-SUR-CHÉRAN - FRANCE
GALDERMA EST. 1981

Printing Colors
PMS 432U
DIELINES

Nursing mothers: After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though ROZEX blood levels are significantly lower than those achieved after oral metronidazole, 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.

INTERACTION WITH OTHER MEDICATIONS AND OTHER FORMS OF INTERACTION

No drug-drug or drug-disease interactions were observed in any subjects of the population. The well documented disulfiram-like effect of metronidazole with alcohol consumption was not reported in any of the patients treated with topical metronidazole. This is noteworthy since patients were not restricted from alcohol consumption. Drug-drug and drug-disease interactions are expected to be minimised with the use of topical metronidazole since this low dose affords only minimal serum concentrations but should be kept in mind when Metronidazole topical gel is prescribed for patients who are receiving anticoagulant treatments. 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.

DOSAGE AND ADMINISTRATION

Apply and rub in a thin film of ROZEX twice daily, morning and evening, to the entire affected areas after washing. Significant therapeutic results should be noticed within three weeks. Clinical studies have demonstrated continuing improvement through nine weeks of therapy. Areas to be treated should be cleansed before application of ROZEX. Patients may use cosmetics after application of ROZEX.

OVERDOSAGE

There is no specific antidote for metronidazole overdosage. Therefore, management of the patient should consist of symptomatic and supportive therapy. Due to the minimal systemic blood levels of metronidazole afforded by topical application of the gel, systemic drug overdosage is unlikely. Furthermore, acute oral toxicity studies in rats have shown no toxic action with doses of up to 5g of the gel per kilogram body weight which represents the highest dose used.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

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

SHELF LIFE

This medicine should not be used after the expiry date (Exp. Date) shown on the pack.

STORAGE

Store ROZEX GEL at room temperature (not exceeding 30°C).
Keep out of the reach of children.

CONTAINER

ROZEX Gel is packaged in 15g and 30g collapsible aluminium tubes coated internally with an epoxy-phenolic resin and fitted with white polypropylene screw caps. Not all pack sizes may be marketed.

CAUTION

Do not dispense without prescription.

Manufactured by:
Laboratoires Galderma
ZI Montdésir
74540 Alby-Sur-Chéran - France

Date of last revision: November 2021

GALDERMA P2XXXX-X

Galderma Laboratories		**Printing Colors**
Product code: MOCK UP		PMS 432U
Product description: ROZEX GEL		
Market: EX2		
Article: Leaflet		
Flat size: 180x315	Font size: 11 pt	
Fold size: 180x26,25	Pharmacode: TBD	
GRAPHIC DESIGNER: Bérangère BLANCO *INDUSTRIALIZATION DEPARTMENT* *LABORATOIRES GALDERMA - Z.I. Galderma - 74540 ALBY-SUR-CHÉRAN - FRANCE*	GALDERMA EST. 1981	DIELINES