Public Assessment Report

Hedrin 4% Cutaneous Solution

(dimeticone)

PL 00240/0137
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Thornton & Ross Ltd. a Marketing Authorisation (licence) for the medicinal product Hedrin 4% Cutaneous Solution (PL 00240/0137). This is a pharmacy medicine [P] to eradicate head lice infestations.

Head lice infestation is a parasitic infestation of the hair and scalp particularly occurring in children of school age. Infestation is transmitted by close contact. Dimeticone is widely used as an active ingredient in a number of skin preparations for the treatment of dry skin conditions. This is the first time an application has been made to use dimeticone as a treatment for head lice. The way Hedrin works is not fully understood, it appears to act by disrupting the water balance mechanisms in lice.

The clinical data presented to the MHRA, before licensing, demonstrated that Hedrin 4% Cutaneous Solution kills the head lice. There were no significant safety concerns and it was decided that the benefits of using Hedrin outweigh the risks, hence a Marketing Authorisation has been granted.
# SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Hedrin 4% Cutaneous Solution (PL 00240/0137) to Thornton & Ross Ltd. on 23 November 2005. The product is a pharmacy only medicine.

The application was submitted as a full application according to article 8.3(i) of Directive 2001/83/EC, as amended.

Hedrin 4% Cutaneous Solution contains the active ingredient dimeticone, with the chemical name \(\alpha-\omega\)-bis-trimethylsiloxypolydimethylsiloxane

Hedrin 4% Cutaneous Solution is indicated for the eradication of head lice infestations.

The Hedrin solution acts on the lice by a physical process to cover the lice and disrupt the ability of the lice to manage its water balance so that treated insects fail to excrete surplus water. Hedrin activity is not diminished in insecticide resistant head lice. It is less effective in its ovicidal activity and therefore two applications 7 days apart are required.

Dimeticone has been licensed for at least 33 years, and is widely used as an active ingredient in a number of topical preparations for the treatment of dry skin conditions. This is the first application for the proposed indication.
PHARMACEUTICAL ASSESSMENT

INTRODUCTION

Legal Basis

This is a national full application for Hedrin Lotion, submitted under E.C. Directive 2001/83/EC Article 8.3(i), for an existing active substance dimeticone.

The proposed product is a cutaneous solution containing 4%w/w dimeticone.

The dossier contains preclinical and clinical safety and efficacy data to support the new indication.

Use

Dimeticones are widely used in topical barrier preparations but the proposed use as a pediculicidal agent is novel. The mode of action, not fully elucidated, appears to be related to a disruption of the water balance mechanism in the lice, leading to rupture of gut.

Hedrin is indicated for the eradication of headlice infestations in adults and children over six months of age.

The lotion is applied to dry hair covering the full scalp, left for 8 hours or overnight and washed out with normal shampoo and rinsed with water. The treatment is repeated after 7 days.

Transmissible spongiform encephalopathy (TSE) concerns

The applicant states that there are no ingredients of animal origin.

Background

Dimeticone preparations are licensed in UK as barrier cream (eg, Conotrane 22% w/w cream, PL 00166/0178, granted 1/7/1998), as barrier topical sprays (Sprilon 1%w/w, PL 16431/0020, granted 23/03/2005) and as oral preparations (Unigest tablets, PL 16853/0088, granted 18/04/2005, Bubble Breaker Oral Emulsion, PL 18963/0001, granted 1/5/2002).

DRUG SUBSTANCE

General Information

Name (rINN and Ph Eur): Dimeticone
Chemical name: \(\alpha-\omega\)-bis-trimethylsiloxypolydimethylsiloxane
Other names: Polydimethylsiloxane, Silicone oil, Dimethyl silicone fluid
Molecular formula: \(\text{CH}_3 \left[ \text{Si} \left( \text{CH}_3 \right)_2 \text{O} \right]_n \text{Si} \left( \text{CH}_3 \right)_3\)
Chirality: None
Properties: Dimeticone is a clear, colourless viscous liquid. It is practically insoluble in water, slightly soluble in glycerol, methanol, ethylene glycol, and ethanol. It is miscible with polar solvents such as hexane, toluene, ethyl acetate, methylethyl ketone.
Control of materials

There are no materials of biological origin. An appropriate specification has been provided for the starting material.

Controls of critical steps and intermediates

*In-process monitoring*

Satisfactory controls are in place to ensure the key parameters (viscosity, volatility and traces of catalyst-phosphorus) are suitably controlled in the synthesis of dimeticone.

Process validation and/or evaluation

No formal validation data are provided and accepted as the manufacturer has produced dimeticones for many years using the same process. Satisfactory analytical data from 20 batches of the drug substance confirm good process capability and consistent quality.

Characterisation

The drug substance has been characterised by appropriate methods. Supporting spectra are provided.

Analytical procedures

The analytical procedures used for the control of dimeticone are those described in the Ph.Eur. (appearance, identity, volatile matter, mineral oils and heavy metals) or in-house methods developed. Satisfactory methods are provided for colour (visual comparison with standards), viscosity (rotational or cone and plate viscometer) and all other Ph.Eur. tests.

Reference standards

The reference standard used for the identification of the drug substance is dimeticone CRS. Further reference standards for the drug substance was prepared for use from production batches. A Certificate of Analysis has been provided for the reference standard.

Stability

This is satisfactorily addressed.

The results obtained are within specification and confirm no product degradation.

A satisfactory post-approval stability commitment has been provided.
DRUG PRODUCT

Description and Composition

Hedrin is a cutaneous solution containing 4%w/w dimeticone. Cyclomethicone 5 is present as an excipient.

The drug product is supplied in HDPE bottles (50ml, 100ml, 150ml and 200ml) with an integrated dropper insert and screw cap.

Development Pharmaceutics

Drug substance

The drug substance, dimeticone, is widely used in pharmaceutical and cosmetic industries. It is a clear and colourless fluid that is practically insoluble in water but soluble in non-polar organic solvents. The key pharmacochemical characteristic for the drug substance is its high viscosity, which is required for its pediculicidal activity.

Excipients

Cyclomethicone 5 is a volatile silicone that is widely used in the cosmetic industry as a carrier for other silicones and as an excipient in two UK licensed products. It is a subject of USNF monograph. It is used as the vehicle for solution of the drug substance in the formulation of Hedrin. Upon application, cyclomethicone evaporates, leaving dimeticone on the hair and scalp.

Formulation Development

The development of the dosage form is adequately described. The final formulation contains 4% dimeticone solubilised in cyclomethicone 5 as a volatile carrier.

No overages are included. The procedure allows for adjustment to the carrier amount during blending due to its volatile nature.

The key properties of the drug substance and the drug product are viscosity and volatility respectively. Whilst the high viscosity of Dimeticone is essential for treatment of head lice infestation, the formulation requires a vehicle (Cyclomethicone 5) for homogeneous solubilisation and volatile to enable uniform deposit of drug substance on the hair and scalp.

Container closure system

Stability studies indicate that the plastic lid and HDPE bottle is not affected by long term contact with the product. Pack compatibility studies have been carried out to monitor the interaction between the product and the HDPE bottle. These are satisfactory.

Compatibility

The drug product is not intended to be diluted before use or co-administered with other drugs or used with medical devices.
Manufacture of finished product

Hedrin will be packaged, tested and released for sale in the EU by: Thornton and Ross Ltd, Linthwaite, Huddersfield, Yorkshire HD7 5QH. A satisfactory copy of manufacturing licence ML/240/1 is provided. This site has been approved for the manufacture of other UK licensed products.

Description of the manufacturing process

Satisfactory formula for the proposed batch size, flow diagram and description of manufacture are provided.

The critical step of the manufacturing process has been satisfactorily identified and appropriate in-process controls are in place.

Thornton and Ross have provided satisfactory data for filling six 200L pilot batches into glass and plastic bottles (50ml, 100ml and 200ml). Minor corrective actions were implemented to successfully resolve problems associated with machine setting and filling. All batches met requirements of product specification for samples taken at the beginning, middle and end of filling run.

The product batches are not re-processed.

Control of excipients

Cyclomethicone 5 is used in the formulation as a volatile carrier. Cyclomethicone 5 is a fully methylated cyclic siloxane containing repeating units of the formula: \([-{(CH_3)2SiO-}]_n\), in which n is 4, 5, 6, or a mixture of them (referred D4, D5 and D6).

Cyclomethicone 5 complies with the requirements of the USNF monograph. It is warranted to meet the in-house specification, but routinely performs test for appearance, identification (IR spectroscopy), non-volatile content, D4+D5+D6 and assay for D5, in compliance with the requirements of the USNF monograph. This is accepted.

Compendial methodology is used. The methods for non-volatile content and determination of D4, D5 and D6 and the assay of D5 are satisfactorily validated. The specifications are considered appropriate. A satisfactory Certificate of Analysis for Cyclomethicone 5 is provided.

Control of drug product

Specification

The range of specification tests complies with ICH guidelines and Ph.Eur. requirements for cutaneous preparation.

The specification limits applied at release and shelf life are the same.

The limits for dimeticone content at release and shelf life are in line with current directives and accepted.
Analytical procedures

Satisfactory methodology are provided for the identification of drug product and non-volatile drug substance, for which standard compendial methods are used. The methods used for the determination of viscosity and non-volatile content have been satisfactorily validated for precision, ruggedness, linearity/range and accuracy. The method for assay is suitable for release and shelf life testing.

Batch data

Satisfactory data are provided for batches of drug product, manufactured at full production scale at the proposed site and considered representative of the proposed bulk product.

Reference Samples

The data provided is considered satisfactory.

Container/Closure System

The drug product is packed into 50ml, 100ml, 150ml and 200ml natural, translucent HDPE bottles with an integral dropper insert and screw cap.

The HDPE plastic bottles are suitable for use in food, household and cosmetic products. The bottle cap and dropper inserts are made from polypropylene.

Satisfactory details of specification based on supplier certification and product construction are provided, together with safety compliance statements for the primary packaging components. In-house specification giving details of tests performed on receipt are provided.

Stability of Drug Product

The stability programme complies with current international guidelines. The quality specification is as given by the shelf life finished product specification.

The samples are considered representative of the product to be marketed. All stability batches are manufactured at full production scale.

The programme is to last for 36 months. The stability programme is satisfactory, with the results showing no significant trends in the proposed packs.

A photostability study carried out confirmed the suitability of the proposed primary packs.

Considering the stable nature of the product and supportive stability data, the results support the proposed 24 months shelf life with no special storage conditions.

A commitment to test the first two production batches has been provided.

QUALITY OVERALL SUMMARY

This is satisfactory.
SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PIL and LABELLING

These are satisfactory.

CONCLUSION

A product licence may be granted for this product
DEFINITION

Dimeticone is a poly (dimethylsiloxane) obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane. Different grades exist which are distinguished by a number indicating the nominal viscosity placed after the name.

Their degree of polymerisation \((n = 20 \text{ to } 400)\) is such that their kinematic viscosities are nominally between 20 mm\(^2\) s\(^{-1}\) and 1300 mm\(^2\) s\(^{-1}\).

*Dimeticones with a nominal viscosity of 50 mm\(^2\) s\(^{-1}\) or lower are intended for external use only.*

CHARACTERS

Clear, colourless liquids of various viscosities, practically insoluble in water, very slightly soluble to practically insoluble in ethanol, miscible with ethyl acetate, with methyl ethyl ketone and with toluene.

IDENTIFICATION

A. It is identified by its kinematic viscosity at 25 °C (see Tests).

B. Examine by infrared absorption spectrophotometry (2.2.24) comparing with the spectrum obtained with dimeticone CRS. The region of the spectrum from 850 cm\(^{-1}\) to 750 cm\(^{-1}\) is not taken into account.

C. Heat 0.5 g in a test-tube over a small flame until white fumes begin to appear. Invert the tube over a 2nd tube containing 1 ml of a 1 g/l solution of chromotropic acid, sodium salt R in sulphuric acid R so that the fumes reach the solution. Shake the 2nd tube for about 10 s and heat on a water-bath for 5 min. The solution is violet.

D. In a platinum crucible, prepare the sulphated ash (2.4.14) using 50 mg. The residue is a white powder that gives the reaction of silicates (2.3.1).

TESTS

Acidity

To 2.0 g add 25 ml of a mixture of equal volumes of ethanol R and ether R, previously neutralised to 0.2 ml of bromothymol blue solution R1 and shake. Not more than 0.15 ml of 0.01 M sodium hydroxide is required to change the colour of the solution to blue.

Viscosity (2.2.9)

Determine the kinematic viscosity at 25 °C. For dimeticones, the kinematic viscosity is not less than 90 per cent and not more than 110 per cent of the nominal viscosity stated on the label.

Mineral oils

Place 2 g in a test-tube and examine in ultraviolet light at 365 nm. The fluorescence is not more intense than that of a solution containing 0.1 ppm of quinine sulphate R in 0.005 M sulphuric acid examined in the same conditions.
Phenylated compounds

Dissolve 5.0 g with shaking in 10 ml of cyclohexane R. At wavelengths from 250 nm to 270 nm, the absorbance (2.2.25) of the solution is not greater than 0.2.

Heavy metals

Mix 1.0 g with methylene chloride R and dilute to 20 ml with the same solvent. Add 1.0 ml of a freshly prepared 0.02 g/l solution of dithizone R in methylene chloride R, 0.5 ml of water R and 0.5 ml of a mixture of 1 volume of dilute ammonia R2 and 9 volumes of a 2 g/l solution of hydroxylamine hydrochloride R. At the same time, prepare a standard as follows: to 20 ml of methylene chloride R add 1.0 ml of a freshly prepared 0.02 g/l solution of dithizone R in methylene chloride R, 0.5 ml of lead standard solution (10 ppm Pb) R and 0.5 ml of a mixture of 1 volume of dilute ammonia R2 and 9 volumes of a 2 g/l solution of hydroxylamine hydrochloride R. Immediately shake each solution vigorously for 1 min. Any red colour in the test solution is not more intense than that in the standard (5 ppm).

Volatile matter

For dimeticones with a nominal viscosity greater than 50 mm²·s⁻¹, not more than 0.3 per cent, determined on 1.00 g by heating in an oven at 150 °C for 2 h. Carry out the test using a dish 60 mm in diameter and 10 mm deep.

LABELLING

The label states:

the nominal viscosity by a number placed after the name of the product,

where applicable, that the product is intended for external use.

Ph Eur

Action and use

Pharmaceutical aid.

When dimethicone is demanded, Dimeticone shall be supplied.
PRECLINICAL ASSESSMENT

INTRODUCTION

This is a national application submitted under Article 8.3(i) of Directive 2001/83/EC. The active is dimeticone (referred to as D5D in the nonclinical overview) which is intended for the treatment or eradication of headlice infestations. Dimeticone has been used widely in topical barrier preparations but this is a new indication. The treatment is 2 applications, 7 days apart. The second application is required to kill the lice that have emerged from ova not killed by the initial treatment.

Dimeticone is a linear polymer (polydimethylsiloxane) which contains repeating polymeric units of the formula \[-(\text{CH}_3)\text{2SiO-}\]_n\, with a terminal trimethyl siloxy unit. Dimeticones ranging in viscosity from 0.65 to 3 million cSt are available. Cyclomethicone 5 is the sole excipient and acts as a volatile carrier (96%w/w).

PHARMACODYNAMICS

The mode of action has not been fully elucidated, but it appears to be related to a disruption of water balance mechanism in the lice, leading to rupture of the gut.

Pharmacodynamics for the Proposed Indications

One in vitro study was performed which demonstrated that concentrations of 3-5% dimeticone were effective in causing 98-100% mortality to headlice. Cyclomethicone (vehicle, 100%) alone caused 42.6% mortality. Both dimeticone and the vehicle showed limited ovicidal activity and the second application of the product in the clinical situation would seem justified.

No other studies were performed.

Secondary Pharmacology

No safety studies are available, which the applicant has justified based on (1) the proposed clinical use of the product, (2) the fact that it is not acting in a conventional pharmacological manner, and (3) systemic exposure being at most minimal.

Drug Interactions

Drug interactions are not envisaged.

Assessor’s Comment

Limited data are provided. This is considered acceptable bearing in mind the extensive use of dimeticones (of various viscosity (cSt)) in barrier creams, creams, lotions and ointments and the very limited absorption. Concentrations ranging from 10-30% are used in barrier preparations for the prevention of bedsores and nappy rash. Therefore, the 4% dimeticone in the product is relatively inconsequential, particularly, when considering the two applications separated by a 7 day period.

Section 5.1 of the SPC should indicate that although Hedrin is very effective in killing headlice it is much less effective as an ovicide, hence the need for the second application.
PHARMACOKINETICS

Absorption

The applicant has provided no studies on their dimeticone product. A limited number of *in vitro* and *in vivo* studies have been presented from the literature on the absorption of dimeticone 10 and/or 350 cSt. A study on human skin indicated that approximately 0.5% of a dose applied to the skin could be considered to be bioavailable regardless of the viscosity. An *in vivo* rat study showed that 0-4.4% of a dose applied to the skin was recovered from the carcasses, small but detectable levels were reported in faeces, expired air and subcutaneous swabs (levels not given). A rat study showed that dimeticone was not absorbed when given orally. No significant radioactivity was detected outside the GI tract and virtually the entire dose was recovered from the faeces (99.6-99.8%). Other oral studies in rats and dogs with dimeticone 100, 350, 100 and 1200 cSt confirm the minimal absorption (0.001-0.2%).

Distribution

There is virtually no absorption or distribution.

Metabolism

Following oral administration, dimeticone appears to be eliminated unchanged in the faeces.

Excretion

Excretion is via the faeces with no or very limited radio-labelled material having been detected in urine.

Enzyme Induction/Inhibition

There is no available data.

Assessor’s Comment

The data package is very limited, however, it is evident that absorption can be expected to be very limited from the skin. One might expect the absorption of a high molecular weight dimeticone product to be less than those with low molecular weights as presented in the literature. No information is provided for cyclomethicone.

It is suggested that Section 5.2 of the SPC should indicate that there is little or no absorption of dimeticone from the skin.

TOXICOLOGY

Single Dose Toxicity Studies

In rats, oral administration of the product intended for marketing was not lethal at doses up to 2000 mg/kg. Similar results have been reported with dimeticone 60,000 cSt. Dermal application of undiluted Hedrin to rat skin (equivalent to 2000 mg/kg) for 24 hours did not show any signs of irritation. Clinical signs were restricted to anogenital staining. Weight gain was reduced for the Hedrin treated female group. Application of dimeticone 60,000 cSt to the skin of rabbits (occluded for 24 hours) resulted in evidence of irritation (erythema) in all treated rabbits which resolved. No other signs of toxicity were detected.
Repeated Dose Toxicity Studies

No repeat dose studies have been performed with Hedrin.

A dietary toxicity study in rats (10/sex/group) was presented in which dimeticone 60,000 cSt (equivalent to 730 mg/kg/day) was given for 90 days. This study was conducted in 1957 and was deficient by modern day standards but no toxicity was reported.

A published report of a 13 week dietary rat study (2002, meeting abstract) in which dimeticone 10 and 350 cSt were administered (15/sex/group). Limited details of the findings were reported but consisted of yellow matting of the anogenital region at 5000 ppm, (equivalent to about 250 mg/kg/day), increased food consumption and treatment-related increase in corneal opacities. The later finding may have been related to a local irritant effect to the eyes.

Assessor’s Comment
The above package of data would not normally be considered adequate, however, for a product that is to be administered topically on two occasions only, this gives no cause for concern. The extensive topical use of dimeticone preparations, although not identical to the proposed product, also provides reassurance of the safety of these products.

REPRODUCTION STUDIES

No studies with Hedrin.

A developmental study in rabbits with dimeticone 10 and 350 cSt is presented as a meeting abstract (2002). Rabbits (23/group) were treated at doses of 33,300 and 1000 mg/kg/day by dermal application from GD 6-19. There were no treatment-related findings.

Assessor’s Comment
As the main target population is likely to be children and as dimeticones are already used to prevent nappy rash, the lack of a complete package is not considered to be a problem. In addition, dimeticones are not absorbed to any extent and a full package of studies cannot be justified. Section 4.6 of the SPC originally stated “Although dimeticone has been in widespread use for many years without apparent ill consequence, there are no specific data on its use during pregnancy. Use during pregnancy is inadvisable unless there is a clear need. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible harm”. This statement is considered to be overcautious and there is really no reason why Hedrin could not be used during pregnancy. The final revised Section 4.6 of the SPC is as follows: “There is no data to suggest that Hedrin may not be used in pregnancy”.

MUTAGENIC POTENTIAL

No genotoxicity studies have been conducted with Hedrin.

A standard Ames test with 60,000 cSt dimeticone revealed no evidence of a mutagenic potential.

Assessor’s Comment
Again, this data package would not normally be considered adequate. However, given the topical use and the fact that dimeticones are already in extensive use, a request for further studies would appear rather pointless.
ONCOGENIC/CARCINOGENIC POTENTIAL

No data available.

Assessor’s Comment
This is acceptable given the limited use.

SPECIAL STUDIES

Local Tolerance (including Phototoxicity & Photosensitivity)

A 4 hour semi-occlusive dermal application of Hedrin to NZ rabbit skin did not show any evidence of irritation. Instillation of Hedrin into the conjunctival sac of rabbits produced some conjunctival reddening which resolved within 24 hours and Hedrin was not considered to be an eye irritant. Similar study results have been reported with dimeticone 60,000 cSt.

Skin sensitisation tests with Hedrin and dimeticone 60,000 cSt gave no indications that either product was a skin sensitizer.

OTHER INFORMATION SUPPLIED

Essential Similarity Comparisons

N/A

ENVIRONMENTAL RISK ASSESSMENT

A suitable evaluation of the potential risk to the environment has been presented and although not conventional is adequate to give reassurance that dimeticones are unlikely to be hazardous to the environment.

GOOD LABORATORY PRACTICE (GLP) STATEMENT

The acute toxicological studies conducted with Hedrin were conducted to GLP standard. The GLP status of the other studies is not specifically stated.

THE PHARMACO-TOXICOLOGICAL EXPERT REPORT

The Expert Report gives a reasonable overview of the product based on data from the literature and studies conducted by the applicant. The Expert is suitably qualified.

DISCUSSION

The non-clinical dossier is less than what might be expected for a product for which a marketing authorisation (MA) is applied for under Article 8.3(i). However, dimeticones of varying molecular weights and viscosity have been used extensively in barrier creams/lotions and also in cosmetics, toiletries and as a food additive without any apparent adverse effects. Of primary importance is the lack of absorption of dimeticones through the skin and, therefore, there will be little or no systemic exposure. The limited pharmacokinetic data would indicate that even if ingested, dimeticones are not absorbed from the GI tract either.
The applicant has relied heavily on data relating to other dimeticones to support this application for a marketing authorisation and this is considered to be acceptable as the chemical structure is essentially similar for them all, the only difference being in the number of repeating polymer units.

The applicant has provided no information on cyclomethicone other than the pharmacological study which demonstrated that it had limited pediculidical activity and does not appear to have any significant toxicity in the limited studies in which Hedrin was tested. Cyclomethicone is listed in the Handbook of Pharmaceutical Excipients. Like dimeticone it is not absorbed to any extent.

**OVERALL CONCLUSIONS ON PRODUCT SAFETY**

Overall, there are no preclinical objections to the grant of a MA for Hedrin.

**Major objections**

None

**Points for consideration/clarification**

None
CLINICAL ASSESSMENT

Introduction

This is a national application under EC article 8.3(i) seeking a new indication for the known active substance, dimeticone, cutaneous solution for the treatment of *Pediculus capitis* (head lice).

Therapeutic Class

Ectoparasiticides, inc scabicides  P03AX

Hedrin contains the active substance dimeticone in a 4% w/v solution for the treatment of head lice. Dimeticone has been licensed for at least 33 years, and is widely used as an active ingredient in a number of topical preparations for the treatment of dry skin conditions. This is the first application for the proposed indication. Although the mode of action has not been fully elucidated, it appears to exert its mechanism of action by disrupting the water balance mechanisms in lice.

Background

Head lice are a parasitic infestation of the hair and scalp particularly occurring in children of school age. Infestation is transmitted by close contact. Adult lice lay eggs that cement close to the base of the hair shaft. The eggs take seven days to hatch and the juvenile louse undergoes three developmental stages.

Current treatment for louse infestation is mainly by use of neuroactive insecticides. Most products are incompletely ovicidal and a second application is given seven days later to kill any lice that have hatched from eggs that survived the first application. In recent years head lice resistance to currently used insecticides has appeared, cross-resistance to different insecticides being an issue. In the 1970s, studies suggested that human lice were susceptible to exposure to silicone fluids under some conditions.

Indications

The applicant was seeking the following indication:

For the eradication of head lice infestations, in adults and children over six months of age.

Dose and Dose Regimen

Following assessment of the data, it was determined that the following advice should appear in the SPC.

Adults and children (aged six months and above)

For topical external use only.
Apply sufficient lotion to cover dry hair from the base to the tip to ensure that no part of the scalp is left uncovered. Work into the hair spreading the liquid evenly from roots to tips. Allow hair to dry naturally. Hedrin should be left on hair for a minimum of 8 hours or overnight. Wash out with normal shampoo, rinsing thoroughly with water. Repeat the treatment after seven days.

Children under the age of six months should only be treated under medical supervision.

Consideration for Paediatric use

Hedrin has undergone a paediatric development program.

Assessor's Comment

The applicant has undertaken a development program appropriate for the proposed indication and patient population. It is noted that children under the age of 4 years were excluded from the studies.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction

No specific pharmacokinetic or metabolic studies were undertaken with Hedrin.

Absorption

Absorption studies in rodents and percutaneous absorption studies with human skin in vitro indicate that low levels of dimeticone 10 and 350 cSt are absorbed. For this it was concluded that the much larger molecule of the dimeticone used in Hedrin, either alone or in combination with cyclometicone, would be no more likely to pass transdermally. Evidence from oral dosing studies published in the literature indicates that dimeticone is not absorbed by the gut; it is not broken down or metabolised and is excreted intact.

Assessor’s overall conclusions on pharmacokinetics

The applicant has not undertaken pharmacokinetic studies. Given the active ingredient and the intended route of administration and evidence in the literature this is acceptable.

Pharmacodynamics

Primary pharmacology

No formal human pharmacodynamic studies are included in this application. The mechanism of action has not been fully elucidated. The available evidence suggests that the activity of Hedrin is physical and due to coating of the lice by dimeticone. Dimeticone enters the tracheae of the lice and prevents excretion of water resulting in disruption of gut and other organ functions.

Assessor’s Comments on Clinical Pharmacology

Levels of dimeticone that are absorbed through the skin are low, and were shown to be around 0.5% in pre-clinical studies. Dimeticone products are widely used in topical barrier
preparations for protecting the skin against irritants. Creams, lotions and ointments containing a dimeticone are employed widely for the prevention of bedsores and nappy rash, used topically as wound dressings, and to protect the skin against trauma due to incontinence or discharge from stoma. The amount of dimeticone absorbed percutaneously is unlikely to have a pharmacodynamic effect.

**Statistical assessment**

**Statistical Assessment of Efficacy**

This assessment considers the evidence of efficacy for Hedrin lotion (4% dimeticone), indicated for the eradication of head lice infections. Two clinical trials are presented.

The first (CTMK02) is a study to determine application time and is described briefly under “Clinical Efficacy”. This study compared a once-a-week for two weeks, 20-minute application with a once-a-week for two weeks 8-hour application and concluded that the longer administration was more effective.

The second trial (CTMK01) is considered pivotal. This was a single-centre, randomised, assessor-blind, active-controlled (0.5% w/w phenothrin in an aqueous base), parallel-group study with treatments applied by trained investigators and assessed by different trial investigators who remained blinded to treatment.

The primary endpoint was cure of infestation by Day 14 of the study. Success was defined as being clear on both assessment days after the second administration of treatment (9 and 14). In order to declare equivalence, the two-sided 95% confidence limit of inferiority for the difference in proportion of ‘cures’ was required to be less than 20%. Ovicidal activity was also assessed.

Assessments were made on both the ‘efficacy’ and ‘ITT’ populations, the former being those randomised patients who were treated according to study protocol and the latter being all treated patients with at least one post-baseline assessment.

Of the 260 patients randomised (130 to each group), 5 patients were withdrawn, all on the control arm. Only one of these 5 was excluded from the ITT analysis, which is, therefore, not markedly affected by patients’ withdrawals. The primary ‘efficacy’ (or ‘per protocol’) population included 237 patients, 121 in the test group and 116 in the control group.

In the primary analysis, cure (or re-infection) was achieved by 69.42% of the test group and 77.59% of the control group, a difference of 8.16% with 95% confidence interval –3.02% to 19.34%. The Applicant’s conclusion of non-inferiority is supported in the ITT analysis and in sensitivity analyses excluding dropouts and patients recruited to the trial on more than one occasion (see comments below).

**Statistical Assessor’s Comment**

Evidence of non-inferiority to phenothrin is borderline.

The first concern is the absence of a placebo group. A placebo arm would have been desirable to assist the assessment of assay sensitivity. It is appreciated that this is an uncomfortable condition and outwith considerations of assay sensitivity, the inclusion of a placebo arm might be questionable. Clinical judgement should consider whether the comparator is appropriate and whether it is exhibiting its usual level of efficacy in this study.
The second concern is the choice of non-inferiority margin. It is not clear, and it has not been justified by the applicant, that a potential difference of almost 20% is either a) of no clinical relevance or b) offset by advantages in tolerability/safety. Indeed, the margin is considered wide for the comparison of two active agents. As the response rate on placebo would be expected to be low in this setting (i.e. <10%) it might be considered that the differences between active treatments excluded in this trial provide indirect evidence of superiority to placebo for Hedrin. Clinical judgement must consider whether the potential reduction in efficacy compared with phenothrin is acceptable.

The final major concern is that, even if the choice of delta is considered reasonable, the level of evidence is borderline in this single pivotal study. Furthermore, it is not clear that this open-label, single-centre study will accurately reflect general clinical practice where the lotion will, presumably, not be administered in the clinic.

It is noted that the patient population in the trial is older than that proposed in the SPC. The validity of this extrapolation should be considered.

A number of patients were recruited to the trial more than once. This is inappropriate. However, the issue has been addressed in the sensitivity analyses conducted.

Statistical Assessor’s Overall Conclusions

It is highly appropriate that investigators remaining blind to treatment allocation in this otherwise open-label study conducted the assessments of response. A measure or an indication of the success of this blinding would have been useful. However, given the clear (albeit indirect) evidence of superiority to no treatment, this is not considered crucial for evidence of efficacy.

The trial results are reasonably consistent across the endpoints and analysis populations presented. They indicate borderline evidence of non-inferiority compared with 0.5% w/w phenothrin, though the Applicant’s choice of non-inferiority margin is questioned. Clinical judgement must consider whether the potential reduction in efficacy is of clinical importance or whether it is offset by improved tolerability/safety.

CLINICAL EFFICACY

Introduction

All studies were performed to Good Clinical Practice Guidelines. One pivotal clinical efficacy study (CTMK01) was conducted by the applicant to support the proposed indication. This study involved a controlled comparison of the efficacy of Hedrin and phenothrin (Full Marks Liquid) in subjects with current active head louse infection. In addition to the pivotal efficacy study, the clinical development programme comprised of an uncontrolled Phase II pilot study to evaluate optimum treatment-interval and follow-up regimen (CTMK02). The clinical development programme for Hedrin included a total of 299 subjects of whom 170 were exposed to Hedrin.

Study CTKMK02

This was a randomised pilot study, 35 children and 5 adults with head lice infestation who satisfied study criteria were randomly allocated to receive two treatments, at weekly intervals, of Hedrin applied either for 20 minutes or for 8-hours or overnight. The only significant
difference noted between the two groups was that in the type of hair. In the 20 minute group 95% had normal hair (as distinct from dry or greasy) as compared to 65% in the 8-hour or overnight group.

Based on the absence of live lice at day 14, the success rate of the 8 hour group (90%) was non-significantly superior to that in the 20 minute group (60%, 0.05<p<0.1). The data suggested a reduced risk of reinfections. This study determined that the most suitable follow-up days for the phase III study as days 2, 6, 9 and 14.

Main studies

Study CTMK01

This study was a randomised, assessor blinded, parallel group study of Hedrin in comparison with 0.5% w/w phenothrin in an aqueous base (Full Marks Liquid).

After a preliminary assessment, all patients who satisfied the inclusion criteria were randomised into one of two treatment groups. The main inclusion criterion was active head louse infection defined as the presence of at least one live louse found using detection combing.

All treatments were applied evenly over dry hair and scalp by trained investigators. Sufficient product was applied to wet the scalp and hair and was left on for either 8 hours/overnight (Hedrin) or 12 hours/overnight (phenothrin). The product was then washed off with a supplied shampoo.

Assessor’s comments.
The clinical study protocols were based on a research approach based on criteria from a Cochrane Collaboration protocol. The methodology is appropriate for the evaluation of treatment safety and efficacy. Phenothrin is an appropriate comparator. The studies were observer blind, it would be preferable to see results from a double-blind study, however given the nature of the two products and the different treatment regimes a placebo controlled study would not be feasible. It is unlikely that patients would be able to influence treatment outcome, however they may have been able to break the observer blind if they discussed their treatment during the louse inspection visits.

Study Objectives

The primary efficacy variable was cure of the infestation by day 14 of the study. This was measured by the absence of lice after the second application of treatment. This efficacy variable was split into two components: The first was the killing of lice as demonstrated by the presence of no lice at the assessments at day 9 and at day 14 after the second application of treatment. The second was ovicidal activity as demonstrated by the absence of newly hatched lice following treatment, and following the second application.

Both elements of the efficacy parameter described above may be confused by re-infestation. The post-treatment evaluations enabled investigators to find newly acquired lice (adults or third instar nymphs) at the next assessment combing. The stage of development of the lice would therefore allow reinfecting lice to be distinguished from other lice that had emerged from eggs surviving treatment.
Baseline demographics

The baseline demographics of patients in Study CTMK01 are summarised in the following table:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic</th>
<th>Hedrin (n=130)</th>
<th>Phenothrin (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-6 years</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>7-9 years</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>10-18 years</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>19-30 years</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-40 years</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>41-50 years</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>&gt;50 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td><strong>Infection assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Heavy</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td><strong>Hair length</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Closely cropped</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Above ears</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Ears to shoulders</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Below shoulders</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td><strong>Hair thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fine</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Thick</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Wiry</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hair type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Straight</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Wavy</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Curly</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dry</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Greasy</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>

There was no significant difference in age between the two treatment groups; the median age was 9 years. The distribution of the two groups was very similar in respect of hair length, hair thickness and two classifications of hair type.

**Results**

Outcome was assessed using the following criteria:

Cure: No lice present at day 9 and at day 14.

Ovicidal failure: the following must all have applied:

1. Lice were present at day 9 and/or day 14.
2. At day 9 there were no adult lice or stage 2 or 3 nymphs.
3. At day 14 there were no adult lice or stage 3 nymphs.
Reinfection: the following must have all applied:

1. Lice present at day 9 and/or day 14.
2. No adult lice or stage 1 or 2 nymphs at day 9 or day 14.
3. No stage 3 nymphs at day 9 when stage 1 or 2 nymphs present at day 6.
4. Fewer than 2 stage 3 nymphs at either day 9 or day 14.
5. Fewer than 2 adult lice at either day 9 or 14.

Treatment Failure: Any patient not fitting into one of the criteria above.
Dropout: The patient is a dropout (or non-compliant due to the wrong treatment being given).

There was no significant difference between treatment groups in terms of cure or reinfection, or cure regardless of the absence or presence of dropouts/duplicates.

Assessor’s overall conclusions on clinical efficacy

The results of the pivotal clinical study programme demonstrate that 4% dimeticone is effective at killing head lice, ovicidal activity is limited and a second application of treatment is required. The pivotal clinical study employed an active control, 0.5% phenothrin liquid w/w, the results of this study support the proposed indication and demonstrate that Hedrin is noninferior in efficacy to an appropriate comparator, by the applicants criteria. The overall difference in treatment between the two treatment groups (~8%) is not considered to be clinically significant. Dimeticone is unlikely to be denatured by metabolic activity, and as far as has been determined, Hedrin acts by coating the lice and disrupting water homeostasis, the development of resistance is therefore not anticipated.

CLINICAL SAFETY

Introduction

An evaluation of safety was conducted on all study patients who were randomised into a clinical study and received at least one dose of study drug.

Patient exposure

Two clinical studies were undertaken and a total of 170 patients were exposed to Hedrin. The dose of Hedrin applied as necessary to coat the mass and length of individuals’ hair. The mean dose was 52.37g per treatment in study CTMK01. In study CTMK02 the mean dose was 52.5g for the 20 minute application and 65.4g for the eight hour/overnight application.

Adverse events

The summary of treatment emergent adverse events considered related to treatment observed in controlled studies is shown in the following table:
### Table 2.7.4:6  Treatment emergent adverse events considered to be treatment related, CTKM01

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Treatment group</th>
<th>Adverse event</th>
<th>Severity</th>
<th>Relationship to study</th>
</tr>
</thead>
<tbody>
<tr>
<td>186</td>
<td>Dimeticone</td>
<td>Scalp itching</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>24</td>
<td>Dimeticone</td>
<td>Eye drip</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>140</td>
<td>Dimeticone</td>
<td>Scalp flaky</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>37</td>
<td>Dimeticone</td>
<td>Eye irritation</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>70</td>
<td>Dimeticone</td>
<td>Scalp itching</td>
<td>Moderate</td>
<td>Probable</td>
</tr>
<tr>
<td>65</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>64</td>
<td>Phenothrin</td>
<td>Scratching</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>208</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>170</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Moderate</td>
<td>Possible</td>
</tr>
<tr>
<td>257</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Moderate</td>
<td>Possible</td>
</tr>
<tr>
<td>5</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>94</td>
<td>Phenothrin</td>
<td>Neck stinging</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>73</td>
<td>Phenothrin</td>
<td>Neck stinging</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>72</td>
<td>Phenothrin</td>
<td>Neck itching</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>53</td>
<td>Phenothrin</td>
<td>Scalp itching</td>
<td>Moderate</td>
<td>Probable</td>
</tr>
<tr>
<td>41</td>
<td>Phenothrin</td>
<td>Scalp irritation</td>
<td>Moderate</td>
<td>Probable</td>
</tr>
</tbody>
</table>

### Table 2.7.4:7  Treatment emergent adverse events CTKM02

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Treatment group*</th>
<th>Adverse event</th>
<th>Severity of event</th>
<th>Relationship to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>A</td>
<td>Gastroenteritis</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>41</td>
<td>B</td>
<td>Gastroenteritis</td>
<td>Moderate</td>
<td>Unlikely</td>
</tr>
<tr>
<td>34</td>
<td>B</td>
<td>Gastroenteritis</td>
<td>Moderate</td>
<td>Excluded</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>Gastroenteritis</td>
<td>Mild</td>
<td>Excluded</td>
</tr>
<tr>
<td>43</td>
<td>A</td>
<td>Gastroenteritis</td>
<td>Moderate</td>
<td>Excluded</td>
</tr>
<tr>
<td>30</td>
<td>B</td>
<td>Head cold</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>Headache</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>Itchy rash on arm</td>
<td>Mild</td>
<td>Unknown</td>
</tr>
<tr>
<td>32</td>
<td>A</td>
<td>Limbs aching / sickness</td>
<td>Moderate</td>
<td>Unknown</td>
</tr>
<tr>
<td>33</td>
<td>A</td>
<td>Mouth abscess</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>Scalp flaky</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>28</td>
<td>A</td>
<td>Scalp itchy</td>
<td>Mild</td>
<td>Probable</td>
</tr>
<tr>
<td>20</td>
<td>B</td>
<td>Throat infection</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>19</td>
<td>A</td>
<td>Throat infection</td>
<td>Mild</td>
<td>Unlikely</td>
</tr>
<tr>
<td>25</td>
<td>B</td>
<td>Throat infection / head cold</td>
<td>Moderate</td>
<td>Unlikely</td>
</tr>
<tr>
<td>27</td>
<td>B</td>
<td>Toothache</td>
<td>Mild</td>
<td>Excluded</td>
</tr>
<tr>
<td>21</td>
<td>B</td>
<td>Viral infection</td>
<td>Moderate</td>
<td>Unlikely</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>Viral infection</td>
<td>Mild</td>
<td>Excluded</td>
</tr>
</tbody>
</table>

* A = 20 minute application  
  B = 8 hour/overnight application
For the intent to treat population in study CTMK01 adverse events were reported by 13.1% (17) of the subjects in the Hedrin group and by 20.2% (26) of the subjects in the phenothrin group. Of the treatment-related adverse events a total of five were reported by subjects in the Hedrin group compared to a total of 11 by subjects in the phenothrin group. Only one adverse event was considered treatment related in study CTMK02.

The adverse events related to Hedrin were 3 cases of scalp pruritis, 2 cases of transient mild eye irritation following accidental exposure and one instance of dry skin that was slow to resolve.

**Serious adverse events and deaths**

There were no deaths or serious adverse events related to Hedrin reported in the clinical development programme.

**Laboratory findings and other observations related to safety**

No clinical laboratory evaluations were conducted in the clinical study programme.

Study No 308013364 was carried out to determine the potential of dimeticone to cause skin irritation. In this study, a total of 60 healthy volunteers were treated with a combination of two silicone-based materials (dimethiconol, a similar compound to dimeticone but with a hydroxyl group, and cyclopentasiloxane, identical to cyclomethicone). Skin patches were prepared comprising four 8mm Finn chambers, two of which contained filter paper discs saturated with the test product and two of which acted as blank controls. The order of presentation on the patch was varied according to a balanced experimental design. The patches were worn on the inner forearm for eight hours and the skin checked for abnormal redness or dryness. Volunteers were asked to comment on any itching, soreness or other unusual skin sensations whilst wearing the patch. The skin was checked again the following morning (around 16 hours later). There were no observed reactions to the test product, for any of the 60 volunteers. It was concluded that prolonged exposure to this headlice treatment should not cause irritancy.

The study report for 308013364 also includes reference to a human repeat insult patch test, conducted on 103 volunteers using Dow Corning 200® Fluid. This study comprised three phases. The first phase consisted of nine consecutive patch applications of 0.2mL of the material to the same site every 48 hours under semi-occlusive wraps; the subjects removed the patches after 24 hours of exposure (materials were not re-applied until Monday if applications had been made the previous Friday). Patches were applied to the infrascapular area of the back to one side of the midline. Following the ninth evaluation, the subjects were dismissed for a 12 to 14 day rest period. After the rest period the same dose was used on a previously unexposed site and the volunteers removed the patches after 24 hours; the sites were graded 24 and 48 hours after patch removal (48 and 72 hours after patch application). None of the volunteers exhibited signs of irritation or sensitisation during any part of the study. Therefore the material was not considered sensitising under the conditions of the study.

**Safety in special populations**

There are no data available for the assessment of this product in pregnant or lactating women.
Discontinuation due to AES

There were no discontinuations due to treatment with Hedrin.

Assessor’s overall conclusions on clinical safety

Overall six patients experienced an adverse event that was judged to be related to treatment with Hedrin, this represents 3.5% of the total population of 170. The nature of the patient population is broadly similar to what would be expected in normal use. In general, adverse events were mild and transient. The data from two dermal irritation studies are further reassuring that Hedrin is unlikely to cause skin sensitisation. There were no serious adverse events that were judged to be related to treatment with Hedrin.

POST-MARKETING EXPERIENCE

Not relevant

RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

None

CLINICAL EXPERT REPORT

A clinical overview has been provided.

CONCLUSIONS

This is a national application for a new indication, the treatment of head lice, using the known active substance dimeticone. Due to the probable mechanism of action of the product resistance is unlikely to be an issue with this product. The clinical trial programme has demonstrated that Hedrin is effective at killing head lice and is not inferior in terms of efficacy to a standard treatment, phenothrin, according to the applicants criteria. Dimeticone and cyclometicone have been in use for many years in both medicinal and cosmetic products and there are no known interactions with other medicinal products. Adverse events were mild and transient in nature and the product was well tolerated.

It is noted that no patients under the age of 4 years were included in the development of this product. The applicant is seeking an indication for its use in infants from six months of age. This is considered acceptable given the nature of the active ingredient dimeticone and its safety profile. It is not considered that patient age will have an impact on the efficacy of this product.

Overall it is considered that this product has a positive benefit/risk profile.

CLINICAL AND PRE-CLINICAL ASSESSORS’ CONCLUSIONS

On the basis of materials provided in support of safety and efficacy, the assessors are able to recommend that a marketing authorisation can be granted for Hedrin 4% lotion.
OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Hedrin 4% Cutaneous Solution 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.

PRECLINICAL

The mechanism of action of dimeticone has not been fully elucidated. The available evidence suggests that the activity of Hedrin is physical and due to coating of the lice by dimeticone. Dimeticone enters the tracheae of the lice and prevents excretion of water resulting in disruption of gut and other organ functions.

Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY

The indication finally requested is eradication of headlice infestations.

The results of the pivotal clinical study programme demonstrate that 4% dimeticone is effective at killing head lice, ovicidal activity is limited and a second application of treatment is required. The pivotal clinical study employed an active control, 0.5% phenothrin liquid w/w, the results of this study support the proposed indication and demonstrate that Hedrin is not inferior in efficacy to an appropriate comparator, by the applicant’s criteria. The overall difference in treatment between the two treatment groups (~8%) is not considered to be clinically significant.

No clinically significant safety concerns were identified.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and adequate efficacy has been demonstrated for this medicinal product. The risk-benefit assessment is therefore considered to be favourable.
### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application for Hedrin 4% Cutaneous Solution on 27 April 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks the MHRA informed the applicant that its application was considered valid on 14 May 2004.</td>
</tr>
<tr>
<td>3</td>
<td>The MHRA’s assessment of the submitted data was completed on 21 October 2004.</td>
</tr>
<tr>
<td>4</td>
<td>The MHRA’s assessment report was considered by the Committee on Safety of Medicines (CSM) on 15 December 2004.</td>
</tr>
<tr>
<td>5</td>
<td>The applicant was informed that CSM recommended approval of the application subject to amendments to the product particulars (SPC, PIL and Labelling) on 20 December 2004.</td>
</tr>
<tr>
<td>6</td>
<td>The applicant informed the MHRA that it would accept the CSM recommendation on 24 December 2004.</td>
</tr>
<tr>
<td>7</td>
<td>The applicant submitted its updated product particulars on 23 March 2005.</td>
</tr>
<tr>
<td>8</td>
<td>Further information was requested from the company on 8 June 2005.</td>
</tr>
<tr>
<td>9</td>
<td>The applicant submitted its response to further information requests on 30 June 2005.</td>
</tr>
<tr>
<td>10</td>
<td>Additional information was requested from the company on 22 September 2005.</td>
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<td>12</td>
<td>The MHRA completed its assessment of the updated product particulars on 11 November 2005.</td>
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<td>13</td>
<td>The application was determined on 23 November 2005.</td>
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HEDRIN 4% CUTANEOUS SOLUTION (DIMETICONE) PL 00240/0137

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hedrin® 4% cutaneous solution

Packaging to state:
   Hedrin 4% lotion
   dimeticone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dimeticone 4% w/w

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Cutaneous solution.

Hedrin is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hedrin is indicated for the eradication of headlice infestations.

4.2. Posology and method of administration

Adults and children (aged six months and above)

For topical external use only.

Apply sufficient lotion to cover dry hair from the base to the tip to ensure that no part of the scalp is left uncovered. Work into the hair spreading the liquid evenly from roots to tips. Allow hair to dry naturally. Hedrin should be left on hair for a minimum of 8 hours or overnight. Wash out with normal shampoo, rinsing thoroughly with water. Repeat the treatment after seven days.

Children under the age of six months should only be treated under medical supervision.

4.3. Contraindications

Hypersensitivity to any of the ingredients

4.4. Special warnings and precautions for use

Discontinue at the first appearance of a skin rash or any other signs of local or general hypersensitivity.
For external use only.

If accidentally introduced into the eyes, flush with water.

4.5. **Interactions with other medicinal products and other forms of interaction**

Dimeticone is not known to interact with other drugs.

4.6. **Pregnancy and lactation**

There is no data to suggest that Hedrin may not be used in pregnancy.

4.7. **Effects on ability to drive and use machines**

None known.

4.8. **Undesirable effects**

Dimeticone is usually well tolerated. Minor adverse events include an itchy or flaky scalp and dripping/irritation around the eyes.

4.9. **Overdose**

There are no known recognised symptoms of overdose.

It is unlikely that Hedrin® lotion will enter the bloodstream via scratched skin however if this does occur, available data suggests it will be rapidly eliminated unchanged. If the lotion were to be accidentally ingested, again, the available data suggests that there are no specific safety concerns.

No special procedures are likely to be needed.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

The solution contains dimeticone, which is used in many pharmaceutical and cosmetic preparations. A 4% concentration has been found to affect the physico-physiological activity of lice. It is less effective in its ovicidal activity and therefore two applications 7 days apart are required.

Hedrin contains no neurotoxic organophosphate insecticides and therefore does not work by acting on specific enzymes within the louse. The Hedrin solution acts on the lice by a physical process to cover the lice and disrupt the ability of the lice to manage its water balance so that treated insects fail to excrete surplus water. Hedrin activity is not diminished in insecticide resistant head lice.

5.2. **Pharmacokinetic properties**

Hedrin is applied topically to the affected area but there is little or no absorption of Hedrin through the skin.
5.3. Preclinical safety data

There are no further relevant data.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cyclomethicone 5

6.2. Incompatibilities

None known.

6.3. Shelf life

Two years, when stored unopened.

6.4. Special precautions for storage

This product does not require any special storage conditions.

6.5. Nature and contents of container

HDPE dropper containers with screw caps; 50, 100, 150 and 200ml capacity.

6.6 Special precautions for disposal

Care should be taken as the product may cause a slip hazard if accidentally spilt onto smooth surfaces.

7. MARKETING AUTHORISATION HOLDER

Thornton & Ross Ltd
Linthwaite
Huddersfield
HD7 5QH
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL00240/0137

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/11/2005

10 DATE OF REVISION OF THE TEXT

23/11/2005
Patient Information Leaflet

MHRA; PAR – Hedrin 4% Cutaneous Solution (dimeticone) PL 00240/0137

1 What is Hedrin® Lotion and what does it do?
The name of your medicine is Hedrin® Plus. It is a, cream-based solution and it is available in 50ml, 500ml and 2000ml packs. It contains 4% per cent dimeticone, as the active ingredient. Dimeticone is a silicon compound, widely used in the cosmetic industry, which is highly effective against head lice.
Hedrin® Plus contains Carbopropylamine N
dimethylaminoethanol (CDE) which evaporates after application leaving the active ingredient in the hair.
Dimeticone is not a chemical poison. It works by a physical process which effectively cracks and dries the lice.

2 Before using Hedrin®

Do not use Hedrin®

Fare an antiparasitic other than the ingredients listed.

Use in pregnancy and breastfeeding: Hedrin® Lotion may be used during pregnancy and breastfeeding.

3 How to use Hedrin®

Hedrin® is available for adults and children aged 6 months and over.

If you are a member of the family who has lice then both the male and female members of the family should be treated. Ask your pharmacist or health care professional for more information.

4 Possible side effects

If you experience any side effects or symptoms of adverse reactions please contact your health care professional for advice.

5 Storing Hedrin®

Keep out of the reach and sight of children.

The medicine must be kept in a cool, dry, light-protected container. Store below 25°C.

We recommend that you store your protection seal in a cool, dry place in a tin. All Hedrin® is supplied in a tin and a slip label.
Labels/Packaging

![Hedrin 4% Lotion](image)

- Skin friendly
- Odourless
- Easy to apply
- No organo-phosphates

50ml
Labels/Packaging

HOW TO APPLY:
• Apply sufficient dose weekly over three to four weeks, until the scalp is fully covered.
• Work into the hair spreading the liquid evenly from the roots to tips. Allow the hair to dry naturally.
• Leave on the hair for at least 8 hours or overnight.
• Wash the hair with normal shampoo, rinse thoroughly with water and dry.
• It is important that Hedrin® is applied again after seven days to deal with any lice which may hatch in that time. Failure to repeat the treatment may result in the return of infestation.
• If accidentally introduced into the eyes, flush with water.

IMPORTANT!
Do not use if you are sensitive to any of the ingredients in Hedrin®

Children under 6 months should only be treated under medical supervision.

Do not continue using Hedrin® if a skin rash or other signs of hypersensitivity occur. Take care if accidentally spilled as Hedrin® may cause a slip hazard.

Hedrin® is a registered Trade Mark of Perrigo & Ross Ltd.

PEEL BACK GREEN TAB
Labels/Packaging
IMPORTANT: Please read the enclosed information leaflet carefully before use.

Hedrin® solution is applied to the scalp and skin and is the external use only.

Do not use if you are sensitive to any of the ingredients in Hedrin®

Children under 6 months should only be treated under medical supervision.

HOW TO APPLY:

- Apply sufficient lotion evenly over the scalp to ensure that the scalp is fully coated.
- Work into the hair, rubbing the liquid evenly from the roots to tips. Allow the hair to dry naturally.
- Leave on the hair for at least 8 hours or overnight.
- Wash the hair with normal shampoo, rinse thoroughly with water and dry.

If accidentally introduced into the eyes, rinse with water, do not continue using Hedrin® if a skin rash or other signs of hypersensitivity occur.

FOR EXTERNAL USE ONLY

ACTIVE INGREDIENTS / INGREDIENTS AT WORK:
- Dimethicone 5%

KEEP OUT OF REACH OF CHILDREN

Takes care. Protect your family from head lice.

BN:

DRA:

EXP:

MHRA: PAR – Hedrin 4% Cutaneous Solution (dimethicone) PL 00240/0137
IMPORTANT:

Please read the enclosed information leaflet carefully before use.

Hedrin® Lotion is for the treatment of head lice in adults and children aged 6 months and over.

HOW TO APPLY:

- Apply sufficient lotion evenly over dry hair ensuring that the scalp is fully covered.
- Work into the hair spreading the liquid evenly from the roots to tips.
- Allow the hair to dry naturally.
- Leave on the hair for at least 8 hours or overnight.
- Wash the hair with normal shampoo, rinse thoroughly with water and dry.
- It is important that Hedrin® Lotion is applied again after seven days to deal with any lice which may hatch in that time. Failure to repeat the treatment may result in the return of a heavy infestation.
- If accidentally introduced into the eyes, flush with water.
- Do not continue using Hedrin® if a skin rash or other signs of hypersensitivity occur.

FOR EXTERNAL USE ONLY

Hedrin® solution is applied to the hair and scalp and is for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision.

Take care if accidentally splashed as Hedrin® may cause a slip hazard.

Active ingredient: Dimeticone 4%. Also contains Cyclomethicone 5%.

KEEP OUT OF REACH AND SIGHT OF CHILDREN. Keep in original carton.

Hedrin® solution is applied to the hair and scalp and is for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision.

Take care if accidentally splashed as Hedrin® may cause a slip hazard.

Active ingredient: Dimeticone 4%. Also contains Cyclomethicone 5%.

KEEP OUT OF REACH AND SIGHT OF CHILDREN. Keep in original carton.

Hedrin® solution is applied to the hair and scalp and is for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision.

Take care if accidentally splashed as Hedrin® may cause a slip hazard.

Active ingredient: Dimeticone 4%. Also contains Cyclomethicone 5%.

KEEP OUT OF REACH AND SIGHT OF CHILDREN. Keep in original carton.
Labels/Packaging
Labels/Packaging
Hedrin® Lotion is for the treatment of head lice in adults and children aged 6 months and over.

**IMPORTANT:** Please read the enclosed information leaflet carefully before use. Hedrin® solution is applied to the hair and scalp and is for external use only.

Do not use if you are sensitive to either of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision.

### HOW TO APPLY:

1. Apply sufficient lotion evenly over dry hair ensuring that the scalp is fully covered.
2. Work into the hair, spreading the liquid evenly from the roots to the tips. Allow the hair to dry naturally.
3. Leave on the hair for at least 8 hours or overnight.
4. Wash the hair with normal shampoo, rinse thoroughly with water and dry.

It is important that Hedrin® lotion is applied again after seven days to deal with any lice which may hatch in that time. Failure to repeat the treatment may result in the return of a house infestation.

If accidentally introduced into the eye, flush with water. Do not continue using Hedrin® if a skin rash or other signs of hypersensitivity occur.

**FOR EXTERNAL USE ONLY**

**ACTIVE INGREDIENT:** Dimeticone 4% w/w.

**ALSO CONTAINS:** Clyrethroidin.

**KEEP OUT OF REACH AND SIGHT OF CHILDREN.**

Take care if accidentally spilled as Hedrin® may cause a skin irritant. Keep in a cool place.

**Braun & Allisons**

Thermo & Sons Ltd, Huddersfield, HD2 1SH, UK.

MHRA: PAR – Hedrin 4% Cutaneous Solution (dimeticone) PL 00240/0137
Hedrin solution supplied to the hair and scalp and is for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision. Take care if accidentally applied as Hedrin® may cause a skin irritation.

Active Ingredient: Dimeticone 4% w/w.

Also contains Cetyl alcohol 4%.

Keep out of reach and sight of children.

150ml e P

MHRA: PAR – Hedrin 4% Cutaneous Solution (dimeticone) PL 00240/0137
IMPORTANT

Please read the enclosed information leaflet carefully before use.

Hedrin** solution is for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin**

Children under 6 months should only be treated under medical supervision.

Take care if accidentally spilled as Hedrin** may cause a slip hazard.

Active ingredients:
Dimeticone 4% w/w
Also contains Cypermethric 5.

Skin friendly
Discreet
Easy to apply
No oily residue

KEEP OUT OF REACH AND SIGHT OF CHILDREN
Keep in original container.

FOR EXTERNAL USE ONLY
IMPORTANT:
Please read the enclosed information leaflet carefully before use.
Hedrin Solution is for the treatment of head lice and is a very effective and rapid cures for head lice and nits.
HOW TO APPLY:
- Apply sufficient lotion evenly over the hair and scalp and a for external use only. Do not use if you are sensitive to any of the ingredients in Hedrin.
- Keep out of the reach of children. Take care if accidentally swallowed or inhaled.
- Active ingredient: Dimethicone 4% w/w. Also contains Cyclomethicone 5.
- KEEP OUT OF REACH OF CHILDREN.
- Keep in original container.

Hedrin 4% LOTION

A new way to eradicate head lice

Skin friendly
Odourless
Easy to apply
No organophosphates

200ml € P
Hedrin® Lotion is for the treatment of head lice in adults and children aged 6 months and over.

IMPORTANT: Please read the enclosed information leaflet carefully before use. Hedrin® solution is applied to the hair and scalp and is for external use only.

Do not use if you are sensitive to either of the ingredients in Hedrin®.

Children under 6 months should only be treated under medical supervision.

HOW TO APPLY:

- Apply sufficient lotion evenly over dry hair ensuring that the scalp is fully covered.
- Work into the hair spreading the liquid evenly from the roots to tips. Allow the hair to dry naturally.
- Leave on the hair for at least 8 hours or overnight.
- Wash the hair with normal shampoo, rinse thoroughly with water and dry.
- It is important that Hedrin® Lotion is applied again after seven days to deal with any lice which may hatch in that time. Failure to repeat the treatment may result in the return of a louse infestation.
- If accidentally introduced into the eyes, flush with water. Do not continue using Hedrin® if a skin rash or other signs of hypersensitivity occur.

FOR EXTERNAL USE ONLY

ACTIVE INGREDIENT: Dimeticone 4% w/w.
Also contains Cypermethrin 5%.

KEEP OUT OF REACH AND SHARP OF CHILDREN.
Take care if accidentally splashed as Hedrin® may cause a slip hazard. Keep in original carton.

Bn:

MHRA: PAR – Hedrin 4% Cutaneous Solution (dimeticone) PL 00240/0137

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IMPORTANT:
Please read the enclosed information leaflet carefully before use.

Hedrin® Lotion is for the treatment of head lice in adults and children aged 6 months and over.

HOW TO APPLY:
- Apply sufficient lotion evenly over dry hair ensuring that the scalp is fully covered.
- Work into the hair spreading the liquid evenly from the roots to tips, allowing the hair to dry naturally.
- Leave on the hair for at least 3 hours or overnight.
- Wash the hair with normal shampoo, rinse thoroughly with water and dry.
- It is important that Hedrin Lotion is applied again after seven days to deal with any lice which may hatch in that time. Failure to repeat the treatment may result in the return of a louse infestation.
- If accidentally introduced into the eyes, flush with water.
- Do not continue using Hedrin if a skin rash or other signs of hypersensitivity occur.

FOR EXTERNAL USE ONLY

Hedrin® Lotion is applied to the hair and scalp and is for external use only.

Do not use if you are sensitive to either of the ingredients in Hedrin.

Children under 6 months should only be treated under medical supervision. Take care if accidentally spilled as Hedrin® may cause a skin rash.

Active ingredient:
Dimeticone 3% w/w
Also contains Cystomethicone 5% w/w

KEEP OUT OF REACH AND SIGHT OF CHILDREN.
Keep original container.

MHRA: PAR – Hedrin 4% Cutaneous Solution (dimeticone) PL 00240/0137
Labels/Packaging