



# **Public Assessment Report**

## **National Procedure**

**Permethrin 5% w/w Cream**  
**permethrin**

**PL 20117/0361**

**Morningside Healthcare Limited**

## LAY SUMMARY

### Permethrin 5% w/w Cream permethrin

This is a summary of the Public Assessment Report (PAR) for Permethrin 5% w/w Cream. It explains how this product 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 this product.

For practical information about using Permethrin 5% w/w Cream, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What is Permethrin 5% w/w Cream 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 Lyclear Dermal Cream.

Permethrin 5% w/w Cream is used to treat infestations of scabies and crab lice on the body.

#### **How does Permethrin 5% w/w Cream work?**

This medicine contains the active ingredient permethrin, which belongs to a group of medicines called pyrethroids. Pyrethroids kill mites such as scabies and crab lice.

#### **How is Permethrin 5% w/w Cream used?**

The pharmaceutical form of this medicine is a cream and the route of administration is cutaneous.

Patients should apply the cream to clean, dry, cool skin. Patients should not take a hot bath or shower immediately before treatment. They should carefully apply a thin layer of cream to the skin.

#### To treat scabies

Adults and adolescents over 12 years of age should apply up to 30 g of cream (corresponding to one tube of 30 g). Children aged from 6 to 12 years should apply up to 15 g of cream (corresponding to ½ tube of 30 g). Children aged from 2 months to 5 years should apply up to 7.5 g of cream (corresponding to ¼ tube of 30 g).

There is only limited amount of data available in newborns and infants under 2 months and no dose can be recommended. Permethrin 5% w/w Cream should not be used in this age group unless advised by a doctor and treatment should only be given under close medical supervision.

#### To treat crab lice

Adults over 18 years of age should apply up to 30 g of cream (corresponding to one tube of 30 g).

Patients should take care not to allow the cream to get into the eyes or come into contact with mucous membranes (inside the nose or throat, genital region) or open wounds. If accidental contact occurs, patients should rinse thoroughly with water.

Adults should apply the cream to the whole body including the neck, palms of the hands and soles of the feet. The head and face can be spared unless this area includes places affected by scabies (itch mites).

When applying the cream, the areas between the fingers and toes (also under the finger and toe-nails), the wrists, elbows, armpits, external genitalia and buttocks should be especially carefully treated.

When treating crab lice in adults, any facial hair (beards moustaches) and eyelashes should be checked for the presence of live lice and eggs. Cream should be applied to any facial hair, carefully avoiding eyes. If live lice or eggs are found on the eyelashes they should be removed carefully using tweezers. Cream should not be applied to the eye lashes because the cream can cause moderate eye irritation.

Children should apply the cream uniformly to the whole body, including the palms of the hands, soles of the feet, neck, face, ears, and scalp. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared. Children should not lick the cream from their hands. If necessary, children should wear gloves.

Elderly patients (over 65 years) should use the cream in the same way as other adults but in addition, the face, ears and scalp should also be treated. Care should be taken to avoid applying the cream to areas of skin around the eyes.

One application of Permethrin 5% w/w Cream is usually sufficient. The cream should be left on the skin for at least eight hours, for example, overnight. Patients should avoid bathing, showering or washing during this period. If, by way of an exception, patients have to wash their hands within the eight-hour period, then they should reapply the cream to the hands and wrist area. The same applies if patients have to wash other parts of treated skin (buttocks, external genitalia). After at least eight hours, patients should take a shower or wash the skin with soap and water.

Provided these instructions for use are followed, a single application is generally sufficient for successful treatment. However, in cases of persistent or renewed infestation, it may be necessary to repeat the treatment after 14 days.

For further information on how Permethrin 5% w/w Cream is used, refer to the package leaflet and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

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

**What benefits of Permethrin 5% w/w Cream have been shown in studies?**

As Permethrin 5% w/w Cream is a hybrid medicine, studies in patients consist of tests to determine that it is therapeutically equivalent to the reference medicine.

**What are the possible side effects of Permethrin 5% w/w Cream?**

As Permethrin 5% w/w Cream 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 SmPC available on the MHRA website.

**Why was/were Permethrin 5% w/w Cream approved?**

It was concluded that, in accordance with EU requirements, Permethrin 5% w/w Cream 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 Permethrin 5% w/w Cream?**

A Risk Management Plan (RMP) has been developed to ensure that Permethrin 5% w/w Cream 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 Permethrin 5% w/w Cream**

A Marketing Authorisation for Permethrin 5% w/w Cream was granted in the UK on 04 March 2021.

The full PAR for Permethrin 5% w/w Cream follows this summary.

This summary was last updated in April 2021.

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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 Permethrin 5% w/w Cream (PL 20117/0361) could be approved.

The product is approved for the following indication:

For the treatment of scabies in adults and children aged from 2 months, and crab lice in adults.

The principal physiological action of permethrin in lice is the induction of electrochemical abnormalities across the membranes of excitable cells, leading to sensory hyperexcitability, incoordination and prostration. It is assumed that the mode of action against mites is similar.

This application was submitted under Regulation 52B of the Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Lyclear Dermal Cream, that has been licensed within the EU for a suitable time, in line with the legal requirements.

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.

A national marketing authorisation was granted in the UK on 04 March 2021.

## II QUALITY ASPECTS

### II.1 Introduction

This product consists of a white to off-white, smooth, homogeneous cream. Each 30 g tube of cream contains 1500 mg permethrin.

In addition to permethrin, this product also contains the excipients butylhydroxytoluene (E321), carbomers, refined coconut oil, glycerol (E422), glycerol monostearate 40-55, isopropyl myristate, liquid paraffin mixture/lanolin alcohol, macrogol (2) cetyl ether, macrogol cetostearyl ether, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, sodium hydroxide (E524) and purified water.

The finished product is packaged in 30 g collapsible aluminium tubes, fitted with white conical polypropylene caps. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

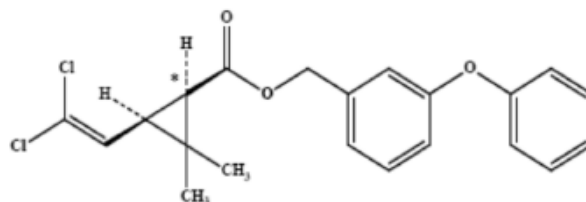
### II.2 ACTIVE SUBSTANCE

#### rINN: Permethrin

Chemical Name: Mixture of the cis and trans isomers of (3-Phenoxy phenyl) methyl (1RS, 2RS)-2-(2,2-dichloroethenyl)-3,3-dimethyl cyclopropane-1-carboxylate

Molecular Formula:  $C_{21}H_{20}Cl_2O_3$

Chemical Structure:



its epimer at C\* and their enantiomers

Molecular Weight: 391.29

Appearance: Colourless or slightly brownish viscous liquid, semi-solid or crystalline solid

Solubility: Practically insoluble in water, very soluble in heptane, freely soluble in anhydrous ethanol, sparingly soluble in ethylene glycol

Permethrin is the subject of a European Pharmacopoeia monograph.

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.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

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.

With the exception of liquid paraffin/lanolin alcohol mixture, no excipients of animal or human origin are used in the final products.

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(s)**

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 no special storage conditions, is acceptable.

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 permethrin 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**

An Environmental Risk Assessment (ERA) has been provided. The results of the ERA show that there is unlikely to be a risk of increased environmental exposure with the use of this product.

Following the intended use of this active substance a serious harmful effect on aquatic organisms (daphnia and fish) and terrestrial organisms (plants) is expected after passage of the sewage treatment plant.

### **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, the applicant submitted the following therapeutic equivalence study.

#### Therapeutic equivalence study 1

This study was a Phase III, double-blind, multicentre, randomised, parallel-group, active-controlled clinical study, to compare the efficacy and safety of Permethrin 5% w/w Cream with Lyclear Dermal Cream, in subjects with scabies.

Subjects were administered a single application of either the test or reference product on a dry and cool body surface, once in a week. The cream was allowed to remain in contact with the skin for at least 8 hours overnight. Subjects received a maximum of three applications (once a week) depending on whether there was presence of scabies lesions and continuous itching after the first and second applications, hence the total duration of study varied from 7 days to 21 days, based on the subject's response.

Overall, 83 subjects were screened, and 80 subjects were randomised in the study. One subject was excluded from the per protocol (PP) efficacy analysis due to protocol deviation. The safety set included all the randomised subjects who were exposed to double blind study medication. Responders were defined as subjects with no scabies remaining and at least 50% improvement in the visual analogue scale (VAS) score for pruritus.

Each evaluable subject in both treatment arms reported no remaining scabies and at least 50% reduction in the VAS score for pruritus during the 7-21 days of the treatment period. The

total number of mean lesions decreased by 38.85 in the test arm and by 43.77 in the reference arm and the difference of 4.92 between both the treatments was not statistically significant. Every subject (100%) reported 'No pruritus' in self assessed pruritus reduction during the 7-21-day treatment period. For the percentage change in assessment of pruritus using the VAS score, an average of 98.33% improvement in the test arm and 100% in the reference arm was identified.

Therapeutic equivalence was shown between the test and reference products. For the purposes of this application, Permethrin 5% w/w Cream can be considered therapeutically equivalent to Lyclear Dermal Cream.

#### **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 an RMP, in accordance with the requirements of Regulation 182 of the Human Medicines Regulation 2012, 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 is recommended for this application.

### **V USER CONSULTATION**

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with the requirements of Regulation 267 of the Human Medicines Regulations 2012, as amended (previously article 61(1) of Council Directive 2001/83/EC).

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Regulation 260(3) of The Human Medicines Regulation 2012, as amended (previously Articles 59(3) and 61(1) of Council Directive 2001/83/EC). The results show that the PIL 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.

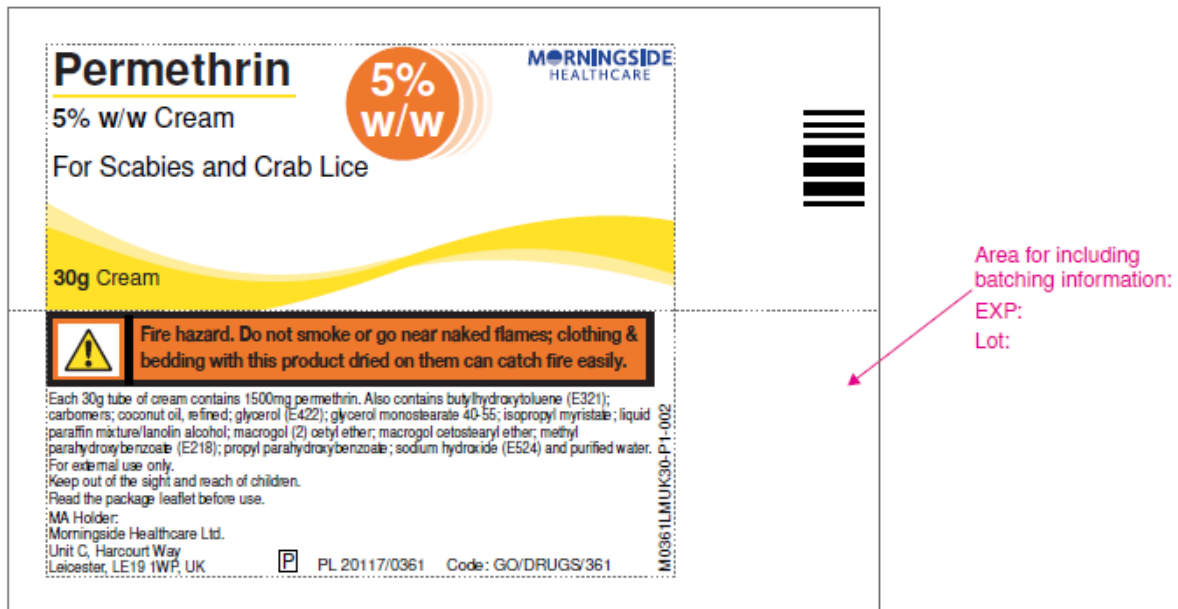
Extensive clinical experience with permethrin is considered to have demonstrated the therapeutic value of the product.

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.

In accordance with Regulation 203(2) of The Human Medicines Regulation 2012, as amended, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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



**TABLE OF CONTENT OF THE PAR UPDATE**

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 marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

<b>Application type</b>	<b>Scope</b>	<b>Product information affected</b>	<b>Date of grant</b>	<b>Outcome</b>	<b>Assessment report attached Y/N</b>