

Rozex 0.75% w/w Cutaneous Emulsion
(Metronidazole)

PL 10590/0036

UKPAR

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Rozex 0.75% w/w Cutaneous Emulsion

PL 10590/0036

LAY SUMMARY

On 21st May 2013, the MHRA granted a Marketing Authorisation (licence) for the medicinal product Rozex 0.75% w/w Cutaneous Emulsion (PL 10590/0036). This is a prescription only medicine (POM).

This medicine is prescribed by a doctor for a skin condition called rosacea. Rozex helps to treat the pimples, pustules (spots) and redness found with this condition.

Rozex contains the active substance metronidazole. Metronidazole belongs to a group of medicines called antiprotozoal and antibacterial agents and has been shown to help to control infection and inflammation in certain skin problems, such as rosacea.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of treatment with Rozex 0.75% w/w Cutaneous Emulsion outweigh the risks; hence a Marketing Authorisation has been granted.

Rozex 0.75% w/w Cutaneous Emulsion

PL 10590/0036

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Rozex 0.75% w/w Cutaneous Emulsion (PL 10590/0036) to Galderma (UK) Limited, on 21st May 2013. This prescription only medicine (POM) is indicated for the treatment of inflammatory papules, pustules and erythema of rosacea.

This application was submitted under Article 10.3 of 2001/83 EC, as amended, as a hybrid application. The reference medicinal product for this application is Rozex Gel (PL 10590/0016), which was first licensed in the UK to Galderma (UK) Ltd, on 4th January 1995.

Metronidazole is an antiprotozoal and antibacterial agent which is active against a wide range of pathogenic micro-organisms. The mechanisms of action of metronidazole in rosacea are unknown but available evidence suggests that the effects may be antibacterial and/or anti-inflammatory.

A summary of pharmacovigilance system (PMFS) has been submitted. This is satisfactory.

PHARMACEUTICAL ASSESSMENT

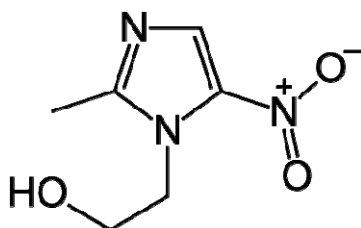
DRUG SUBSTANCE

Nomenclature

rINN: Metronidazole

Chemical Names: 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol

Structure:



Molecular Formula: C₆H₉N₃O₃

Molecular Weight: 171.15 g/mol

Appearance: White, bright fluid lotion

Solubility: Soluble in water.

Metronidazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance metronidazole are covered by a European Directorate for the Quality of Medicines healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients carbomer 941, benzyl alcohol (E1519), glycerol, macrogol 400, steareth-21, glyceryl stearate/PEG-100 stearate, stearyl alcohol, light liquid paraffin, cyclomethicone, potassium sorbate (E202), lactic acid and/or sodium hydroxide solutions to adjust pH and purified water.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of carbomer 941, steareth-21, glyceryl stearate/PEG-100 stearate and cyclomethicone which are covered by an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that none of the excipients are of animal or human origin.

Pharmaceutical development

The objective of the pharmaceutical development programme was to obtain a stable product containing metronidazole that could be considered a hybrid medicinal product of Rozex 0.75% Gel (Galderma (UK) Ltd).

Comparable impurity profiles are provided for this product versus the originator product.

Manufacture

Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The product is supplied either in high density polyethylene (HDPE) tubes with polypropylene screw caps containing 15, 30 and 50 g.

Or

High density polyethylene (HDPE) bottles with polypropylene screw caps with a pack size of 60 ml.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, shelf-lives of 2 years for unopened tube and bottle and 60 days after first opening have been set.

The storage conditions are “Do not store above 25°C” and “Do not refrigerate or freeze”. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are pharmaceutically satisfactory.

Only text version of the PIL and labels are approved. The Marketing Authorisation holder (MAH) has committed not to market the product until separate applications are made to comply with Article 59 and Article 61(3) of the Directives, as amended, with respect to the product information.

The MAH has also stated that not all licensed pack sizes may be marketed. They have committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form

The MAA form is pharmaceutically satisfactory.

Expert Report/Quality Overall Summary

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There are no objections to the approval of this product from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of metronidazole are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

There are no objections to the approval of this product from a non-clinical point of view.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted 7 studies (5 to evaluate the cutaneous safety and clinical pharmacology of the product and 2 efficacy studies).

Study 1. CG.03.SRE.2061

This was a single-blinded, randomised, intra-individual controlled study, designed to evaluate the ability of Rozex emulsion/lotion and its vehicle to cause local skin irritancy. The study was conducted over a 21-day period.

Twenty five healthy volunteers (12 female), aged 19-33 were enrolled. Two occlusive patches were applied on either side of their vertebral column, one containing 0.75% metronidazole lotion, (Rozex Lotion), the other vehicle. Patches were replaced every 24 hours during the week and after 72 hours at the weekend (Fifteen times over the three-week period.)

An irritancy index was adopted, scoring localised irritancy on a range of 0 to 4. Mean indices were 0.03 and 0.06 for the lotion and vehicle respectively. The materials were thus considered to be non-irritant. No other adverse events were noted.

Study 2. CG.03.SRE.2069

This again was a single-blinded, randomised, intra-individual controlled study, designed to assess the phototoxic potential of Rozex lotion. A single study centre was employed.

Twelve volunteers (8 female) aged 21-49 were enrolled. As described above two occlusive patches were applied to either side of the vertebral column, though both on this occasion contained metronidazole 0.75% lotion. The lotion's vehicle was also applied to an adjacent skin area, together with an untreated control patch. After six hours all patches were removed and one set of sites irradiated with a UVA light source. No significant phototoxic reaction was noted between one and seventy-two hours post irradiation.

Study 3. CG.03.SUM.0468

This was a double-blinded intra-individual controlled trial, designed to evaluate the potential for metronidazole lotion to produce contact sensitisation following repeat applications over a 14 week period.

Two-hundred and thirty three healthy subjects were recruited, (173 female), aged 18-78, (mean 47.2 years.). The study consisted of three phases. A three week induction period, during which nine patch applications of both the lotion and its vehicle were applied. A 14 day "rest" period, and finally a re-application of identical patches to previously unexposed sites in the sixth week was carried out. This last set of patches were removed at 48 hours and evaluated for signs of sensitisation at 48 and 96 hours.

Two-hundred and sixteen subjects completed the study, with no discontinuation attributed to the test materials. Three individuals demonstrated mild to moderate

cutaneous reactions to the 1.3% benzyl alcohol used as a preservative in the vehicle. No other adverse events were reported.

Study 4. CG.03.SRE.2068

This was a single-blinded intra-individual controlled trial assessing the photosensitising potential of Rozex lotion after repeated applications and localised irradiation.

Involving twenty-five healthy volunteers, (17 female), aged 22-49, (mean 36 years), the study was again divided into three phases. During the initial three week induction period, 50µl of both the lotion and vehicle were applied under an occlusive patch twice weekly to the lumbar area. A control area was also selected. Each of the three sites was irradiated with UVA+UVB light at the time of the patches being changed.

Following a two week "rest period", both the lotion and vehicle were reapplied for 24 hours, and then re-irradiated with a low intensity UVA light source. These were again compared to control areas. A visual scoring of the test areas apparently showed no photoallergic reaction.

Thirteen non-serious adverse events occurred throughout the study together with a single case of severe gastroenteritis. None of these were considered related to the test substances.

Study 5. CG.03.SUM.0443

This was an open, randomised four-way cross-over study, designed to determine the pharmacokinetic and bioavailability characteristics of two topical metronidazole formulations, 0.75% metronidazole lotion and cream, compared to a 250 mg oral metronidazole tablet and a topical 0.75% metronidazole gel. The trial was conducted at a single study centre.

Twelve healthy volunteers were included in the study aged 24-34. Subjects took either a single 250 mg metronidazole tablet following a 12 hour fast, or applied 1 g, (7.5 mg of metronidazole) of metronidazole lotion, cream or gel to their face. Individuals fasted for a further 3 hours following the oral dose, or refrained from washing or applying other preparations to their face for 24 hours, with the topical formulations.

Plasma levels of both metronidazole and the metabolite hydroxymetronidazole were measured over the 48 hours following administration and a complete urinary collection also carried out. Analysis was by high performance liquid chromatography, (HPLC).

Tabulated results are given in Tables 1 and 2 for measured plasma metronidazole concentrations. Results for hydroxymetronidazole were broadly similar. A seven day washout period was allowed between study arms.

Tables 1 & 2 Comparative pharmacokinetic parameters for plasma metronidazole concentrations between the four formulations

Metronidazole Concentration , ng/ml		
	Cream 7.5mg	Lotion 7.5mg
C max (ng/ml)	32.9 ± 10.6	34.4 ± 11.4
T max (hours)	10.62 ± 6.82	9.36 ± 2.47
AUC(0-24 hr)ng.h/ml	600.0 ± 185.1	634.1 ± 213.1
AUC(0-infinity)	912.7 ± 379.7	971.1 ± 433.6
% in Urine	12.7 ± 4.6	13.0 ± 3.9

Metronidazole Concentration , ng/ml		
	Gel 7.5mg	Tablet 250mg
C max (ng/ml)	29.1 ± 6.7	7248 ± 3019
T max (hours)	8.51 ± 2.84	1.51 ± 1.39
AUC(0-24 hr)ng.h/ml	555.6 ± 124.2	58504 ± 11724
AUC(0-infinity)	814.8 ± 251.4	67207 ± 15380
% in Urine	11.0 ± 4.4	32.8 ± 8.2

As might be expected the pharmacokinetic parameters for the oral metronidazole tablet were significantly different to those for the topical formulations.

In comparison to the topical gel the AUC_{∞} was 8.6% greater for the cream, (95% Confidence Interval -7.2 to + 26.9%), and 15% greater for the lotion, (95% Confidence Interval -1.6 to + 34.5%). Neither T_{max} values nor the percentage of metronidazole undergoing urinary excretion were significantly different at the 95% confidence level between the three topical formulations.

As might be expected the pharmacokinetic parameters for the oral metronidazole tablet were significantly different to those for the topical formulations.

The rate and extent of metronidazole absorption after topical application of either the cream or lotion, was not significantly different to that seen with the currently marketed metronidazole gel.

EFFICACY

The applicant reports the results of a single double-blind Phase III clinical trial (Study 6.CG.03.SUM.0469), undertaken on patients with mild to moderate rosacea. A second multicentre trial, (Study 7.CG.03.SPR.2560) was ongoing at the time of assessment.

In addition a further 17 clinical study reviews and 19 published reports are provided, in which metronidazole formulated either as a cream or gel was used in the treatment

or rosacea. A further 4 studies are referenced where metronidazole gel has been evaluated for indications other than rosacea.

Study 6.CG.03.SUM.0469

This was a double-blind, vehicle controlled study, conducted in patients with moderate to severe rosacea. Topical metronidazole lotion 0.75% was evaluated for safety and efficacy compared to its vehicle. Stated as having been conducted according to Good Clinical Practice the study was undertaken at six centres in the United States.

One hundred and forty-four subjects were enrolled (107 female), aged 23-81 (mean 48 years). Enrolment depended on the following criteria:-

- i) Presence of between 6-50 papules or pustules.
- ii) Presence of moderate to severe erythema.
- iii) Presence of telangiectasia
- iv) An ability/willingness to cooperate and provide informed consent.

Patients were instructed to apply a thin layer of blinded lotion to the entire facial area, after washing with a skin cleanser provided by the applicant. The lotion was to be applied twice daily, morning and evening, for twelve consecutive weeks. Cosmetics were allowed after the lotion had dried. Evaluation was carried prior to the start of the study and at 3, 6, 9 and 12 weeks.

Efficacy was determined by the following four parameters:-

- i) Inflammatory lesion count (papules and pustules)
- ii) Erythema
- iii) Telangiectasia
- iv) Investigator's and Medical Monitor's global assessment of an improvement in the rosacea

In addition safety was evaluated on the basis of the subject's subjective assessment and the monitoring of adverse events. A "Quality of Life" questionnaire was also completed by each individual.

Results to Study 6.CG.03.SUM.0469 (CR.U9418)

i) Inflammatory Lesion Count:-

Of the 144 patients enrolled, evaluation was undertaken on 128. The remaining 16 individuals were excluded for reasons ranging from, an interfering concomitant medication, to non-compliance and extended delays between evaluation visits. No exclusion was directly attributable to the medication.

The mean lesion count was reduced by both treatments, though significantly fewer were present in the metronidazole-treated subjects than those treated with the vehicle. A 52% reduction was seen in the metronidazole group (mean lesions reducing from 15.8 to 6.8) and a 22% reduction in those in the vehicle group (a reduction of 16.1 to 11.8 lesions).

Table 3. Mean Lesion Counts at Baseline and Endpoint as judged by Investigator

	Baseline		Endpoint		% Reduction	% Reduction p-value
	No of Patients	No of Lesions	No of Patients	No of Lesions		
Rozex Lotion	66	15.8	66	6.8	52%	p<0.01
Vehicle	62	16.1	62	11.8	22%	

Tables 4 and 5. Percent Reduction in Inflammatory Lesion Counts

	Total	Metronidazole Lotion				Vehicle				p-value
		>50%		<50%		>50%		<50%		
	N	N	%	N	%	N	%	N	%	
Endpoint	128	43	65.2	23	34.8	21	33.9	41	66.1	p<0.01

	Total	Metronidazole Lotion				Vehicle				p-value
		>25%		<25%		>25%		<25%		
	N	N	%	N	%	N	%	N	%	
Endpoint	128	51	77.3	15	22.7	31	50.0	31	50.0	p<0.01

As shown in Tables 4 and 5, 65.2% of metronidazole treated subjects had a greater than 50% improvement in inflammatory lesions opposed to 33.9% in those treated with vehicle alone.

ii) Erythema:-

Scored on a four-point scale; none, mild, moderate or severe, both metronidazole lotion and vehicle demonstrated a similar reduction in erythema at all assessment points throughout the study. No statistical difference (p>0.5) existed between the two treatment groups.

iii) Telangiectasia:-

This was again scored on a four-point scale ranging from absent to severe. A slight trend existed indicating improving symptomology with the metronidazole lotion. This was not though considered to be of significance clinically.

iv) Investigator's and Medical Monitor's Global Assessment

The Investigator's global assessment was based on a subjective impression of inflammation and erythema, scored on a six-point gradation scale.

At the endpoint, the combined assessments revealed that 43.5% of individuals administered the vehicle had worsened or unchanged symptoms, opposed to 19.7% in those prescribed the metronidazole lotion. Likewise 65.1% of subjects prescribed metronidazole lotion had a definite or marked improvement in symptoms compared to 33.9% in those administered the vehicle.

The Medical Monitor's assessment was based upon a subjective assessment of photographs taken of subjects at the baseline and endpoint visits. Again a six point gradation scale was employed. The two assessments broadly agreed.

Quality of Life Questionnaires

From the 144 individuals included in the study, 137 questionnaires were evaluated. The remaining seven patients had either been dropped from the study or filled the form out incompletely. Both treatments indicated an improvement in the quality of life, though that gained from using metronidazole lotion was statistically greater.

Safety

A subjective assessment of skin dryness, stinging/burning sensation and pruritus showed subjective improvements in both groups, with over 90% of patients reporting absent or mild cutaneous symptoms.

Eighty-four patients reported 194 medical events (42 patients in each group reporting 103 and 91 events respectively.) No serious event was attributed to either the lotion or vehicle.

Conclusions to Study 6.CG.03.SUM.0469 (CR.U9418)

This study adequately demonstrates the efficacy of topical metronidazole lotion to reduce the numbers of inflammatory lesions in rosacea over a twelve week period. This is supported by a global improvement in the condition. No significant clinical benefit though can be assigned to the active over the vehicle with respect to improvements in erythema or telangiectasia.

Adequate safety is demonstrated.

Other Clinical Studies

The applicant has conducted a European multicentre trial, (1.CG.03.SPR.2560), comparing the safety and efficacy of metronidazole 0.75% lotion to metronidazole 0.75% gel in the treatment of rosacea. The trial's protocol is provided but no results or conclusions were available for assessment of this application.

A further 9 study reports are included referring to metronidazole 0.75% gel and 8 performed using metronidazole 0.75% cream conducted by Galderma. These evaluated the safety and efficacy of both products in the treatment of rosacea and perioral dermatitis in the case of the gel. No issues were raised in this report.

Published Reports

Thirty-two literature reports are also provided, dating from the first acknowledged use of metronidazole in the treatment of rosacea in 1983. The formulations used had metronidazole concentrations ranging from 0.5-5.0%, were creams or suspensions and were applied once or twice daily for one to four months.

These reports confirm the efficacy of metronidazole to be superior to the vehicle alone and comparable to oral tetracycline. The safety of the formulations is confirmed.

SAFETY**Metronidazole 0.75% Lotion**

The subject of this application, metronidazole 0.75% Lotion, has been shown to be safe as a topical formulation both in Phase I (n=307) and Phase III (n=144) studies.

Metronidazole 0.75% Cream and Gel- Phase I & III Studies

Both the essentially similar product metronidazole 0.75% Gel and the related Cream formulations have demonstrated adequate safety in their Phase I, (n=327) and III, (n=947) studies. No evidence is presented of contact dermatitis or phototoxicity. Mild symptoms of irritation, dryness or a worsening of the rosacea occurred in 1-2% of the subjects. The post-marketing pharmacovigilance data from Rozex Gel and Rozex Cream also do not raise any serious clinical issue in the context of this application.

Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Marketing Authorisation Application (MAA) Forms

The MAA form is medically satisfactory.

Conclusion

There are no objections to the approval of this product from a clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Rozex 0.75% w/w Cutaneous Emulsion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

The studies showed that the pharmacokinetic parameters for the oral metronidazole tablets were significantly different to those for the topical formulations. The rate and extent of metronidazole absorption after topical application of lotion was not significantly different to that seen with the currently marketed metronidazole gel or the cream.

The study carried out to determine the efficacy of topical metronidazole lotion has adequately demonstrated reduced numbers of inflammatory lesions in rosacea over a twelve week period. Adequate evidence is provided of the Emulsion's efficacy and safety, in the treatment of rosacea.

Safety

Metronidazole 0.75% Lotion has been shown to be safe as a topical formulation both in Phase I and Phase III studies. Both the essentially similar products metronidazole 0.75% Gel and the related Cream formulation have demonstrated adequate safety in their studies. No evidence is presented of contact dermatitis or phototoxicity. Mild symptoms of irritation, dryness or a worsening of the rosacea occurred in 1-2% of the subjects.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with metronidazole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Rozex 0.75% w/w Cutaneous Emulsion**PL 10590/0036****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation application on 4 th February 1998
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15 th November 2006
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 4 th November 2010, 4 th August 2011, 24 th May 2012, 30 th October 2012 and on the clinical section 17 th May 2007
4	The applicant responded to the MHRA's requests, providing further information to the quality section on , 20 th May 2011, 4 th May 2012, 20 th September 2012, 29 th January 2013 and on the clinical section on 17 th June 2009
5	The application was determined on 21 st May 2013

SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING

LABEL

Front:

Rozex[®]
0.75% w/w Cutaneous Emulsion
Metronidazole
For the topical treatment of rosacea
Net Wt. PACK SIZE
Galderma logo

Back:

TO BE USED ONLY AS DIRECTED BY YOUR DOCTOR
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
DO NOT STORE ABOVE 25°C
DO NOT REFRIGERATE OR FREEZE
REPLACE CAP AFTER USE
WARNING: AVOID CONTACT WITH THE EYES
IF ACCIDENTAL CONTACT SHOULD OCCUR, WASH WITH LARGE
AMOUNTS OF WARM WATER OR EYE WASH
CONTAINS STERAYL ALCOHOL AND POTASSIUM SORBATE WHICH
MAY CAUSE LOCAL SKIN REACTIONS (E.G. CONTACT DERMATITIS)
CONTENTS: Metronidazole 0.75% w/w, carbomer 941, benzyl alcohol (E1519),
glycerol, macrogol 400, cyclomethicone, potassium sorbate (E202), steareth-21,
glyceryl stearate/PEG-100 stearate, stearyl alcohol, light liquid paraffin, lactic acid qs,
sodium hydroxide qs and
purified water.
PLEASE READ THE ENCLOSED LEAFLET BEFORE USE
PL 10590/0036 PA 590/10/3
Marketing Authorisation Holder:
Galderma (UK) Limited,
Meridien House, 69-71 Clarendon Road,
Watford, Herts, WD17 1DS, UK
® Trade Mark
Batch Number:
Use Before:
FOR EXTERNAL USE ONLY
POM
CARTON

Front Panel:

Rozex[®] 0.75% w/w Cutaneous Emulsion (Rozex Emulsion in Braille)
Metronidazole
For the topical treatment of rosacea
Net Wt. PACK SIZE
Galderma logo

Side Panel 1:

Rozex[®] 0.75% w/w Cutaneous Emulsion
Metronidazole
For the topical treatment of rosacea

Galderma logo

Side Panel 2:

CONTENTS: Metronidazole 0.75% w/w

carbomer 941, benzyl alcohol (E1519), glycerol, macrogol 400, cyclomethicone, potassium

sorbate (E202), steareth-21, glyceryl stearate/PEG-100 stearate, stearyl alcohol, light liquid

paraffin, lactic acid qs, sodium hydroxide qs and purified water.

PLEASE READ THE ENCLOSED LEAFLET BEFORE USE

WARNING: AVOID CONTACT WITH THE EYES

IF ACCIDENTAL CONTACT SHOULD OCCUR, WASH WITH LARGE AMOUNTS OF WARM WATER OR EYE WASH

CONTAINS STERAYL ALCOHOL AND POTASSIUM SORBATE WHICH MAY CAUSE LOCAL SKIN REACTIONS (E.G. CONTACT DERMATITIS)

Rear Panel:

PL 10590/0036 PA 590/10/3

Marketing Authorisation Holder:

Galderma (UK) Limited, Meridien House, 69-71 Clarendon Road, Watford, Herts, WD17

IDS, UK

® Trade Mark

POM

TO BE USED ONLY AS DIRECTED BY YOUR DOCTOR

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

DO NOT STORE ABOVE 25°C

DO NOT REFRIGERATE OR FREEZE

REPLACE CAP AFTER USE

Top Flap:

Rozex® 0.75% w/w Cutaneous Emulsion

Metronidazole

Bottom Flap:

Batch Number:

Use Before:

FOR EXTERNAL USE ONLY