Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Mupirocin 20 mg/g Nasal Ointment

(Mupirocin calcium)

PRODUCT LICENCE NUMBER: PL 15011/0023
EUROPEAN PROCEDURE NUMBER: UK/H/6688/001/DC

INFECTOPHARM Arzneimittel und Consilium GmbH

LAY SUMMARY
Mupirocin 20 mg/g Nasal Ointment
(Mupirocin calcium)

This is a summary of the Public Assessment Report (PAR) for Mupirocin 20 mg/g Nasal Ointment. It explains how Mupirocin 20 mg/g Nasal Ointment was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Mupirocin 20 mg/g Nasal Ointment.

This product will be referred to as 'Mupirocin Nasal Ointment' in this lay summary for ease of reading.

For practical information about using Mupirocin Nasal Ointment patients should read the package leaflet or contact their doctor or pharmacist.

What is Mupirocin Nasal Ointment and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Bactroban 2% Nasal Ointment.

This medicine is used:
- to kill a group of bacteria in the nose called 'Staphylococci'
- this group includes MRSA (Methicillin-resistant *Staphylococcus aureus*)
- this ointment is for use in the nose only.

How does Mupirocin Nasal Ointment work?
This medicine contains the active substance mupirocin calcium which is an antibiotic that works by killing staphylococcal bacteria from the nasal passages.

How is Mupirocin Nasal Ointment used?
The pharmaceutical form of this medicine is an ointment and the route of administration is nasal (the medicinal product is applied inside the nostrils).

The patient should always use this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

Using this medicine
Adults (including the elderly) and children from one year of age:
Mupirocin Nasal Ointment should be applied to the anterior nares (inside the nostrils) two to three times a day.

Children under one year of age:
Mupirocin Nasal Ointment should not be used in children under one year of age.

Patients with renal impairment:
No dosage adjustment is necessary.

Patients with hepatic impairment:
No dosage adjustment is necessary.

Using this medicine
This medicine is usually applied to the nose two to three times a day.

For further information on how Mupirocin Nasal Ointment is used, including directions for application, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Mupirocin Nasal Ointment have been shown in studies?
Because Mupirocin Nasal Ointment is a hybrid medicine, studies in healthy volunteers consist of tests to determine that it is therapeutically equivalent to the reference medicine.

What are the possible side effects of Mupirocin Nasal Ointment
Because Mupirocin Nasal Ointment is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Mupirocin Nasal Ointment approved?
It was concluded that, in accordance with EU requirements, Mupirocin Nasal Ointment has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Mupirocin Nasal Ointment?
A Risk Management Plan (RMP) has been developed to ensure that Mupirocin Nasal Ointment is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Mupirocin Nasal Ointment
A Marketing Authorisation for Mupirocin Nasal Ointment was granted in the UK on 14 February 2019.

The full PAR for Mupirocin Nasal Ointment follows this summary.

This summary was last updated in March 2019.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Mupirocin Nasal Ointment (PL 15011/0023; UK/H/6688/001/DC) could be approved.

The product is indicated for the treatment of the following:
The elimination of nasal carriage of staphylococci, including methicillin resistant S*taphylococcus aureus* (MRSA) in adults, adolescents and children aged one year and older.

The Reference Member State (RMS) for this procedure was the UK and the Concerned Member States (CMSs) were France, Netherlands, Portugal, Greece, Austria, Germany, Hungary, Slovak Republic, Italy, Poland, Spain and the Czech Republic.

Mupirocin is a topical antibiotic produced through fermentation by *Pseudomonas fluorescens*. Mupirocin inhibits isoleucyl transfer-RNA synthetase, thereby arresting bacterial protein synthesis.
Mupirocin has bacteriostatic properties at minimum inhibitory concentrations and bactericidal properties at the higher concentrations reached when applied locally.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of the reference medicinal product Bactroban 2% Nasal Ointment (PL 00038/0347), which was granted a product licence in the UK to Beecham Group plc on 07 March 1988.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a hybrid medicinal product of a reference product that has been licensed for over 10 years.

Data from one therapeutic equivalence study was submitted with this application. This study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 208) on 25 January 2019. After a subsequent national phase, a licence was granted in the UK on 14 February 2019.

II QUALITY ASPECTS

II.1 Introduction

Each 1 g of nasal ointment contains 20 mg of the active substance mupirocin calcium.

In addition to mupirocin calcium this product also contains the excipients paraffin, white soft and bis-diglyceryl polyacyladipate-2.

The finished product is packaged in aluminium tubes with epoxy-phenolic inner lacquer, fitted with a HDPE nozzle and HDPE screw cap containing 3 g or 5 g ointment.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Mupirocin calcium

Chemical Name: Mupirocin calcium

Molecular Formula: Calcium bis[9-[[(2E)-4-[(2S,3R,4R,5S)-3,4-dihydroxy-5-[[(2S,3S)-3-[(1S,2S)-2-hydroxy-1-ethylpropyl]oxiranyl]methyl]tetrahydro-2H-pyran-2-yl]-3- methylbut-2-enoyl]oxy]nonanoate dihydrate

Chemical Structure: $C_{52}H_{86}CaO_{18}.2H_2O$

Molecular Weight: 1075
Appearance: A white or almost white powder
Solubility: Very slightly soluble in water, sparingly soluble in anhydrous ethanol and in methylene chloride

Mupirocin calcium is the subject of a European Pharmacopoeia monograph.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product(s).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A 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 and has shown satisfactory results.

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

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage conditions 'Do not store above 25 °C', is acceptable. The tube contents can be used for up to 7 days after first opening.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of mupirocin calcium are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, data from one therapeutic equivalence study has been submitted with this application. This study was conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

In support of the application(s), the applicant submitted the following therapeutic equivalence study:

STUDY:

A prospective, monocentric, randomised, double-blind, three-armed, placebo-controlled "clinical endpoint bioequivalence study" to evaluate the efficacy and safety of the eradication of *Staphylococcus aureus* by intranasal treatment with two 2 % mupirocin ointments.

The single-centre, parallel group, randomised, double-blind therapeutic equivalence study (ESMUP) compared the test product Mupirocin 20 mg/g Nasal Ointment (INFECTOPHARM Arzneimittel und Consilium GmbH) versus the reference product Bactroban 2% Nasal Ointment (Beecham Group plc) in the efficacy and safety of the eradication of *Staphylococcus aureus* by intranasal treatment in healthy subjects.

Patients were randomised to one of the following treatments in a 3:3:1 ratio (respectively):

- INVESTIGATIONAL PRODUCT: Mupirocin 20 mg/g Nasal Ointment (INFECTOPHARM Arzneimittel und Consilium GmbH)
- COMPARATOR: Bactroban 2% Nasal Ointment (Beecham Group plc)
- PLACEBO: vehicle base (INFECTOPHARM Arzneimittel und Consilium GmbH)

Design

The therapeutic equivalence study (ESMUP) was based on FDA Draft Guideline https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm217147.pdf (in the absence of a specific EU guideline for topical mupirocin in this indication), and taking into account previous Scientic Advice (MHRA).

Method of Application

A small amount of ointment (about the size of a match head) was to be administered into each nostril three times per day (morning, lunchtime, evening) for a duration of 5 days. The treatment period of 5 days was followed by 3 ± 1 days of follow-up.

Objectives and Endpoints

The study was intended to establish therapeutic equivalence of the proposed new test formulation compared to the Bactroban reference ointment in terms of eradication of nasal

colonisation with *S. aureus* based on the study hypothesis that the former would be equivalent to the comparator Bactroban Nasal Ointment 2 % with regard to the primary objective. (therapeutic equivalence, $\delta = 0.2$ – see *sensitivity analysis* below).

Primary endpoint
Treatment success at the final visit on Day 8 (48 - 96 hours after the end of treatment; defined as complete eradication of *S. aureus*, i.e. a negative nasal culture for all *S. aureus* strains).

Secondary endpoints
Sensitivity analysis - comparing the treatment success rate of Bactroban with that of vehicle in the per protocol (PP) population. Sensitivity with regard to the chosen δ of $\pm$ 0.20 would be considered to be proven, if the δ did not exceed 50 % of the difference between the treatment success rate in the Bactroban group and in the vehicle group.

Efficacy
95 % confidence interval (CI) on treatment success rates at the final visit for differences between the test Mupirocin 20 mg/g Nasal Ointment group and the Bactroban Nasal Ointment group in the full-analysis (FA) population.

95 % CI on treatment success rates at the final visit for differences between test Mupirocin 20 mg/g Nasal Ointment group and the vehicle group in the FA and PP population.

95 % CI on treatment success rates at the final visit for differences between Bactroban Nasal Ointment group and the vehicle group in the FA and PP population.

Comparison of treatments on treatment success rates at the final visit in the FA and PP population using Fisher's exact tests.

Comparison of treatments on dropout rates at the final visit in the safety evaluable (SE) population using Fisher's exact tests.

Safety
Monitoring of serious and causally related adverse events. The safety variables (adverse events, serious adverse events, drop-outs) were analysed by descriptive statistics.

Results
Based on the Applicants primary analysis (PP population), 81.2 % of the subjects in the test Mupirocin 20 mg/g Nasal Ointment group and 81.6 % of the subjects in the Bactroban 2% Nasal Ointment group showed treatment success (negative bacterial cultures on Day 8). In contrast, only 3 subjects (8.8 %) receiving vehicle had a negative bacterial culture at Day 8.

The two-sided 95 % CI for the difference of the likelihoods of treatment success in the two active treatment groups was found to be [- 0.120; + 0.113] (lower limit; upper limit).

A summary of the results for the test and reference products are presented below:

Table: Primary Analysis: 95% CI for Differences of Treatment Success Rate (PP)

95% Confidence Interval for Differences of Treatment Success Rate on Final Visit V8 (PP)				
Comparison	**Difference**	**ASE**	**Lower 95% CI Limit**	**Upper 95% CI Limit**
Investigational Product vs. Comparator	-0.004	0.055	-0.120	0.113

Table: Sensitivity Analysis: 95% CI for Differences of Treatment Success Rate (PP)

95% Confidence Interval for Differences of Treatment Success Rate on Final Visit V8 (PP)				
Comparison	**Difference**	**ASE**	**Lower 95% CI Limit**	**Upper 95% CI Limit**
Comparator vs. Vehicle	0.727	0.062	0.586	0.868

Sensitivity, with regard to the chosen δ of ± 0.20, was proven because the δ does not exceed the predefined limit of 50 % of the difference (0.5*0.727=0.3635) between the treatment success rate in the Bactroban 2% Nasal Ointment (Comparator) and Vehicle group.

Based on the PP population the two-sided 95 % CI for the difference of the likelihoods of treatment success in the Comparator and in the Vehicle group was found to be [0.586; 0.868] (lower limit; upper limit). This CI was not contained within [- 0.20; + 0.20] and therefore, as expected, no equivalence between the Comparator and the Vehicle was shown.

As expected, there was no equivalence between the Comparator (Bactroban 2% Nasal Ointment) and Vehicle and no equivalence between the Investigational Product [Mupirocin 20 mg/g Nasal Ointment (INFECTOPHARM Arzneimittel und Consilium GmbH)] and the Vehicle. The comparisons of both active treatments to the Vehicle using the Fisher's Exact Test showed significantly higher treatment success rates for both active treatment groups ($p < 0.0001$ for both active treatment groups, in the PP population and in the FA population). No discrepancies for the above-mentioned efficacy analyses were found between the statistical results in the PP and FA population. The analysis of the primary objective in the FA population showed a lower limit of -0.116 and an upper limit of 0.112 of the two-sided 95 % confidence interval for the difference of the likelihoods of treatment success in the two active treatment groups.

Conclusion

Therapeutic equivalence was shown between the test and reference product. For the purposes of this application Mupirocin 20 mg/g Nasal Ointment (INFECTOPHARM Arzneimittel und Consilium GmbH) can be considered therapeutically equivalent to Bactroban 2% Nasal Ointment (Beecham Group plc).

IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation(s) is recommended for this application.

V USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

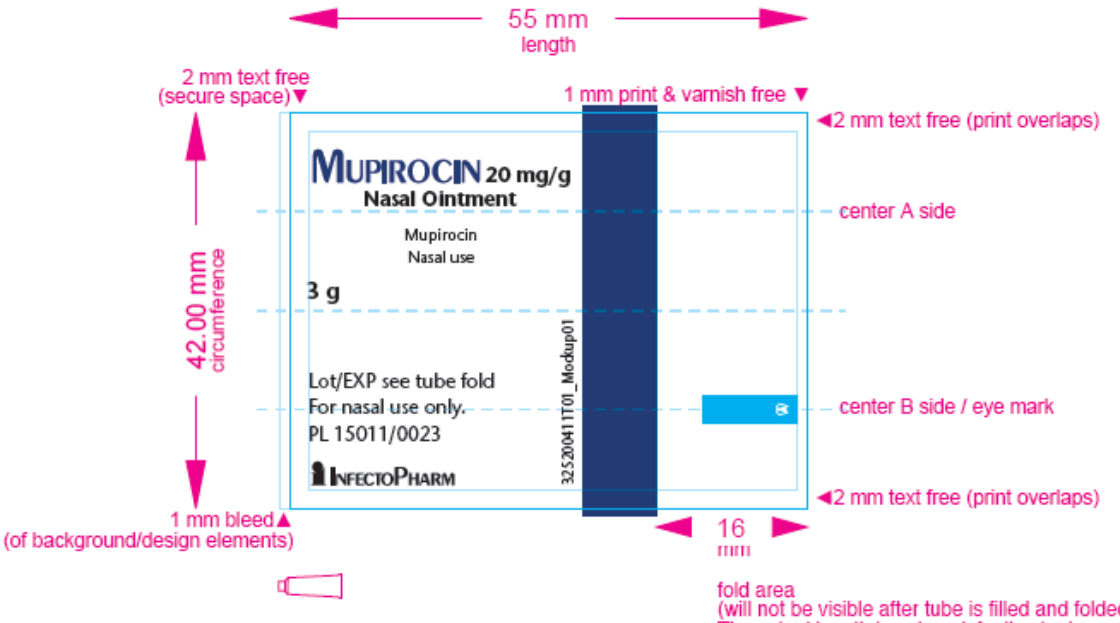
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

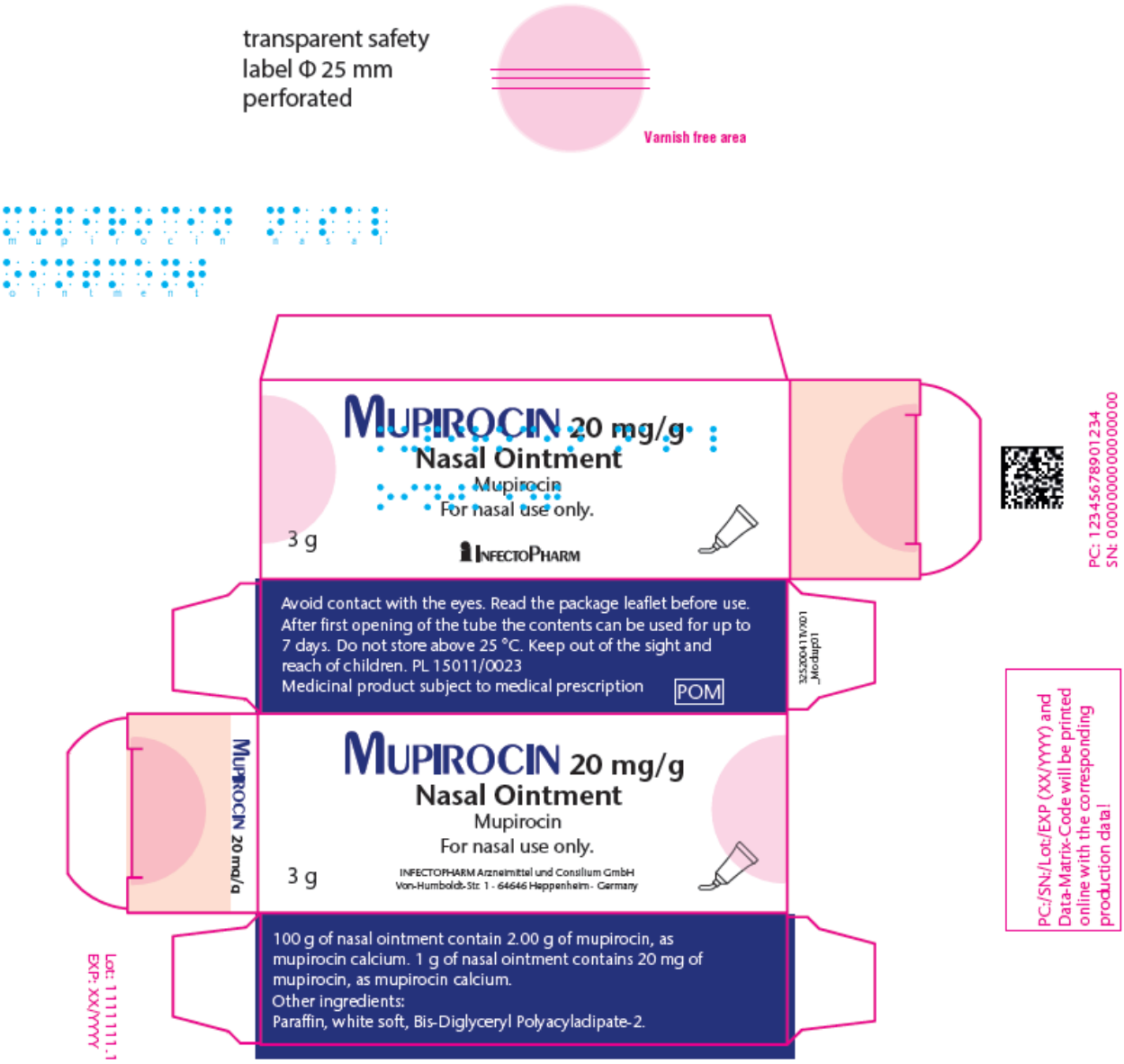
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines. The SmPC is consistent with the reference product.

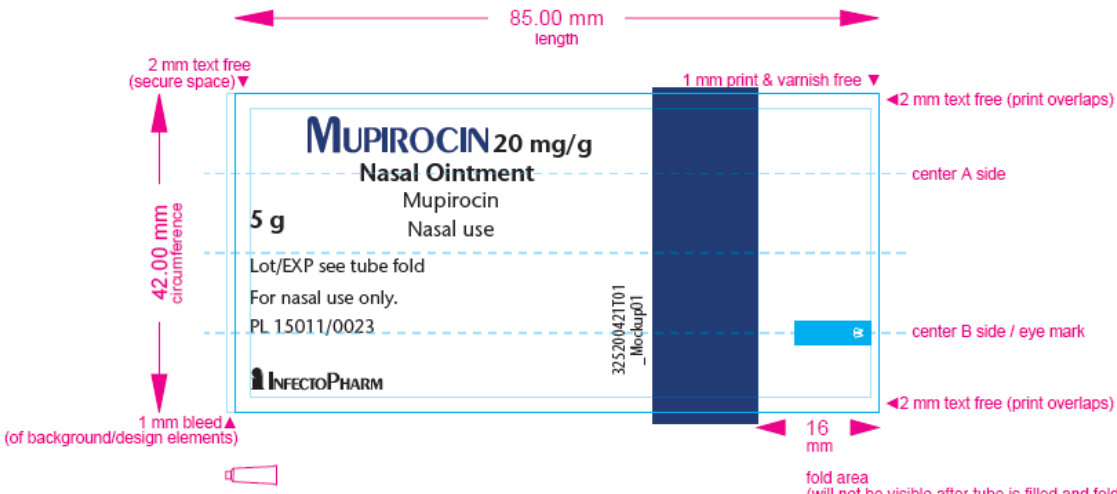
In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.



fold area for diameter 13,5 mm (DIN 5060)
double fold: 12 mm
triple fold: 16 mm
saddle fold: 20 mm


transparent safety label Φ 25 mm perforated
Varnish free area
mupirocin nasal ointment
MUPIROCIN 20 mg/g
Nasal Ointment
Mupirocin
For nasal use only.
3 g
INFECTOPHARM
PC: 1234567890 1234
SN: 00000000000000
Avoid contact with the eyes. Read the package leaflet before use.
After first opening of the tube the contents can be used for up to 7 days. Do not store above 25 °C. Keep out of the sight and reach of children. PL 15011/0023
Medicinal product subject to medical prescription
POM
325200411V001 _Modup01
MUPIROCIN 20 mg/g
MUPIROCIN 20 mg/g
Nasal Ointment
Mupirocin
For nasal use only.
3 g
INFECTOPHARM Arzneimittel und Consilium GmbH
Von-Humboldt-Str. 1 - 64646 Heppenheim - Germany
100 g of nasal ointment contain 2.00 g of mupirocin, as mupirocin calcium. 1 g of nasal ointment contains 20 mg of mupirocin, as mupirocin calcium.
Other ingredients:
Paraffin, white soft, Bis-Diglyceryl Polyacyladipate-2.
Lot: 11111111
EXP: XX/YYYY
PC:/SN:/Lot:/EXP (XX/YYYY) and Data-Matrix-Code will be printed online with the corresponding production data!



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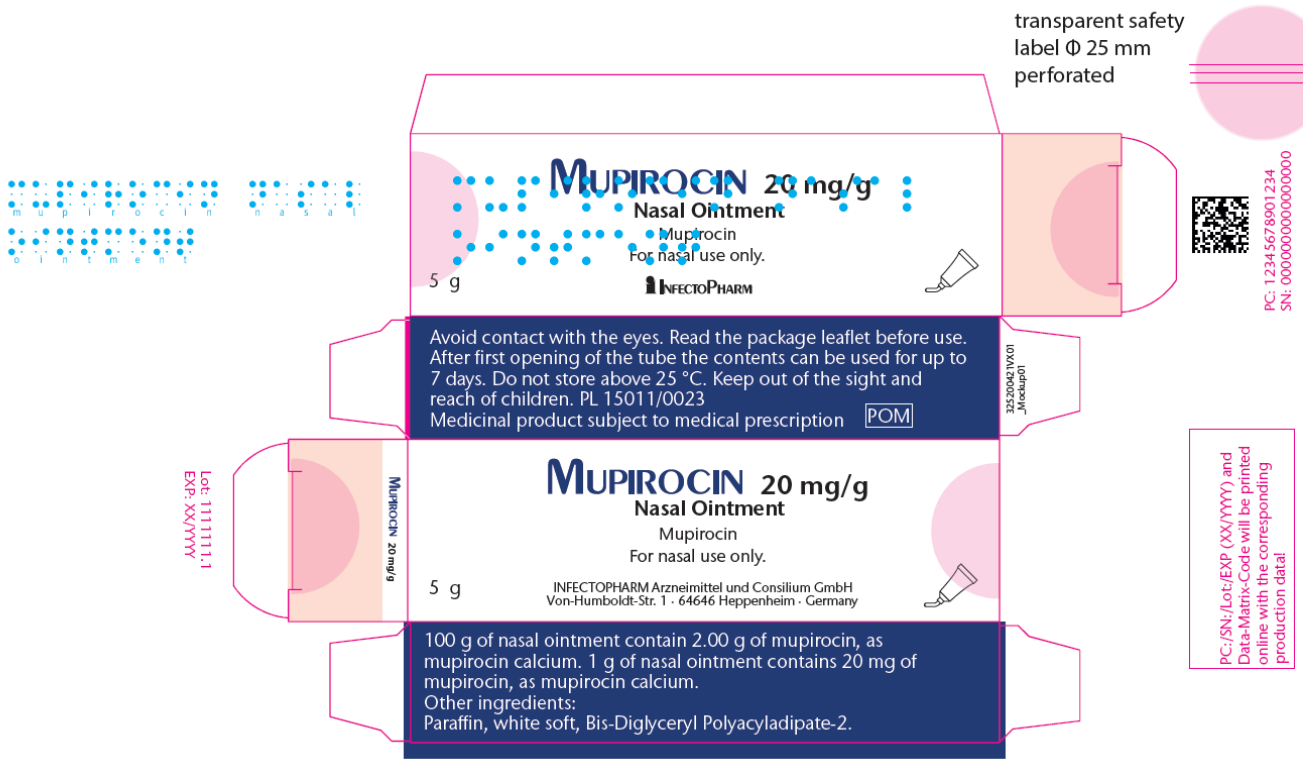

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Outcome**	**Assessment report attached Y/N**