Public Assessment Report

Mutual Recognition Procedure

Metroxx 0.75% Gel
Metrosa 7.5mg/g Gel

UK/H/820/01
UK MA number: PL 13159/0006

Dr August Wolff GmbH & Co. KG

Metroxx 0.75% Gel
Metrosa 7.5mg/g Gel

LAY SUMMARY

Austria, Belgium, Estonia, Germany, Finland, Hungary, Lithuania, Latvia and The Netherlands have agreed to grant Marketing Authorisations to Dr August Wolff GmbH & Co. KG for the medicinal product Metroxx 0.75% Gel/Metrosa 7.5mg/g Gel following acceptance of the UK marketing authorisation. This is a prescription only medicine [POM] used for the treatment of rosacea (redness in the face, sometimes together with raised areas of the skin that contain pus).

The active ingredient, metformin, acts against some of the fungi and other organisms that can affect the skin, and also, in patients suffering from rosacea, it can relieve the condition by acting against the inflammation which happens when the condition becomes troublesome.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Metroxx 0.75% Gel/Metrosa 7.5mg/g Gel outweigh the risks, hence the UK marketing authorisation has been approved.

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Module 1

Information about initial procedure

Product Names	Metroxx 0.75% Gel Metrosa 7.5mg/g Gel
Type of Application	Known active substance Initial application Bibliographic, Article 10.1(a)(ii) Chemical Substance Prescription only
Active Substance	Metronidazole
Form	Gel
Strength	0.75%w/w
MA Holder	Dr August Wolff GmbH & Co. KG
RMS	United Kingdom
CMS	Austria, Belgium, Estonia, Germany, Finland, Hungary, Lithuania, Latvia and The Netherlands
Procedure Number	UK/H/820/01
Timetable	MRP Day 0: 27 January 2006 MRP Day 50: 18 March 2006 MRP Day 85: 22 April 2006 MRP Day 90: 27 April 2006

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Metrosa 7.5 mg/g Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 7.5 mg metronidazole.
Excipient: 30 mg propylene glycol / gram Gel
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
A smooth clear to turbid colourless to faintly yellow gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the topical treatment of Rosacea (inflammatory papulopustules rosacea related).

4.2 Posology and method of administration

Method of administration: Cutaneous use.

Adults and the elderly: Apply a thin film of the gel to the affected areas twice daily for four weeks. Treatment may be continued for a further four weeks if necessary.

Use in children and adolescents: Not recommended as clinical trials have not been undertaken.

4.3 Contraindications

Hypersensitivity to the active substance “metronidazole” or to any of the excipients.

4.4 Special warnings and precautions for use

Avoid contact with the eyes. If contact should occur, wash out of the eyes carefully with warm water.

Metrosa contains propylene glycol, which may cause skin irritation.

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 derivative and should be used with care in patients with evidence of, or history of blood dyscrasia.

Extensive exposure of treated sites to ultraviolet or strong sunlight should be avoided during use of Metrosa. UV-radiation may inactivate metronidazol. The efficacy may be reduced, but no phototoxicity was demonstrated by clinical results.

Unnecessary and prolonged use of this medication should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

In the case of oral metronidazole, there have been a small number of reports of a disulfiram-like reaction if alcohol is taken concomitantly. Although the systemic absorption of metronidazole from topical presentations is slight this interaction might be seen.

Oral metronidazole has been reported to potentiate the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin is not known.

4.6 Pregnancy and lactation

Metrosa should not be used if pregnant or if breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The adverse effects by cutaneous use are only local.
Uncommon (>1/1000, <1/100) there are skin and subcutaneous tissue disorders like dryness, peeling, or itching.

4.9 Overdose

Overdosage is not to be expected with this preparation. Any excess gel may be removed by washing with warm water. Appropriate gastric emptying may be used, if considered necessary, should accidental ingestion occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Chemotherapeutics for topical use
ATC Code: D06BX01

Metronidazole is a 5-nitroimidazole derivative with activity against anerobic protozoa and bacteria, due probably to an interference with DNA by a metabolite of the metronidazole.

The precise mode of action of metronidazole in Rosacea is not known. It has been suggested that it has an anti-inflammatory effect due to an anti-oxidant activity affecting neutrophil cell function, or that it acts as a parasiticide towards *Demodex folliculorum*.

5.2 Pharmacokinetic properties

The gel is applied topically for its local action.

In humans, systemic absorption of 1g gel with 7.5mg metronidazole after topical application is low (1% of oral dose). Quantifiable serum levels are in the range 25-66 ng/ml and c_{max} is < 5 % of that observed after a 30 mg oral dose (41 ng/ml vs. 850 ng/ml); t_{max} is prolonged, 5.98 hours compared to 0.97 hours orally.

5.3 Preclinical safety data

Single dose studies in mouse and rat by oral, intraperitoneal and intravenous routes show a low order of toxicity. Repeat dose studies (oral and intravenous) in mouse, rat, dog, and monkey indicate a no-effect level of 75 mg/kg/day.

Reproductive studies showed no evidence of embryotoxicity or teratogenicity in mouse, rat and rabbit (oral and intravenous). Reversible male infertility was observed in rats treated with 400 mg/kg/day.

Metronidazole is mutagenic in bacteria and fungi, but is regarded as non-genotoxic in mammalian species.

No phototoxic or photogenotoxic effects were seen in studies in Chinese hamster lung cells.

Carcinogenicity studies in mouse and rats showed an increased incidence of tumour, but recent epidemiological studies in human showed no increased cancer risk.

No local dermal toxicity (irritation, sensitisation) was seen in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenoxyethanol
Propylene glycol
Hypromellose
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

54 months. Shelf life after first opening is 1 month.

6.4 Special precautions for storage

Do not store above 25 °C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Aluminium tube, fitted with a polyethylene (HDPE) screw cap.
Pack sizes: 25g, 30g, 40g, or 50g.
Not all pack sizes are marketed.

6.6 Special precaution for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dr. August Wolff GmbH & Co. KG Arzneimittel
Sudbrackstrasse 56, 33611 Bielefeld, Germany
e-mail: info@wolff-arzneimittel.de

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

04/2006

Module 3

Patient Information Leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER

Metrosa 7.5 mg/g Gel
Metronidazole

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT METROSA IS AND WHAT IT IS USED FOR

Metrosa is an antiinflammatory gel to be applied on the skin.
Metrosa is used for the treatment of rosacea (redness in the face, sometimes together with additional pustules) when the condition suddenly gets worse, and the inflammation becomes troublesome.

Metronidazole acts against some of the fungi and other organisms that can affect the skin, and also, in patients suffering from rosacea, it can relieve the condition by acting against the inflammation which happens when the condition becomes troublesome.

2. BEFORE YOU USE METROSA

Do not use Metrosa
if you are hypersensitive (allergic) to Metronidazole or any of the other ingredients listed below

Take special care with Metrosa
Do not let the gel come into contact with the eyes. If it does, wash the gel carefully out of the eyes with warm water.

Use Metrosa with care if you suffer or suffered in the past from blood dyscrasia.

Do not go out into strong sunlight, or use UV lamps while you are using this product. Avoid prolonged and unnecessary use of this medicine.

Use in children and adolescents
Metrosa should not be used in children and adolescents.

Using other medicines
Using Metrosa could interfere with drugs used to thin the blood (anticoagulants) such as warfarin and coumarin. Contact your doctor for advice if you are taking medicines to thin your blood, or if you suffer for any other blood disorders.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Metrosa with food and drink
Food and meals can be consumed with only one exception: It is best not to take alcohol while using the gel, as there is a very small possibility of a reaction that might you feel sick or nauseous.

Pregnancy and breast-feeding
You should not use the gel if you are pregnant or if you are breast-feeding. If you are, or think you may be, pregnant, or wish to breast-feed, please make sure your doctor knows of this immediately.

Driving and using machines
You are allowed to drive and use machines since there are no effects known on the ability to drive.

Important information about some of the ingredients of Metrosa
Propylene glycol may cause skin irritation. Should this occur, stop using the medicine and consult your doctor.

3. HOW TO USE METROSA

Metrosa gel is for cutaneous use only.

Unless your doctor has told you differently, apply a 2 - 3 cm line of gel to the affected areas and rub it gently into the skin. Use the gel **twice each day**, for up to four weeks.

Always use Metrosa exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you use more Metrosa than you should
If you apply too much of the gel, simply wipe off the excess with a clean tissue. The gel is for use on the skin only. If you, or anyone else, should accidentally swallow a quantity of the gel, tell your doctor at once, or go to the nearest hospital casualty department.

If you forget to use Metrosa
If you forget to use the gel, then use it as soon as you remember, unless the next application is due within about two or three hours, in which case omit the forgotten dose.

If you stop using Metrosa
If you stop using the gel, contact your doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Metrosa can cause side effects, although not everybody gets them.

Uncommonly (between one and ten per 1000 treated patients), you may notice
- dryness
- peeling or
- itching

after using the gel. If this should become troublesome, stop using the gel and tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE METROSA

Keep out of the reach and sight of children.

Do not use Metrosa after the expiry date which is stated on the tube. The expiry date refers to the last day of that month.

Do not store above 25 °C. Do not refrigerate or freeze the gel.

Use within 1 month of first opening.

6. FURTHER INFORMATION

What Metrosa contains
The active substance is Metronidazole
1 g of gel contains 7.5 mg metronidazole
The other ingredients are phenoxyethanol, propylene glycol, hypromellose, and purified water.

What Metrosa looks like and contents of the pack
It is made available as a collapsible aluminium tube containing 25 g, 30 g, 40 g or 50 g of the gel (not all pack sizes will be market at time).

Marketing Authorisation Holder and Manufacturer
Dr. August Wolff GmbH & Co. KG Arzneimittel
Sudbrackstraße 56, D-33611 Bielefeld, Germany
Phone: +49 (0)521 8808-05; Fax: +49 (0)521 8808-334
E-Mail: info@wolff-arzneimittel.de

This medicinal product is authorised in the Member States of the EEA under the following names:

Estonia, Germany, Hungary, Latvia, Lithuania:	Metrosa 7.5 mg/g Gel
Austria, Belgium, Finlandia, The Netherlands:	Nidazea 7.5 mg/g Gel
United Kingdom:	Metroxx 0.75 % Gel

This leaflet was last approved in 04/2006

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Metrosa 7.5 mg/g Gel
Metronidazole

1 g of gel contains 7.5 mg metronidazole

Other ingredients: Propylene glycol, hypromellose, phenoxyethanol, purified water
Contains propylene glycol - Read the package leaflet before use

Gel
25 g
30 g
40 g
50 g

Cutaneous use

Read the package leaflet before use

Keep out of the reach and sight of children

Avoid contact with the eyes

Expiry date:

Store below 25 °C and do not freeze or refrigerate

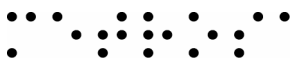
Dr. August Wolff GmbH & Co. KG Arzneimittel
Sudbrackstraße 56, 33611 Bielefeld, Germany

Marketing authorisation number: (*national number*)

Lot:

Medicinal product subject to medical prescription

*Braille (Metrosa)**:*



PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Metrosa 7.5 mg/g Gel
Metronidazole

1 g of gel contains 7.5 mg metronidazole

Other ingredients: Propylene glycol, hypromellose, phenoxyethanol, purified water
Contains propylene glycol - Read the package leaflet before use

Gel
25 g
30 g
40 g
50 g

Cutaneous use

Read the package leaflet before use

Keep out of the reach and sight of children

Avoid contact with the eyes

Expiry date:

Store below 25 °C and do not freeze or refrigerate

Dr. August Wolff GmbH & Co. KG Arzneimittel
Sudbrackstraße 56, 33611 Bielefeld, Germany

Marketing authorisation number: (*national number*)

Lot:

Medicinal product subject to medical prescription

Scientific discussion during the initial procedure

1. INTRODUCTION

1.1 RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the reference member state (RMS) considered that the application for Metroxx 0.75% Gel in the treatment of acute exacerbations of acne rosacea, could be approved. A national marketing authorisation was granted on 15 November 2004.

1.2 EXECUTIVE SUMMARY

Problem statement

These mutual recognition applications consider a bibliographic application for Metroxx 0.75% Gel.

The product was granted a marketing authorisation in the UK on 15 November 2004. With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, Dr August Wolff GmbH & Co. KG, is applying for marketing authorisations for Metroxx 0.75% Gel in Estonia, Germany, Hungary, Latvia and Lithuania.

Regarding patient user testing and harmonisation of the PIL, as far as the UK is concerned these will be completed within 12 months. As far as the individual member states in the MRP are concerned, a timetable will be agreed in discussion with each of the individual concerned member states (CMSs) to meet the requirements of that CMS.

About the product

Metroxx 0.75% Gel contains the well-established active substance, metronidazole, in a topical gel formulation and is for the treatment of acute exacerbations of acne rosacea.

Metronidazole has been used clinically for more than 40 years. It is a 5-nitroimidazole derivative, with activity against anaerobic protozoa and bacteria, due probably to an interference with DNA by a metabolite of metronidazole.

Orally, metronidazole is active against anaerobic protozoa such as *Entamoeba histolytica, Giardia intestinalis* and *Trichomonas vaginalis*. Most obligate anaerobes are susceptible to metronidazole, such as Clostridium spp., and some facultative anaerobes, such as Campylobacter (Helicobacter) spp. It has also been used locally in the form of suppositories and pessaries.

The development programme

The objective of the development programme was to formulate a robust, stable, acceptable aqueous gel formulation of metronidazole 0.75% that was easily applied, non-sticky and left no visible film after application.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

No new preclinical studies were conducted, which is acceptable given that the legal basis for this application was Article 10.1(a)(ii) of Directive 2001/83/EC, a bibliographic application.

No clinical studies were conducted, which is acceptable given that the legal basis for this application was Article 10.1(a)(ii) of Directive 2001/83/EC, a bibliographic application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

2. QUALITY ASPECTS

2.1 INTRODUCTION

This is a standard abridged application for a topical gel, containing metronidazole 0.75%w/w as the active ingredient. The application has been made under Article 10.1(a)(ii) of Directive 2001/83/EC, as amended, supplemented by clinical data.

The product is intended for topical administration in the treatment of acute exacerbations of acne rosacea. Metroxx Gel is intended to be applied as a thin film to the affected areas twice daily for 4 weeks, continuing for a further 4 weeks, if clinically necessary.

The applicant already has UK Marketing Authorisations for identical preparations Skinola Gel PL 13159/0001 (granted 28 July 1995) and Metrosa Gel 0.75% PL 13159/0004 (granted 7 June 1999). Metrosa Gel was approved as a piggy-back to Skinola Gel.

2.2 DRUG SUBSTANCE

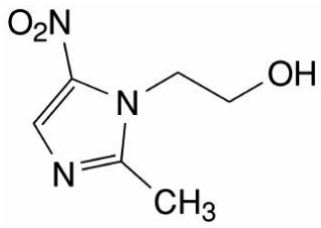
The drug substance has been used in granted topical preparations, including the applicant’s own products, Skinola Gel and Metrosa Gel.

General Information

Nomenclature

rINN:	Metronidazole
Compendial name:	Metronidazole (Ph.Eur)
Chemical Name:	2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethanol.

Structure



Molecular Formula:	$C_6H_9N_3O_3$
Molecular Weight:	171.2

General Properties

Appearance: White or yellowish, crystalline powder.
Solubility: Slightly soluble in water, in acetone, in alcohol and in methylene chloride.
Melting Point: 159˚C to 163˚C.

Manufacture

Manufacturers
Description of Manufacturing Process and Process Controls
Control of Materials
Controls of Critical Steps and Intermediates

These are covered by the EDQM Certificate of Suitability.

Characterisation

Elucidation of Structure and Other Characteristics

This is covered by the EDQM Certificate of Suitability.

Impurities

This is covered by the EDQM Certificate of Suitability. The Certificate states that water is used in the last step of synthesis.

Control of drug substance

Specification
Analytical Procedures
Validation of Analytical Procedures
Batch Analyses
Justification of specification

The drug substance is tested in accordance with the Ph.Eur. monograph. Certificates of Analysis from both the drug substance manufacturer and the finished product manufacturer (Dr August Wolff GmbH and Co, Arzneimittel) have been provided. No analytical validation data are supplied. This is acceptable as Ph.Eur. methods are used.

Reference Standards or Materials

Metronidazole Ph.Eur. CRS is used as primary reference standard; working standards are validated against this primary reference standard. This is satisfactory.

Container/closure system

The drug substance is packed in sealed double PE bags and placed in fibreboard drums.

Stability

Stability data for six batches of metronidazole stored at 40°C/75%RH for 6 months and seven batches stored at 25°C/60%RH for up to 60 months have been provided. These data show no significant changes in appearance, identification, melting range, assay and impurities in the batches tested under accelerated or long-term conditions and demonstrate that the drug substance is stable for up to 60 months when stored at 25°C/60%RH. Based on these data, the re-test period of 60 months is satisfactory.

Literature references have been provided for photo stability studies performed, which indicate that metronidazole is photolabile and should be protected from direct sunlight.

2.3 MEDICINAL PRODUCT

Description and composition of the drug product

Smooth clear to turbid, colourless to faintly yellow gel.

Composition:

Ingredients	Quantity	Reference Standard	Function
Metronidazole	0.75%w/w	Ph.Eur.	Active
Phenoxyethanol		Ph.Eur.	Preservative
Propylene glycol		Ph.Eur.	Vehicle
Methylhydroxypropyl cellulose 4000		Ph.Eur.	Thickener
Purified water		Ph.Eur.	Vehicle

The gel is contained in collapsible aluminium tubes, with a sealing band and is fitted with a polyethylene cap.

Pharmaceutical Development

The aim of the development programme was to formulate an aqueous gel that was easily applied, non-sticky and left no visible film after application. Very little development pharmaceutics data is provided. According to the expert most of the formulation requirements were obtained by use of well-recognised excipients.

The function of each excipient has been explained and justification given for its choice - hypromellose 400 (viscosity adjuster), propylene glycol (humectant), phenoxyethanol (preservative) and purified water (vehicle). Three preservative efficacy systems were considered before selection of the final preservative. BP preservative efficacy tests showed adequate preservative efficacy for all three preservative systems. Phenoxyethanol was chosen because it is well tolerated and has a low allergising potential.

The final formulation was compared to Metrogel (Sandoz, UK) in an *in-vitro* diffusion test, using nude mouse kin membrane. The applicant has provided details of the methods used and the results provided show that the two products have similar characteristics.

The formulation for all clinical trial batches is claimed to be the same as that proposed in this application.

No specific studies were performed to investigate the compatibility between the product and container as the applicant considered that water-based cellulose gel and other ingredients were not aggressive to collapsible Al tubes that are internally coated with epoxy resin. A similarly packaged product, Neutratop has been marketed in the UK since 1999 with no compatibility problems.

Manufacture

Manufacturers

Batch release is carried out at Dr August Wolff GmbH & Co KG Arzneimittel, Sudbrackstrasse 56, 33611 Bielefeld, Germany. This site has been approved for use in granted topical preparations marketed in the UK.

Batch formula

A satisfactory manufacturing formula is provided for a production batch size. No overages are included or required.

Description of manufacturing process and process controls

The equipment used are stated. All manufacturing equipment are cleaned and checked for cleanliness before use. A satisfactory description is provided on the manufacturing method. The resultant gel is sampled and after QC release filled into tubes, sealed and packaged.

In-process controls during manufacture include checks on the complete dissolution of metronidazole crystals and checks for absence of lumps and undispersed aggregates of methylhydroxypropyl cellulose. Before filling, the tests for release according to the finished product specification are carried out. After filling the product is tested again for appearance, identity and microbiological purity. Controls applied are considered satisfactory.

Control of critical steps and intermediates

There are no critical steps in the manufacturing process.

Process validation and/or evaluation

No specific process validation data are provided for this product. According to the applicant the manufacturing process is relatively standard and manufacture of an aqueous cellulose type gel is claimed to be without any technical difficulties. The manufacturer has also claimed to have several years of manufacturing experience of the product. In-process controls ensure the complete dissolution of the drug and incorporation of hypromellose in the solution mix.

In addition, the applicant has committed to providing data from the first production-scale batches produced and has provided a copy of the formal validation programme to be followed for production-scale batches. It includes satisfactory checks during the preparation of solution, suspension, and final gel. During filling, checks are made of viscosity, fill weight, active and preservative assays, and microbial testing. The equipment to be used for production scale batches will be comparable to that used for pilot scale batches.

Overall the data provided is acceptable.

Control of excipients

All added ingredients comply with their respective Ph.Eur monographs. Certificates of Analysis have been provided for all excipients showing compliance with their respective Ph.Eur. monographs. The dosage form manufacturer performs full testing to Ph.Eur. for purified water, hypromellose and phenoxyethanol. Propylene glycol is tested for identity (A-D), appearance, relative density and refractive index by the dosage form manufacturer, with all other test results taken from the supplier.

Excipients of human and animal origin

None of the materials used in the manufacture of the product are of human or animal origin. Supporting certification is provided.

Control of drug product

Specifications

The finished product specification is satisfactory. Controls on microbiological quality are in line with Ph.Eur. requirements and are satisfactory.

Analytical procedures
Validation of analytical procedures

Analytical methods used have been satisfactorily described. Methods are general pharmacopoeial procedures or BP/Ph.Eur.

Batch analysis

Batch analytical data are provided for three consecutive pilot scale batches. All batches comply with the proposed specification.

The finished product specification was changed during the national assessment. In view of this, the applicant provided additional batch analysis data for three batches.

Justification of specifications

Satisfactory justifications are given for the specifications proposed.

Reference standards or materials

The reference standards used are Metronidazole Ph.Eur CRS, 2-methyl-5-nitroimidazole BPCRS or Ph.Eur CRS. Phenoxyethanol complies with BP/Ph.Eur. requirements. A satisfactory Certificate of Analysis is provided for the in-house reference sample.

Container closure system

Collapsible aluminium tubes with epoxy-phenol resin combination as internal protective lacquer (TU 25/N 48169/H) and white polyethylene (HDPE) screw cap. The lower end of the tubes is coated internally with a sealant lacquer. Manufacturers of the various components are stated. The internal tube lacquer complies with FDA requirements for resinous and polymeric coatings which may be safely used as food contact surfaces for packaging of food products. The sealant lacquer also complies with FDA requirements for materials suitable for food contact use. The HDPE screw cap complies with Ph.Eur. and EC requirements. Suppliers/manufacturers specifications for the packaging materials have been submitted and are all satisfactory.

Pack size: 25g, 40g and 50g.

Stability

Shelf-life: 54 months; Storage conditions: Do not store above 25C. Do not refrigerate or freeze the gel. In-use shelf-life: 1 month.

Stability data are provided for batches filled into the proposed immediate packaging material. Drug substance used in all finished product batches was from one batch. Samples have been stored at 25C/60% RH for over 60 months.

The proposed shelf-life and storage proposals are generally satisfactory. The applicant has also provided results from preservative efficacy testing for two batches, which show compliance with the current Ph.Eur requirements for preservative efficacy. The applicant has committed to putting the first three production-scale batches on ICH follow-up stability studies.

In-use stability data satisfactorily supports the in-use shelf life of 1 month for this product.

Regional Information

The process validation plan for 3 full-scale production batches is outlined and is satisfactory.

A copy of the EDQM Certificate of Suitability is provided.

The applicant has confirmed that the product complies with current CPMP-CVMP requirements on minimising the risk of transmitting animal spongiform agents via human and medicinal products. Supporting declarations are also provided by manufacturers of active and excipients.

Clinical module

Protocol Dr August Wolff/01: A double-blind, double-dummy study has been undertaken to compare the effectiveness of 0.75% metronidazole gel and tetracycline in the treatment of papulo-pustular rosacea. The study was carried out during September 1993-March 1999. Three batches of the metronidazole gel (Skinola Gel) have been used. In response to a question during the national assessment, confirmation was provided that Skinola Gel is the same as the product proposed for marketing.

Protocol 05: A comparative study of cutaneous levels of metronidazole after topical application in normal volunteers has been sponsored by the applicant. The study was designed to compare the percutaneous penetration of the applicant's formulation with MetroGel (Sandoz, UK). The study was a double-blind study using a single investigator. Twenty-four normal subjects were used and subjects were randomly allocated to four groups of 6 individuals. The test and reference products were applied to the flexor aspect of the forearms, one to each arm. Approximately 0.1g of gel was rubbed into the skin. After 30 minutes, samples of the stratum corneum and full thickness skin were removed from six subjects and repeated at 1, 2 and 4 hours for the remaining groups of six subjects. The levels of metronidazole in tissue samples were determined by an HPLC method. The HPLC method with detection at 324nm has been adequately described and validated.

Protocol CSL 03: Metronidazole gel 0.75% and the gel base with four other topical formulations have been tested in 102 healthy volunteers, to assess their irritancy and sensitisation potential. The study was a single centre; double blind study and was

designed as a repeat insult patch test investigation consisting of six applications over a 15-day irritancy phase and a challenge on day 22 to determine irritancy. All six products were tested under occlusion using a 12-mm aluminium Finn chamber on Scanpor tape.

Protocol CSL 04: A single-centre, double-blind randomised study to determine the photo toxicity potential of metrondazole gel and base formulation in 12 normal volunteers.

Batch numbers and batch sizes of all batches used in the clinical trials have been provided and batch analytical results for these are satisfactory.

Quality Overall Expert

The Quality Expert has appropriate qualifications and has provided a satisfactory report.

2.4 PHARMACEUTICAL CONCLUSION

It is recommended that a product licence should be granted.

3. NON-CLINICAL ASPECTS

3.1 INTRODUCTION

This is a standard abridged application for Metroxx Gel containing 0.75%w/w of the active ingredient metronidazole and submitted under Article 10.1a(ii) of Directive 2001/83/EC.

The proposed formulation is intended for topical application, in the treatment of acute exacerbations of acne rosacea for up to 8 weeks. The applicant has marketing authorisations in the UK for similar topical products, namely Skinola Gel (PL13159/0001) and Metrosa Gel 0.75% (PL13159/0004).

Expert report

A pharmaco-toxicological Expert Report has been supplied. This consists of a critical review of the toxicology of metronidazole with reference to published literature. The pharmacology of metronidazole is also briefly discussed. Unfortunately, the published literature has not been submitted in support of this application.

3.2 DISCUSSION ON THE NON-CLINICAL ASPECTS

Metronidazole, a 5-nitro-imidazole derivative, is an antimicrobial medicine with activity against anaerobic bacteria and protozoa. The pharmacology and toxicology of metronidazole are well established, and have been adequately reviewed by the Expert.

The source of active ingredient has been previously used in other UK medicinal products and impurities are controlled according to a previously granted drug master file and do not raise any safety concerns.

The main concern with this type of application is whether systemic absorption of metronidazole is considerably higher than other marketed metronidazole formulations. Apparently, there are no preclinical pharmacokinetic data with topically applied metronidazole. In monkeys, metronidazole (1mg/kg) applied to vagina was extensively absorbed systemically (bioavailability was 73%). However, in humans, systemic absorption of 1g metronidazole 0.75% applied to the skin was very low (approximately 1% of that seen after an oral dose) such that serum concentrations of metronidazole were in the range 25-66ng/ml and C_{max} was 20% of that observed after a 30mg oral dose (41ng/ml vs 850ng/ml).

Metronidazole is extensively metabolised by the liver. One of its two major metabolites, namely 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite) has 30-65% of the biological activity of the parent drug and a longer elimination half-life than the parent compound. It is not known whether this active hydroxy metabolite is formed following topical administration of metronidazole. However, in view of the low systemic absorption of parent drug when applied to human skin, plasma levels of the active hydroxy metabolite, if formed, are unlikely to be of safety concern.

Considering the low systemic concentrations of metronidazole anticipated with the proposed formulation, the existing safety margins are unlikely to be eroded with this new topical formulation at the proposed dose regimen and there are no preclinical objections to grant a Marketing authorisation for Metroxx Gel.

3.3 CONCLUSION

There are no preclinical objections to grant of a Marketing Authorisation for Metroxx Gel.

4. CLINICAL ASPECTS

4.1 INTRODUCTION

This is an abridged standard licensing application of metronidazole gel for cutaneous use regarding the treatment of acute exacerbations of acne rosacea. It is submitted under Article 10.1a(ii) of Directive 2001/83/EC. The application is based on reference to bibliography and supplementary clinical studies with this particular gel.

Background

Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

Indications

For the treatment of acute exacerbations of acne rosacea

Assessor's comment

This indication is appropriate.

Dose & dose schedule

Adults and the elderly: Apply a thin film of the gel to the affected areas twice daily for four weeks. Treatment may be continued for a further four weeks if necessary.

Use in children: Not recommended.

Toxicology

This has been assessed separately. An increased number of tumours have been reported in studies with high doses of metronidazole in rats and mice. The issue of carcinogenicity in animal studies is discussed in the toxicology assessment. Clinically, this subject has also been reviewed. There appears to be no evidence to date to substantiate an increased risk of cancer in humans.

4.2 PHARMACOKINETICS

The gel is applied topically for its local action. There is limited data on absorption using a 0.75% gel. The five studies reviewed in this application show that use of 1g of gel (7.5mg metronidazole) topically results in blood levels ranging from undetectable to about 1% of the C_{max} seen from oral dosing.

4.3 PHARMACODYNAMICS

The precise mode of action of metronidazole in acne rosacea is not known. It has been suggested that it has an anti-inflammatory effect due to an anti-oxidant activity affecting neutrophil cell function, or that it acts as a parasiticide towards *Demodex folliculorum*.

4.4 CLINICAL EFFICACY

The applicant has submitted a critical review of thirty-two published studies and clinical trials. Copies of these publications are provided.

One double-blind, placebo-controlled study conducted in Sweden, involving 81 patients, showed that topical metronidazole at a concentration of 1% in a cream base was effective topical therapy for rosacea. Another double-blind study comprising 51 patients, compared 1% metronidazole cream with systemic oxytetracycline; although both groups demonstrated a high degree of improvement there was no difference between the two groups.

Another, double-blind, placebo-controlled study investigated 59 subjects treated for 9 weeks with metronidazloe 0.75% gel or base alone. Statistically significant reductions in erythema and global improvement were seen in the metronidazole group compared with placebo. However, selective measurements of telangiectasia showed no improvements with either metronidazole or placebo.

Another double-blind study consisting of 33 patients compared 0.75% metronidazole gel versus tetracycline treatment over a 9-week period. There was no statistically significant difference between the two groups. However, the study was relatively

small with only 16 patients in treatment group and does not show clear improvement of the rosacea by both treatments.

In another double-blind, randomised study had two treatment groups: (A) topical metronidazole 0.75% gel BID (plus oral placebo tetracycline) or (B) oral tetracycline 500mg (plus gel base BID). Treatment period was 9 weeks with a 3-week follow-up period. Seventy-four subjects were recruited and 64 were available for per-protocol analysis of efficacy. Assessments were at weeks 0, 3, 6, 9 and 12 (follow-up). The primary efficacy variable was defined as the total number of inflammatory lesions. The results of each of the two centres and the combined findings are summarised in table 1 below.

Table 1 Mean total number of inflammatory lesions

	Treatment A			Treatment B		
	Cardiff	Gdansk	Combined	Cardiff	Gdansk	Combined
Week 0	42.05	75.00	56.30	38.29	64.38	49.57
Week 3	22.60	40.00	30.06*	17.13	30.06	23.81*
Week 6	13.44	14.14	13.75*	8.38	16.21	12.44*
Week 9	9.71	9.29	9.52*	6.50	9.86	8.31*
Week 12	8.69	10.71	9.63*	4.70	8.14	6.71*

* $p<0.001$ for difference from Week 0

Both treatments showed significant improvement ($p<0.001$), with the most rapid improvement occurring during the first 3 weeks, at which stage the tetracycline group was significantly better than metronidazole ($p<0.05$), although this difference disappears at weeks 6 and 9. At follow-up the metronidazole group remains much the same but there is continued improvement in the tetracycline group with a significant difference at twelve weeks ($p<0.01$).

One study took a different approach of using topical metronidazole 0.75% gel in combination with tetracycline initially to control the rosacea, and then continuing with BID application of gel to maintain control. The study was in two parts, an open portion initially in which 113 patients were enrolled and treated with a combination of oral tetracycline plus topical metronidazole 0.75% gel. Successfully treated patients (88) were entered into the second part of the study which was randomised, double-blind, placebo controlled comparing metronidazole 0.75% gel BID with the gel base (placebo) in a long term (6 month) follow-up. The rationale was to cease oral tetracycline as soon as remission occurred to avoid the risk of systemic complications and adverse events from the use of long term systemic antibiotics. The primary criteria for assessing efficacy were again inflammatory lesion counts. The results are summarised in table 2 below.

Table 2 Summary of response to treatment with topical Metronidazole 0.75% Gel or Placebo

	Metronidazole		Placebo	
	Week 12	Week 24	Week 12	Week 24
% Patients Relapsing	23	23*	21	42
% Patients free of Inflammatory Lesions	32	53	24	32
Mean No. of Inflammatory Lesions		3.3**		5.8
% Erythema rated as 0 or Mild		74		55

* $p<0.05$
** $p<0.01$ at both 12 and 24 weeks

The results of this maintenance treatment study showed that metronidazole 0.75% gel significantly prolonged the disease-free interval and minimised recurrence.

Assessor's comments

The results of the studies presented show that this formulation of topical metronidazole 0.75% gel is probably as effective as oral tetracycline in the treatment of rosacea.

4.5 CLINICAL SAFETY

In general, the incidence of dermatological reactions is low. The applicant has provided a review with reference to the published clinical trials. The commonest events are erythematous rash and localised skin reactions. In reports of three studies, the irritancy and sensitisation potential of Metroxx gel was examined by the standard repeat insult technique in 102 subjects. Metroxx was shown to be non-irritant with a moderate potential for sensitisation. Photosensitivity potential was studied in 12 healthy volunteers using the standard technique and the results showed no evidence of phototoxicity.

Skin penetration compared with Metrogel was examined by using the skin surface biopsy (skin snipping) technique to remove five successive samples following application of Metroxx and Metrogel in 24 subjects. All analyses were blind. Small differences were detected indicating that Metroxx seemed to penetrate the stratum corneum at a greater rate.

Assessor's comment

It would appear that the absorption of Metroxx is faster than that of Metrogel preparation. However, the average dose applied to the face is less than 4mg metronidazole daily. Even if this was absorbed in total, blood levels would still be very low compared with the doses of up to 2g daily orally, where the absorption is known to approach 100%. Therefore, topical usage can be said to provide a wide therapeutic margin of safety.

4.6 DISCUSSION

Metronidazole has been used in clinical practice in the UK for well over 30 years. It has a recognised efficacy and acceptable safety profile. Topical metronidazole has been licensed for the treatment of rosacea for more than 10 years in a number of countries including the UK, USA and France.

With regards to current application, sufficient clinical information has been submitted. When used as indicated, Metroxx Gel 0.75% has a favourable benefit-to-risk ratio. The hazard associated with Metroxx Gel appears to be low and acceptable when considered in relation to its therapeutic benefits.

Expert report

A satisfactory Clinical Expert Report has been submitted with appropriate CV.

4.7 CONCLUSION

Marketing authorisation may be granted on medical grounds.

5. OVERALL CONCLUSION, RISK-BENEFIT ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Metroxx 0.75% Gel/Metrosa 7.5mg/g Gel is 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

Considering the low systemic concentrations of metronidazole anticipated with the proposed formulation, the existing safety margins are unlikely to be eroded with this topical formulation.

CLINICAL

Metronidazole has been used in clinical practice in the UK for well over 30 years. It has a recognised efficacy and acceptable safety profile. Topical metronidazole has been licensed for the treatment of rosacea for more than 10 years in a number of countries including the UK, USA and France.

No new or unexpected safety concerns arise from this application.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The hazard associated with Metroxx 0.75% Gel/Metrosa 7.5mg/g Gel appears to be low and acceptable when considered in relation to its therapeutic benefits. The risk-benefit assessment is therefore considered to be favourable.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, it was considered that the application for Metroxx 0.75% Gel/Metrosa 7.5mg/g Gel in the treatment of rosacea, could be approved for use as described in the Summary of Product Characteristics.