

**LYTHRIN 1% W/W CRÈME RINSE
(PERMETHRIN)**

PL 04149/0003

UKPAR

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PL 04149/0003

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ovelle Limited a Marketing Authorisation (licence) for the medicinal product Lythrin 1% w/w Crème Rinse (PL 04149/0003) on 12th June 2007. This is a pharmacy medicine (P), available by supply through pharmacies.

Lythrin 1% w/w Crème Rinse is a smooth white lotion containing the active ingredient permethrin, which belongs to a group of medicines called pyrethroids, which are anti-parasitic agents. Lythrin 1% w/w Crème Rinse is used for the topical treatment of head lice infestations.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Lythrin 1% Crème Rinse outweigh the risk; hence a Marketing Authorisation has been granted.

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(PERMETHRIN)**

PL 04149/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Ovelle Limited a Marketing Authorisation for the medicinal product Lythrin 1% w/w Crème Rinse (PL 04149/0003) on 12th June 2007. The product is a pharmacy medicine (P), available by supply through pharmacies.

The application was submitted as a national, abridged, complex, bibliographic application, for an active of well-established use, according to Article 10(a) of Directive 2001/83/EC, as amended. For topical products containing known constituents, there is a requirement to demonstrate compliance with the CPMP Notes for Guidance on 'Clinical requirements for locally applied, locally acting products, containing known constituents', where an appropriate clinical trial(s) using the product formulation under consideration is performed. In respect of this, the applicant stated that the present application is in line with the guideline and the clinical and toxicological overviews justify the omission of original clinical and non-clinical data.

Lythrin 1% w/w Crème Rinse is presented as a smooth white lotion (cutaneous emulsion), containing the active ingredient permethrin. It is indicated for the treatment of head lice (*Pediculus capitis*) infestations, and is suitable for use in adults and children over 6 months of age. 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.

Permethrin is a synthetic pyrethroid with potent insecticidal activity. It has been in use for more than 20 years for the treatment of ectoparasitic infestations such as scabies and pediculosis caused by the human head louse *Pediculus Capiti*. The originator product, Lynclear, has been available for more than 10 years.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

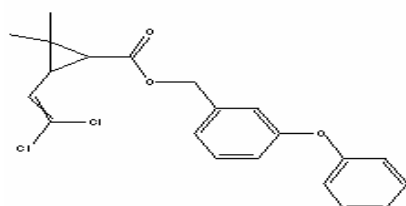
Permethrin

Nomenclature:

INN: Permethrin

Chemical name: 3-phenoxybenzyl (1R)-cis-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

Structure:



Molecular formula: C₂₁H₂₀Cl₂O₃

Molecular weight: 391.3

CAS No: 52645-53-1

Physical form: A crystalline solid, semi-solid or viscous liquid. When heated to 65-70°C it is a clear straw coloured free-flowing liquid

Chirality: Permethrin is a mixture of four stereoisomers due to the chirality of the cyclopropane ring. The cis:trans isomer ratio is 1:3 and the optical ratio of 1R:1S is 1:1 (i.e a racemic mixture). Therefore Permethrin contains the [1R, trans], [1R, cis], [1S, trans] and [1S, cis] isomers in the approximate ratio of 3:1:3:1

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is satisfactory.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The active substance, permethrin, is stored in appropriate packaging. It is packed in 25kg polyethylene lined steel drums filled to 5kg. Specifications and Certificates of Analysis have been provided for all packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated for active substance stored in similar packaging to the commercial packaging. This data demonstrates the stability of the drug substance and supports a shelf life of 24 months, when stored in the proposed packaging.

DRUG PRODUCT

Description & Composition

Lythrin 1% w/w Crème Rinse is presented as a smooth white lotion (cutaneous emulsion), containing the active ingredient permethrin.

Other ingredients consist of pharmaceutical excipients, namely benzyl alcohol, propylene glycol, hydroxycetyl hydroxyethyl dimonium chloride, cetostearyl alcohol, cetareth-20, light liquid paraffin, carbomer, sodium hydroxide solution, and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exceptions of permethrin, which complies with satisfactory specifications set by the DMF holder; and hydroxycetyl hydroxyethyl dimonium chloride and cetareth-20, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

There are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

The excipient, hydroxycetyl hydroxyethyl dimonium chloride, is a novel excipient and is discussed in the Pre-clinical and Clinical Assessment sections of this report.

There were no overages used.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is packed in a white 59ml HDPE (High Density Polyethylene) bottle with a LDPE screw cap that incorporates a flip-up applicator. A fine-toothed comb is provided with the bottle. The bottle is packaged with the PIL and comb into a cardboard outer carton. There are 2 pack sizes available: 1 x 59ml bottle pack and 2 x 59ml bottle pack.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. The storage instructions are 'Do not store above 25°C' and 'Keep container in the outer carton in order to protect from light'.

Bioequivalence Study

There was no bioequivalence study carried out to support this application. The legal basis of the application is that it is bibliographic; therefore, a bioequivalence study is not required.

Product Information

The approved SPC, leaflet, and labelling are satisfactory.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A marketing authorisation may be granted.

PRE-CLINICAL ASSESSMENT

I INTRODUCTION

The application was submitted as a bibliographic, national application, for an active of well-established use, according to Article 10(a) of Directive 2001/83/EC, as amended

The product is a liquid formulation containing the well-established active ingredient permethrin, a photostable pyrethroid that is used as a contact insecticide. It is intended for cutaneous use for the treatment of head lice in adults and children over six months.

The preclinical expert report consists of a review of the published literature.

I.1 GOOD LABORATORY PRACTICE (GLP) ASPECTS

The GLP status of the published studies cannot be established but the expert notes that much of the data has been peer reviewed by institutions such as the World Health Organisation (WHO) and the International Agency for Research on Cancer (IARC).

II PHARMACODYNAMICS / PHARMACOKINETICS / TOXICOLOGY

No formal pharmacodynamic studies on permethrin are reported in the literature, presumably because it was developed as a contact insecticide rather than as a medicinal product. Because of its high ovicidal activity and persistence on hair, it has been widely used as a treatment for ectoparasites. The absence of new pharmacology and pharmacodynamic studies was justified on this basis.

The synthetic pyrethroids delay closure of the sodium channel, apparently by holding the activation gate in the open position. The effects of pyrethroids on the central nervous system have led to the suggestion that they act via antagonism of gamma-aminobutyric acid (GABA)-mediated inhibition, modulation of nicotinic cholinergic transmission, enhancement of noradrenaline release or actions on calcium ions. However, since neurotransmitter-specific pharmacological agents offer only poor or partial protection against poisoning, it is unlikely that one of these effects represents the primary mechanism of action of the pyrethroids, and most neurotransmitter release is secondary to increased sodium entry.

II.1 Pharmacokinetics

In mice, dermal absorption and distribution of permethrin were rapid. In rats dosed intravenously with 46mg/kg or orally with 460mg/kg, the elimination half-life and mean residence time from plasma were 8.67 and 11.19 hours after intravenous and 12.37 and 17.77 hours after oral administration. The total plasma clearance was independent of dose and was 0.058l/h. Oral absorption was slow and the bioavailability was 60.69%. Pyrethroids have been found to accumulate in nervous tissue. In humans, approximately 0.5 – 1.0% of dermal doses was recovered from the urine.

Permethrin is rapidly metabolised in rats and other species by ester cleavage and hydroxylation. The relative resistance of mammals to the pyrethroids is almost wholly attributable to their ability to hydrolyse the pyrethroids rapidly to their inactive acid and alcohol components, since direct injection into the mammalian central nervous

system leads to effects similar to those seen in insects. The metabolites of permethrin, m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, were detected in plasma and in all selected tissues for forty-eight hours after dosing, suggesting a combination of metabolism by the tissues and diffusion into them from the blood. The metabolites and their oxidation products are rapidly excreted in the urine. No accumulation of the parent compound or metabolites has been found.

II.2 Toxicology

The data indicate that permethrin is of a low acute toxicity in a range of mammalian species by common routes of exposure.

The liver was a target organ following repeated dosing. At high doses, axonal swelling, myelin degeneration, vacuolation and swelling of unmyelinated fibres, and hypertrophy of Schwann cells were seen. The lowest no observed effect level (NOEL) in the rat of 20mg/kg/day by the dietary route for periods of 90 days or over gives a ten-fold margin over the largest recommended dose in a 6-month child weighing 6kg.

A large number of genotoxicity studies have been published. In the Ames tests, negative results were obtained. In both human lymphocytes and Chinese hamster ovary cells, numerical chromosomal aberrations were found in the absence of S9. These were also found in the bone marrow of Wistar rats at doses between 12.6 and 125.7mg/kg. The lowest dose represents a margin of six over the largest recommended dose in a 6-month child weighing 6kg.

Carcinogenicity studies in mice and rats (four in each species) did not reveal any evidence of carcinogenicity. IARC monographs state that there are no carcinogenicity data available in humans and that there is inadequate evidence for the carcinogenicity of permethrin in animals.

The expert notes that the data on reproductive toxicity of permethrin reflect its development as a pesticide, and that there are sufficient data to assess the potential for reproductive toxicity in respect of the current application. Three 3-generation studies in rats at doses between 100 and 2,500mg/kg/day did not reveal any evidence of effects on reproduction. No evidence of teratogenicity was found in embryofetal toxicity studies at dietary doses of 4 to 4,000mg/kg/day or at gavage doses 22.5 to 225mg/kg/day. In Dutch rabbits at doses of 600 to 1,800mg/kg/day, maternal toxicity and embryotoxicity were seen but there was no evidence of teratogenicity.

In mice dosed from day 7 to day 12 of pregnancy at doses up to 150mg/kg/day, there were no effects on foetal morphology at term, nor were there any signs of interference with development of pups born naturally and reared to 3 weeks post-weaning. In rats dosed from day 9 to day 14 of gestation at doses up to 50mg/kg/day, the high dose was associated with ataxia, tremors and a slight reduction in body weight in the females. Foetal loss was slightly increased and there was a slight reduction in ossification at the high dose. There were no effects in the pups born naturally and reared to six weeks of age.

In the rabbit, permethrin has been found to cause irritation to both intact and abraded skin. Undiluted permethrin but not a 40% solution was found to cause slight ocular irritation in rabbits.

Reference is also made to an epidemiological study following patients receiving a permethrin 1% crème rinse (Nix). Follow-up safety information was collected between 7 and 14 days following treatment. No serious, unexpected adverse events were recorded in 18,950 patients who received permethrin.

Permethrin is reported not to cause sensitisation in guinea pigs.

III EXCIPIENTS / IMPURITIES / RESIDUAL SOLVENTS

Hydroxycetyl hydroxyethyl dimonium chloride (Dehyquart® E-CA)

The excipients are commonly used in topical formulations, with the exception of hydroxycetyl hydroxyethyl dimonium chloride. This excipient has not been used previously in a licensed medicinal product in the UK and, while used commonly in cosmetics, must be regarded as a novel excipient. Full preclinical data was, therefore, requested.

Hydroxycetyl hydroxyethyl dimonium chloride (Dehyquart® E-CA) is a cationic surfactant used as an excipient in Lythrin 1% w/w Crème Rinse at a concentration of 2.0% w/w in the finished product. The excipient is used as a conditioning agent in shampoos and hair after-treatments.

Preclinical toxicity data were provided by the manufacturer in a summary report. The toxicological tests were conducted in accordance with SCCNFP – Note for Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation and were in compliance with OECD Principles of Good Laboratory Practice. Classification with respect to individual study endpoints was carried out in accordance with the Criteria for Classification and Labelling of Dangerous Substances in the European Union, Directive 67/548 EEC as amended.

Minimal absorption of Dehyquart® E-CA is anticipated following topical application of Lythrin 1% w/w Crème Rinse. This excipient is used in a rinse-off product with a limited contact period (recommendation - 10 minutes).

The oral LD50 was estimated to be 4,500 mg/kg. On the basis of this result, the product does not require classification and labelling with respect to acute toxicity.

No repeat dose toxicity data are available. Lythrin 1% w/w Crème Rinse, containing Dehyquart® E-CA, is intended for use for a limited period, infrequently, in a rinse-off product with a short contact period. The absence of repeat dose toxicity data is not considered to be critical to the safety evaluation of this excipient.

Dehyquart® E-CA was evaluated in an Ames test using *S typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of metabolic activation using rat liver homogenate from rats pre-treated with Arochlor 1254. The test substance concentrations employed were 10, 20, 40, 60, 80 and 160 µg/plate. No information on the cytotoxicity of Dehyquart® E-CA is included in the manufacturer's summary report and there is no justification of the selected high dose level which is significantly below the limit dose of 5,000µg/plate recommended in current guidance. In view of the chemical class of Dehyquart® E-CA, it is probable that test substance concentrations in excess of 160µg/plate were cytotoxic. The report

states that Dehyquart® E-CA did not induce reverse mutation in any of the tester strains in either the presence or absence of metabolic activation.

No carcinogenicity data are available and no reproductive toxicity data are available.

Dehyquart® E-CA (28% active material) was evaluated in a skin irritation test conducted in accordance with OECD Guideline 404 using five albino rabbits (Kleinrusse Chbb: HM). A four-hour contact period under occlusive conditions was used. Strong erythema and oedema, necrotic skin changes and the formation of scar tissue were observed. Undiluted Dehyquart® E-CA is, therefore, classified and labelled as corrosive (R34).

A human patch test was also performed with a dilution of Dehyquart® E-CA containing 1% active material. A total of 16 panellists received occluded topical applications of 70 µl aliquots which were applied to the upper arm by means of Finn chambers and remained in skin contact for 24 hours. The diluted product was classified as 'well skin compatible'.

It is unclear from the manufacturer's report whether or not an eye irritation test in accordance with OECD Guideline 405 was conducted. In view of the fact that the undiluted product (28% active material) was classified and labelled as corrosive, it would be reasonable to assume that the undiluted product would be corrosive in the rabbit eye and that it was not necessary to conduct this study.

An eye irritation test was conducted in the rabbit with a dilution of Dehyquart® E-CA containing 4% active material. A single instillation of 0.1 ml of the diluted test substance was made in the eyes of four rabbits and the eyes were evaluated 24, 48, 72 and 96 hours after instillation. No reactions of the cornea or iris were observed. Moderate conjunctival irritation was recorded which had resolved in three rabbits by day 2 and in all rabbits by day 3. The manufacturer's report concludes that exposure to a dilution of Dehyquart® E-CA containing 4% active material should not result in adverse reactions in the eye if the eye is rinsed immediately after contact.

The sensitising potential of Dehyquart® E-CA was investigated in female guinea pigs (Pirbright White) using the Magnusson–Kligman method (Maximisation test). No evidence of sensitisation was seen. Classification and labelling of Dehyquart® E-CA in respect of sensitising potential was, therefore, unnecessary.

The data provided in the manufacturer's summary report suggest that Dehyquart® E-CA in Lythrin 1% w/w Crème Rinse as an excipient, at a concentration of 2.0 % w/w, is unlikely to present any toxicologically important risk to the patient in terms of skin or eye irritation or sensitisation. The negative Ames test provides some assurance that Dehyquart® E-CA is unlikely to be a strong mutagen; however the absence of cytotoxicity data in the summary report precludes justification of the high dose level employed in this assay. The absence of a full mutagenicity test battery leaves some doubt regarding the mutagenic potential of this excipient.

Data on cationic surfactants as a class suggest that transdermal absorption of Dehyquart® E-CA is unlikely to be of toxicological importance. Transdermal

absorption of Dehyquart® E-CA is further limited by the short contact period (10 minutes) recommended in the Product Information Leaflet.

Assessor's comment

It is concluded that the applicant has provided sufficient information to give reassurance that the inclusion of the excipient Dehyquart® E-CA is unlikely to result in undue toxicity. There is no repeat-dose toxicity data but since the product is for single application this is acceptable.

*In relation to the genetic toxicity data, there has been only one study conducted, an Ames test. While there is justification to request that a chromosome aberration test be conducted, it is acknowledged that Dehyquart® E-CA is available in products that can be bought and used without restriction. Exposure will be limited and systemic absorption is unlikely to occur so there is less need for an *in vivo* micronucleus test. However, in consideration of these issues, the SPC was amended to disclose the fact that Dehyquart® E-CA has not been subjected to full genotoxicity testing.*

Benzyl alcohol

The non-clinical overview does not include mention of any impurities, and any impurities of concern have not been identified. Benzyl alcohol is used as a preservative at a concentration of 1.10%. There are no data in animals or discussion on the potential for dermal absorption of benzyl alcohol. While the product is intended for short-term, single use, potentially repeated after two weeks, infants of six months are included in the patient population and some discussion of the safety of benzyl alcohol and potential for absorption in juveniles is necessary.

Absorption of benzyl alcohol in infants

Benzyl alcohol, a bacteriostatic agent used in many parenteral preparations, is present as an excipient in Lythrin 1% w/w Crème Rinse at a concentration of 1.10% w/w. In man, topically applied benzyl alcohol is metabolised in the liver or kidney to benzoic acid and a proportion of the plasma benzoic acid is normally detoxified by glycine conjugation to hippuric acid. Both benzoic acid and hippuric acid are excreted in the urine.

Both benzyl alcohol and its metabolite benzoic acid have Acceptable Daily Intakes (ADIs) established by the World Health Organisation of 5mg/kg, i.e. for a child of approximately 6 months of age and approximately 6 kg body weight, the ADI would be 30 mg. No published data on the *in vivo* absorption of benzyl alcohol through adult or infant human skin were identified.

Absorption of the related molecule, benzyl acetate, through full-thickness human skin *in vitro* is reported to be $5.5 \pm 0.1\%$ of the applied dose ($1.8 \pm 0.0 \text{ mg/cm}^2$) (mean \pm SD, n = 12) at 24 hours and $17.8 \pm 3.3\%$ of the applied dose ($5.9 \pm 1.1 \text{ mg/cm}^2$) at 72 hours.

The dermal flux for benzyl alcohol across human skin *in vitro* was reported to be 0.073 mg/sq cm/hr, indicating a low rate of dermal uptake. The percentage of the applied dose that penetrated through human skin *in vitro* in six hours was 1.42 percent for adult skin and 0.73 percent for full term infant skin.

The maximum total exposure to benzyl alcohol following a maximum recommended single treatment with Lythrin 1% w/w Crème Rinse (two bottles each of 59ml) is 1.32 ml (SG 1.045) or 1.38g. Assuming worst case absorption criteria as reported for adult human skin *in vitro* in six hours, the potential absorption of benzyl alcohol equates to:

$$\frac{1.42}{100} \times 1.38 \text{ g} = \sim 20 \text{ mg}$$

which, for a child of 6 kg body weight, equates to 3.3 mg/kg.

The applicant notes that this excipient is used in a rinse-off product with a limited contact period (the Product Information Leaflet recommends a contact period of 10 minutes and indicates that ‘application for longer than 10 minutes will not give better results’). No published evidence of active transport of benzyl alcohol across human skin *in vitro* or *in vivo* has been identified. If it is assumed that absorption of benzyl alcohol *in vivo* occurs as a linear diffusion process, then the limited 10 minute contact period would be expected to reduce the absorption by a factor in the order of 10/360 compared with the value quoted for absorption through adult human skin *in vitro* of 1.42% of the applied dose in six hours. This would reduce the absorption of benzyl alcohol during the recommended 10 minute use of Lythrin 1% w/w Crème Rinse to a value in the order of 0.04% of the applied dose. The estimated absorption of benzyl alcohol would then be:

$$\frac{0.04}{100} \times 1.38 \text{ g} = \sim 550 \text{ } \mu\text{g}$$

which, for a child of 6 kg body weight, equates to $\sim 93 \text{ } \mu\text{g/kg}$.

The ‘gaspings syndrome’ reported in premature neonates following exposure to benzyl alcohol used as a preservative in solutions used to flush umbilical catheters was associated with exposures to benzyl alcohol in the range 99-234 mg/kg/day. In addition, the high concentrations of benzyl alcohol and low concentrations of hippuric acid in the urine of these neonates suggests that the immaturity of the detoxification process increased their sensitivity to the toxic effects of benzoic acid.

The applicant concludes that worst case estimates suggest that absorption of benzyl alcohol in a 6kg infant following a maximum recommended single treatment with Lythrin 1% w/w Crème Rinse (two bottles each of 59ml) is likely to be in the range 93 $\mu\text{g/kg}$ to 3.3 mg/kg, and within the ADI of 5 mg/kg established by the World Health Organisation. It is probable that exposure would be towards the lower end of this range. ‘Gaspings syndrome’ in premature neonates, which was associated with benzyl alcohol toxicity, occurred at exposures in the range 99-234 mg/kg/day. The immaturity of the metabolic detoxification processes in premature neonates in which benzyl alcohol toxicity occurred probably increased their sensitivity to benzyl alcohol.

On the basis of the available data, benzyl alcohol exposure of infants following the use of Lythrin 1% w/w Crème Rinse, as recommended in the Product Information Leaflet, is unlikely to constitute a toxicological risk.

IV NON-CLINICAL OVERVIEW

A satisfactory non-clinical overview is provided, and has been prepared by an appropriately qualified expert. It contains a satisfactory review of thirty-seven relevant publications.

V SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The approved SPC is satisfactory.

VI CONCLUSION

This application has not revealed any evidence of untoward toxicity on the part of the active ingredient, or the excipients of Lythrin 1% w/w Crème Rinse.

All issues having been resolved, there are no preclinical objections to the grant of a licence.

CLINICAL ASSESSMENT

I INDICATIONS

Lythrin 1% w/w Crème Rinse is indicated for the treatment of *Pediculus capitis* (head lice) infestations.

The indication is consistent with other products containing permethrin as an active substance and is supported by the literature.

II POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with the literature.

III TOXICOLOGY

No new data has been submitted and none are required for this type of application.

A pre-clinical expert report has been provided by an appropriately qualified consultant. This is satisfactory.

IV CLINICAL PHARMACOLOGY

Pharmacokinetics

No specific pharmacokinetic or metabolic studies were undertaken with Lythrin 1% w/w Crème Rinse. The pharmacokinetic properties of this active substance are well established and described in the literature.

There are few human data available on systemic exposure or kinetics following application to the skin. Some pre-systemic metabolism occurs in the skin. Absorbed permethrin is rapidly metabolised by ester hydrolysis, most likely in the liver, and the products are excreted primarily in the urine.

In an *in vitro* study of percutaneous penetration of ¹⁴C-labeled pesticides, only 0.62% of the applied dose (200 µg/cm²) of permethrin penetrated human skin over an 8 hr period. Analysis of plasma samples following “whole body” application of 5% permethrin cream to volunteers on two occasions 7 days apart failed to demonstrate detectable permethrin (<5 µg/l). As doses of between 150mg and 660mg permethrin were applied, the absence of detectable drug was taken to indicate that it was not rapidly absorbed and that the extent of absorption was low. Studies in normal volunteers using ¹⁴C-permethrin showed extremely low urinary and faecal amounts of radioactivity (<0.31 µg/l¹), too low to permit analysis of permethrin metabolites. However, combined urinary and faecal data collected over a 5-day post-treatment period, during which the volunteers did not bathe, showed the percutaneous absorption of permethrin to be less than 2% of the applied dose.

The excipients in the formulation of Lythrin 1% w/w Crème Rinse differ from those of the other, similar products. However, the excipients are not considered likely to increase the absorption of permethrin through the skin.

Pharmacodynamics

Permethrin is a synthetic derivative of the insecticide pyrethrum, which was originally obtained from *Chrysanthemum cinerariaefolium*. Pyrethroids have been used in commercial agriculture for more than 100 years. They were noted to have exceptional insecticidal activity with very low mammalian toxicity. Permethrin was first synthesised in 1973.

Pyrethroids are rapidly absorbed by the insect via the mouth, respiratory tract, or the intact cuticle. Pyrethroids primarily affect the sodium channels in the nerve membrane and cause prolongation of the transient increase in sodium permeability associated with membrane depolarisation. After treatment with pyrethroids, the sodium current evoked by a step depolarisation is followed by a prolonged sodium tail after repolarisation of the membrane. Although the primary target tissue is the nervous system, insects are not killed by dysfunction of a single organ but by a complex series of reactions in various organs, such as metabolic exhaustion and paralysis of the nervous system. The insect's initial signs of poisoning are usually loss of coordination and locomotor instability generally referred to as knockdown. Signs of pyrethroid poisoning in the insects and other arthropods generally include hyperexcitation, tremors and convulsions, later followed by paralysis and death.

V CLINICAL EFFICACY

No new data are submitted and none are required for this type of application.

The applicant has submitted a bibliography which is summarised in the clinical overview. The bibliography includes two systematic reviews of permethrin and seven individual studies. The formulation used in the individual studies was a 1% permethrin cream rinse.

Systematic reviews:

Vander Stichele 1995

Twenty eight trials that had been conducted in adults or children infected with head lice were identified. Of the 14 trials rated as having a low to moderate risk of bias, there were only seven where the outcome had been measured clinically by inspection of the scalp to determine cure rate 14 days after treatment. These seven trials described 21 evaluations of eight different compounds and placebo and included five trials with permethrin.

Cure rates of nearly 100% and lower 95% confidence interval limits above 90% were seen in five studies with permethrin. Of the pediculicides studied, only permethrin showed efficacy in more than two studies where the lower 95% confidence limit of cure rate was above 90%.

The authors concluded that sufficient evidence published to confirm efficacy was only available for permethrin.

Dodd 2003

This was a Cochrane Collaboration meta-analysis. Seventy-one studies were identified by a literature search using indication and products as search terms. Of these only four studies were identified, two of which evaluated permethrin, that were

considered to meet the inclusion criteria of adequate randomisation, adequate diagnostic criteria, adequate washout of previous treatment and no concomitant use of physical treatment with chemical treatment. The other two studies considered to be of acceptable quality investigated malathion.

Four of the studies identified by Vander Stichele were not included in the Cochrane review as they were considered to have some methodological flaws not identified at the time of the previous review while one study identified by Vander Stichele as inadequate is included in the Cochrane review.

The criteria applied by Dodd in selecting studies for inclusion in the Cochrane review were:

- presence of live lice or lice and eggs prior to enrolment, not just eggs alone
- no use of any pediculicide in the month preceding enrolment
- no application of combing following treatment with the pediculicide except during detection combing
- efficacy determined by primary cure by day 2, ovicidal effect determined by the need for re-treatment at day 7 and patient completely free of lice by day 14

The conduct of a trial where the presence of live lice is not required was considered by Dodd to not provide an adequate test of efficacy of treatment. Use of pediculicide in the period prior to enrolment could affect outcome due to the presence of residue from the prior treatment so studies not meeting this criterion were not included. Combing was considered to possibly enhance the treatment effect and overestimate efficacy and studies where this was combined with treatment were similarly excluded from review.

The reviewer concludes that:

- Permethrin, synergised pyrethrin and malathion were effective in the treatment of head lice
- The best choice of treatment will depend on local resistance patterns

The studies identified in both these systematic reviews are discussed in the clinical overview and are cited as studies that support the efficacy of Lythrin 1% w/w Crème Rinse.

Individual Studies:

Taplin et al (1986)

This study evaluated the efficacy of permethrin treatment (1% cream rinse) in comparison with placebo in 90 children and adults in the Republic of Panama. Of the 90 participants, 63 were randomised to permethrin or placebo with the remainder receiving lindane as a positive control. No subjects were lost to follow-up. Ovicidal effect was assessed by collecting shafts of hair with viable ova attached before and immediately after treatment and incubating them in individual containers. Percentage mortality of the ova was then calculated. At day 7, all patients treated with permethrin were free of lice compared to 3/34 (9%) treated with placebo. At 14 days after treatment, 28/29 (97%) of patients treated with permethrin were free of lice compared to 2/34 (6%) of placebo-treated patients ($P < 0.001$) and 43% of the lindane-treated group. Permethrin was 70% ovicidal compared to 14% for placebo ($P < 0.001$) and 45% for lindane.

Burgess et al (1994)

This was a two centre trial which took place in Dhaka, Bangladesh. This study compared the effectiveness of permethrin cream rinse (1%) with synergised pyrethrin. Both infested children (aged 7-15) and adults were enrolled on the trial. Of 52 patients identified with lice, 42 were treated with pyrethrin mousse and 10 with permethrin cream rinse. Ovicidal effect of the two treatments was assessed by collecting viable ova from each participant before and immediately after treatment. These were incubated in individual Petri dishes for 14 days and percentage mortality of the ova calculated. The patients were examined for lice on alternate days until day 8 and then again on day 14. None of the patients in either group was found to have lice up to 2 days after treatment. One patient was found to have two moribund hatchlings on day 4. Insufficient patients attended follow-up at 7 and 14 days to assess efficacy at these time points although there was complete cure in those who did present for follow-up. Ovicidal effect was calculated as 8% mortality of ova for permethrin compared with 34.2% mortality of ova for synergized pyrethrin.

Assessor's comment

This study was designed to investigate the treatment effect of synergised natural pyrethrins. The results of the study suggest that pyrethrin mousse is more effective than 1% permethrin.

Bowerman et al (1988)

This study investigated the efficacy of permethrin (1% cream rinse) in comparison to lindane in a randomized, investigator blind study in 1040 children and adults. Efficacy was assessed by the presence of live adult lice and nymphs. Treatment with permethrin was at least 98% efficacious in terms of louse eradication. In comparison, the efficacy of lindane was 90% at 7 days but only 76% at 14 days. This study was excluded from the Cochrane analysis as previous use of pediculicidal agents was permitted up to one week before study start.

Di Napoli et al (1988)

This study compared the efficacy of permethrin (1 % cream rinse) with that of pyrethrin combined with piperonyl butoxide in 435 participants. Most participants were children aged 1-18 although some adult family members also participated in the study. Efficacy was assessed by the presence of live adult lice and nymphs. Treatment with permethrin resulted in 97% of patients becoming lice-free at day 14. This study was excluded from the Cochrane analysis as previous use of pediculicidal agents was permitted up to one week before study start.

Carson et al (1988)

This study compared the efficacy of permethrin (1% cream rinse) with that of pyrethrin combined with piperonyl butoxide in participants aged 4 to 39 years in South Carolina, USA. Seventy-one subjects entered the study and 58 provided complete follow-up data. The presence of lice, nymphs and ova was assessed by inspection. At day 7, 26/27 patients were free of lice and by day 14, all 27 patients treated with permethrin were completely lice free compared with 29/31 (93.5%) of the patients treated with pyrethrin and piperonyl butoxide. This study was excluded from the Cochrane analysis as nit combing following treatment was permitted.

Assessor's Comment

It is not clear from the paper whether this study was masked.

Brandenburg et al (1986)

This study was a large single-blind randomized multi-centre study comparing permethrin (1 % cream rinse) with lindane (1 % shampoo). It was conducted in 573 patients enrolled in eight centres across the USA. Of the 257 patients treated with 1% permethrin, 99% were lice free at day 14. This compared with 85% treated with lindane shampoo. This study was excluded from the Cochrane analysis as previous use of pediculicidal agents was permitted up to one week before study start.

The applicant includes a further study that did not meet the inclusion criteria applied by Vander Stichele and Dodd.

Meinking et al (2002)

This study compared the efficacy of a 1 % permethrin cream rinse with and without combing in a randomized, observer-blinded study in Florida, USA. Ninety-three participants, who were at least two years of age, were randomized to treatment and provided efficacy data. Successful treatment was defined as the absence of live lice. Efficacy was slightly better in subjects who did not have combing in addition to the permethrin treatment. The number of lice-free patients was highest on day 2 (83.1%, no combing; 72.7% with-combing). By day 15 the number of patients that were lice-free had decreased slightly in the no combing group to 78.3% but had remained stable at 72.7% in the with-combing group. Although these data suggest reduced efficacy compared to previous studies and the possible development of resistance, more than three-quarters of the treated patients were lice-free at 15 days.

Overall conclusions on Efficacy

The submitted literature supports the efficacy of permethrin as a pediculicide.

A judgement must be made whether the products studied in the literature can be considered similar to the product for which the Marketing Authorisation application has been made, as they have different formulations. It is claimed that the excipients contained in the product would not be expected to alter the efficacy of permethrin. Given that permethrin is a contact insecticide, and human tissue penetration is not necessary for the efficacy of the product, this assertion is accepted.

VI CLINICAL SAFETY

No new data are submitted and none are required for this type of application.

The safety of permethrin is evaluated in the clinical overview which discusses data from clinical studies, post marketing surveillance and adverse drug reporting. Overall patient exposure is extensive; the main adverse events observed are listed in the SPC of the proposed product. The literature review identifies no new safety issues.

A safety review and literature have been provided for the excipients, hydroxycetyl hydroxyethyl dimonium chloride (which has not previously been used in a licensed medical product) and benzyl alcohol. At the concentrations used in this product they are not expected to cause a new safety concern.

VII EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. It presents a summary of the efficacy and safety of permethrin. An appropriate CV for the expert has been supplied.

VIII PRODUCT INFORMATION:

Summary of Product Characteristics

The final SmPC is satisfactory.

Patient Information Leaflet

The PIL is in line with the approved SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

IX DISCUSSION AND CONCLUSION

This is a national, bibliographic application for Lythrin 1% w/w Crème Rinse. The bibliography is supportive of the efficacy of the active ingredient and provides adequate information regarding safety. Permethrin, as an active ingredient in other formulations, has been licensed for the treatment of head lice for at least 16 years and its well established use is accepted.

No clinical study has been undertaken to demonstrate that the efficacy for this formulation of permethrin will be comparable to the formulations described in the literature. However, given the nature of the product and the mechanism of action, this is acceptable.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the applicant. When used as indicated, Lythrin 1% w/w Crème Rinse has a favourable benefit-to-risk ratio. Therefore, a Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Lythrin 1% w/w Crème Rinse 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.

PRE-CLINICAL

A pre-clinical expert report has been provided by an appropriately qualified consultant, and consists of a review of the published literature. The literature has not revealed any evidence of untoward toxicity on the part of the active ingredient, or the excipients of Lythrin 1% w/w Crème Rinse.

EFFICACY

The published literature supports the efficacy of permethrin as a pediculicide. Permethrin, as an active ingredient in other formulations, has been licensed for the treatment of head lice for more than 10 years and its well established use is accepted.

The literature review identifies no new safety issues or concerns.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with permethrin is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**LYTHRIN 1% W/W CRÈME RINSE
(PERMETHRIN)**

PL 04149/0003

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 16th July 2004
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 26th July 2004
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier and quality dossier on 11th July 2005
- 4 The applicant responded to the MHRA's request, providing further information for the clinical sections and quality sections on 28th June 2006
- 5 Following review of the application the MHRA requested further information relating to the pre- clinical sections on 19th October 2006
- 6 The applicant responded to the MHRA's request, providing further information for the pre- clinical sections on 12th February 2007
- 7 Following review of the application the MHRA requested further information relating to the quality sections on 12th February 2007
- 8 The applicant responded to the MHRA's request, providing further information for the quality sections on 19th March 2007
- 9 The application was determined on 12th June 2007

**LYTHRIN 1% W/W CRÈME RINSE
(PERMETHRIN)**

PL 04149/0003

STEPS TAKEN AFTER AUTHORISATION

Date submitted	Application type	Scope	Outcome
01/08/2007	Label and leaflet changes	Presentation of packaging (labels and leaflets) changed	Application granted 31/10/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Lythrin 1% w/w Crème Rinse is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Lythrin 1% ^w/_w Crème Rinse,
Cutaneous Emulsion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Permethrin 1% ^w/_w
'For full list of excipients, see section 6.1'

3 PHARMACEUTICAL FORM

Cutaneous Emulsion.
Lythrin Crème Rinse is a smooth white liquid preparation for cutaneous application.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lythrin Crème Rinse is intended for the treatment of head lice infestations.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Lythrin Crème Rinse is applied topically and is for external use only.

Adults and children over 6 months:

The lotion should be used after the hair has been washed with a mild non-conditioning and non-medicated shampoo and then towel dried. The bottle should be shaken thoroughly and the hair and scalp should be saturated with the lotion, with particular attention given to the areas at the back of the neck and behind the ears.

The lotion should be left on for 10 minutes. Thereafter, the hair should be rinsed thoroughly with water and combed with an ordinary comb. The hair should then be rinsed again, combed with a fine toothed comb (provided with the pack) to remove dead lice and eggs, and dried in the usual way.

One bottle of Lythrin Crème Rinse is usually sufficient to treat one person with shoulder length hair of average thickness, a little more may be required if the person's hair is especially thick or long. It is very unlikely that more than two bottles will be required per application.

Children: Not recommended for children under 6 months of age, except on advice of a doctor.

Elderly: As for adults.

4.3 CONTRAINDICATIONS

Lythrin Crème Rinse is contraindicated in patients with a known sensitivity to the product, its components and other pyrethroids or pyrethrins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The active ingredient and the product are not known to be irritating to the eyes. However, if the product comes into contact with the eyes, rinse immediately with plenty of water.

Nursing or care staff who routinely use the product should wear gloves in order to avoid potential irritation to the hands.

The effect of this product on artificial hair dyes and perms has not been determined. Although complaints are extremely rare, it is recommended to apply the product to a small section of hair first, before treating the entire scalp.

Lythrin Crème Rinse is for external use only and is suitable for use in adults and children over 6 months of age. The use of Lythrin Crème Rinse in children below the age of 6 months should only be on the advice of a doctor.

Not to be used by persons known to be sensitive to the ingredients.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No adverse effects reported.

4.6 PREGNANCY AND LACTATION

Reproduction studies have been performed in mice, rats and rabbits (200 - 400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are however, only very limited data on the use of permethrin in pregnant women.

Because animal studies are not always predictive of the human response, treatment should be considered during pregnancy only if clearly needed.

Studies following oral administration of permethrin in cattle have indicated that very low concentrations of permethrin are excreted in milk. However, it is not known whether permethrin is excreted in human milk. Whilst it is unlikely that the concentrations of permethrin in the milk will present any risk to the infant, consideration should be given to withholding treatment during nursing or temporarily discontinuing nursing.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No adverse effects reported.

4.8 UNDESIRABLE EFFECTS

Side effects are not common with Lythrin Crème Rinse and if they occur they are usually mild and indistinguishable from the head lice infestation itself. Occasionally, skin irritation, redness or rash may occur.

4.9 OVERDOSE

When applied topically, systemic overdosage with the product is unlikely due to minimal percutaneous absorption.

Indeed, there have been no reports of overdosage associated with the use of the product or other topical permethrin products. On the basis of a review of publically available animal and human-volunteer studies, it is extremely unlikely (even with intended misuse or excessive application) that the amount of permethrin or any of the other constituents, required to produce clinically-relevant toxic effects would be reached. The most likely symptoms and signs following repeated, excessive application are hypersensitivity-type reactions.

Following accidental ingestion, dizziness, nausea, vomiting, diarrhoea, CNS depression or hypotension could potentially occur. In the event of accidental ingestion of the contents of a bottle by a child a doctor should be consulted immediately. Gastric lavage should be considered within two hours of ingestion.

Symptomatic treatment is indicated if any of these reactions occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The ATC code for Lythrin Crème Rinse is P03 A C 04 (Group: Ectoparasiticides, incl. Scabificides, insecticides and repellents). Permethrin may be classified as a Pyrethroid Pesticide. They are highly effective insecticidal neurotoxins, and are effective against head lice and their eggs.

5.2 PHARMACOKINETIC PROPERTIES

Permethrin is practically insoluble in water and is readily metabolised in humans. Hydrolysis of the ester bond, hydroxylation and elimination as glucoside conjugate is the main route of metabolism. Permethrin may persist in the fatty tissues with half-lives of 4 to 5 days in brain and fat. Permethrin does not block or inhibit cholinesterase enzymes.

Permethrin is rapidly metabolised by ester hydrolysis to inactive metabolites which are excreted primarily in the urine.

In vitro studies have shown that permethrin levels on hair are not affected by chlorine in concentrations used in swimming pools.

5.3 PRECLINICAL SAFETY DATA

Published acute toxicity data indicate that permethrin is of low acute toxicity in a range of mammalian species by common routes of exposure. In radiolabel experiments, no accumulation of the parent compounds or of their metabolites was observed.

The lowest NOEL identified was 20 mg/kg/day following dietary administration in the rat for periods from 90 days to 6 months in duration. Assuming a worst case scenario in which a child of six months of age (approximately 6 kg body weight) was treated with the maximum dose topically, the total absorption would be $1,200 \text{ mg} \times 1\% = 12 \text{ mg}$ i.e. $12/6 = 2 \text{ mg/kg}$. The safety margin in this extreme scenario is, therefore, ten-fold compared to the lowest reported NOEL for repeated dietary administration.

In vitro mutagenicity studies indicate that permethrin is universally negative in the Ames test with *Salmonella typhimurium* and *Eschericia coli*. The reported test in Chinese hamster V79 cells was conducted at a very low maximum dose level and the negative result in this assay must be approached with caution. The excipient hydroxycetyl hydroxyethyl dimonium chloride has not been subjected to a full battery of genotoxicity tests. There was no evidence of mutagenicity in an Ames test with *Salmonella typhimurium* but an *in vitro* cytogenicity test in mammalian cells and an *in vivo* micronucleus test have not been conducted.

The available published data indicate that permethrin has the potential to induce numerical chromosome aberrations in both human lymphocytes and in CHO cells in the absence of S9. Perhaps of more importance are the data indicating that exposure of Wistar rats to permethrin in the dose range 12.6 to 125.7mg/kg induced numerical chromosome aberrations in bone marrow. The lowest reported dose to show this effect is approximately six times the worst case topical exposure calculated for Lythrin Crème Rinse.

None of the reported studies demonstrated evidence of carcinogenicity.

There are sufficient published data to confirm that permethrin does not represent a reproductive risk in the intended pharmaceutical application as Lythrin Crème Rinse.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl Alcohol
Propylene Glycol
Hydroxycetyl Hydroxyethyl Dimonium Chloride
Cetostearyl Alcohol
Ceteareth-20
Light Liquid Paraffin
Carbomer
Sodium Hydroxide Solution
Purified Water

6.2 INCOMPATIBILITIES

None reported.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Keep container in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use after the expiry date on the label and carton.

Do not use Lythrin Crème Rinse if there is any visible sign of deterioration of the lotion.

6.5 NATURE AND CONTENTS OF CONTAINER

White 59ml HDPE bottle with LDPE screw cap incorporating flip up applicator. A comb is also provided.

There are 2 pack sizes: 1 x 59ml pack and 2 x 59ml pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Shake bottle thoroughly before use.

Nursing staff routinely using Lythrin Crème Rinse should wear gloves to avoid any irritation to the hands.

7 MARKETING AUTHORISATION HOLDER

Ovelle Ltd.,
Industrial Estate,
Coe's Rd,
Dundalk,
Co. Louth,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04149/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/06/2007

10 DATE OF REVISION OF THE TEXT

12/06/2007

PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BECAUSE IT CONTAINS IMPORTANT INFORMATION FOR YOU.

This medicine is available without a prescription. Nevertheless you will still need to use Lythrin[®] Crème Rinse carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must see a doctor if your symptoms do not improve after using Lythrin[®] Crème Rinse.

In this leaflet:

1. What Lythrin[®] Crème Rinse is and what it is used for
2. Before you use Lythrin[®] Crème Rinse
3. How to use Lythrin[®] Crème Rinse
4. Possible side effects
5. How to store Lythrin[®] Crème Rinse
6. Further information

1. WHAT LYTHRIN[®] CREME RINSE IS AND WHAT IT IS USED FOR

The name of your treatment is Lythrin[®] Crème Rinse. It is a smooth white lotion (cutaneous emulsion) containing the active ingredient permethrin.

Permethrin, the active ingredient in Lythrin[®] Crème Rinse belongs to a group of medicines called **pyrethroids**, which are anti-parasitic agents.

Lythrin[®] Crème Rinse is used for the topical treatment of head lice infestations.

2. BEFORE YOU USE LYTHRIN[®] CREME RINSE

Do not use Lythrin[®] Crème Rinse:

- If you are hypersensitive (allergic) to pyrethroids, pyrethrins or any of the other ingredients of Lythrin[®] Crème Rinse.
- If you had a reaction to this product before.
- On children under 6 months of age, except on the advice of your doctor.

Pregnancy and Breastfeeding:

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

There have been no adverse effects reported.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including those that you have bought yourself.

Take special care with Lythrin[®] Crème Rinse

- Please note that the inactive ingredients, cetostearyl alcohol and propylene glycol may cause skin rashes or irritation.
- Lythrin[®] Crème Rinse should not irritate the eyes. However, care should be taken when applying. If accidental contact occurs, rinse immediately with plenty of water.
- Nursing or care staff who routinely use Lythrin[®] Crème Rinse may wish to wear gloves in order to avoid possible irritation to the hands.
- If one member of the family needs treatment, it is important to check the rest of the family for head lice, and **ONLY THOSE INFECTED SHOULD BE TREATED.**
- The effect of Lythrin[®] Crème Rinse on artificial hair dyes and perms has not been determined, although complaints are extremely rare. It is recommended to apply the product to a small section of hair first, before treating the entire scalp.
- Lythrin[®] Crème Rinse is not affected by the chlorine used in swimming pools, so there is no reason why you cannot swim following treatment.

3. HOW TO USE LYTHRIN[®] CREME RINSE

Always use Lythrin[®] Crème Rinse as your doctor/pharmacist has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose is 59ml (one bottle). It is very unlikely that more than two bottles will be required per application.

Please follow these instructions carefully:



1. Shampoo the hair with a mild shampoo. Do not use a combined shampoo-conditioner or a medicated shampoo. Rinse thoroughly and towel dry so that the hair remains damp.

2. Shake the bottle thoroughly, apply sufficient Lythrin[®] Crème Rinse to saturate the hair, roots and scalp. Work methodically through the hair paying particular attention to the areas behind the ears and around the nape of the neck. For the majority of individuals all of the contents of this pack will be required to ensure that the hair and scalp are saturated. It is advisable to use the full bottle.



3. Leave on the hair for 10 minutes, then rinse and comb with an ordinary comb. An application for longer than 10 minutes will not give better results, but a full 10 minutes is required.

4. Rinse thoroughly with water. After this final rinse and while hair is still wet, use the fine toothed comb (provided with the pack) to remove the lice and eggs. Comb the hair in sections from the roots and work over the whole head in this way. Normal hair dry-ing routines can then be followed.



If you use more Lythrin[®] Crème Rinse than you should

Lythrin[®] Crème Rinse is for external use only. Children should be supervised during use. If you use more Lythrin[®] Crème Rinse than recommended, rinse well with plenty of water.

IF THE PRODUCT IS ACCIDENTALLY SWALLOWED consult a doctor or go to the casualty department at your nearest hospital immediately. Take along any product that is left, the bottle and the label so that the hospital will know the product you have used.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lythrin[®] Crème Rinse can have side effects. However, when they occur they are usually mild and cannot be distinguished from the head lice infestation itself. Occasionally, skin irritation, redness or rash may occur. If you develop any of these, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE LYTHRIN[®] CREME RINSE

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

Do not use after the expiry date stated on the label and carton.

Do not use Lythrin[®] Crème Rinse if you notice any visible signs of deterioration of the lotion.

OTC004V2P1

6. FURTHER INFORMATION

What Lythrin[®] Crème Rinse contains

The active substance is permethrin.

The other ingredients are benzyl alcohol (as a preservative), propylene glycol, hydroxycetyl hydroxyethyl dimonium chloride, cetearyl alcohol, ceteareth-20, light liquid paraffin, carbomer, sodium hydroxide solution and purified water.

What Lythrin[®] Crème Rinse looks like and contents of the pack

Lythrin[®] Crème Rinse is a smooth white liquid preparation for cutaneous application.

The bottle contains 59ml of lotion.

There are 2 pack sizes: 1x59ml pack or 2x59 ml pack

Included in each pack is a fine toothed comb which can be used to remove lice and eggs after treatment.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and Manufacturer is Ovelle Ltd., Coe's Rd, Dundalk, Co. Louth, Ireland.

Tel: +353 (0)42 93 32304

Lythrin[®] Crème Rinse is prepared and packaged for: Kent Pharmaceuticals Ltd, Wotton Road, Ashford, Kent TN23 6LL.

Lythrin[®] is a registered trade mark.

ABOUT HEAD LICE

Interesting fact about head lice

It is estimated that up to half a million children catch head lice each year. Also as with the common cold, anyone can catch lice. So if anyone in your family catches head lice, they are not alone, and it is certainly nothing to be ashamed about!

What are head lice?

Head lice are small insects (their size can vary depending on the stage of their development, but adults are usually between 2-3 mm long when fully grown) which vary in colour from grayish white to brown. They like to set up home in a warm head of human hair and have no preference for the type of hair, be it brunette or blonde, straight or curly, clean or dirty, head lice are not fussy.

There is only one way for head lice to pass from one individual to another and this is by head to head contact. Head lice cannot jump, hop or fly from one person to another, and it is also unlikely for them to be passed on through towels, combs and chair backs.

Head lice spend most of their time on or near the scalp as they need warmth to survive. They grip on the hair by means of special claws and feed on the scalp by sucking blood.

The female louse will lay up to 8 oval shaped eggs every night, gluing them to the base of individual hairs. After about seven days a young louse (nymph) emerges, leaving behind it a white egg shell. These white egg shells remain glued to the hair and are known as nits. The nymph will begin feeding in the same way as the adult and within about 10 days will be mature and capable of breeding.

What to look for?

Due to their size, colour and rapid movement, head lice are difficult to see. The eggs (creamy brown) are a little easier to spot and will be found attached to individual hairs near to the scalp. In contrast, the white nits can often be seen further from the scalp, this is because as the hair grows the nits (which are still glued to the hair shaft) move with it.

The best way to find head lice and their eggs is to run a fine-toothed comb through damp parted hair looking carefully for evidence of lice. Signs to look for include faeces, cast skins or dead lice.

Louse faeces appear as black flecks like dust, often this is rubbed onto collars or the pillow at night resulting in shirts and bed clothes, becoming dirty more quickly than usual.

How to prevent head lice?

Steps that can be taken to reduce the possibility of an infection include:

- Check whole family's hair using a fine toothed detection comb on a regular basis, for any signs of head lice. If live head lice are found it is important to trace the source of the original infection. This may be someone well known to the family, but who may not be aware that they have head lice. If this person is not identified and treated, others can be quickly infected, sometimes within hours after treatment.
- If a child in your family is found to have lice, please inform their school, other parents, Health Visitor and School Nurse.

Getting the best from this treatment

In most cases a single treatment is sufficient to eliminate head lice. Use of hair mousses, gels, sprays, 2 in 1 shampoos and conditioners immediately before treatment can reduce its effectiveness.

Lice may continue to move or twitch up to 24 hours after treatment, this is normal and not a sign of treatment failure.

There is potential for head lice to develop resistance to treatments. If live lice are detected during the 7 days after the first application, a second treatment should be given on day 7. If further treatments are required consult a doctor or pharmacist, continual repetitive treatment should be avoided.

This leaflet was last approved in 03/2007

OTC004V2P1

PATIENT INFORMATION LEAFLET

Lythrin[®]
1% w/w CREME RINSE

PERMETHRIN 1% w/w

HEAD LICE TREATMENT

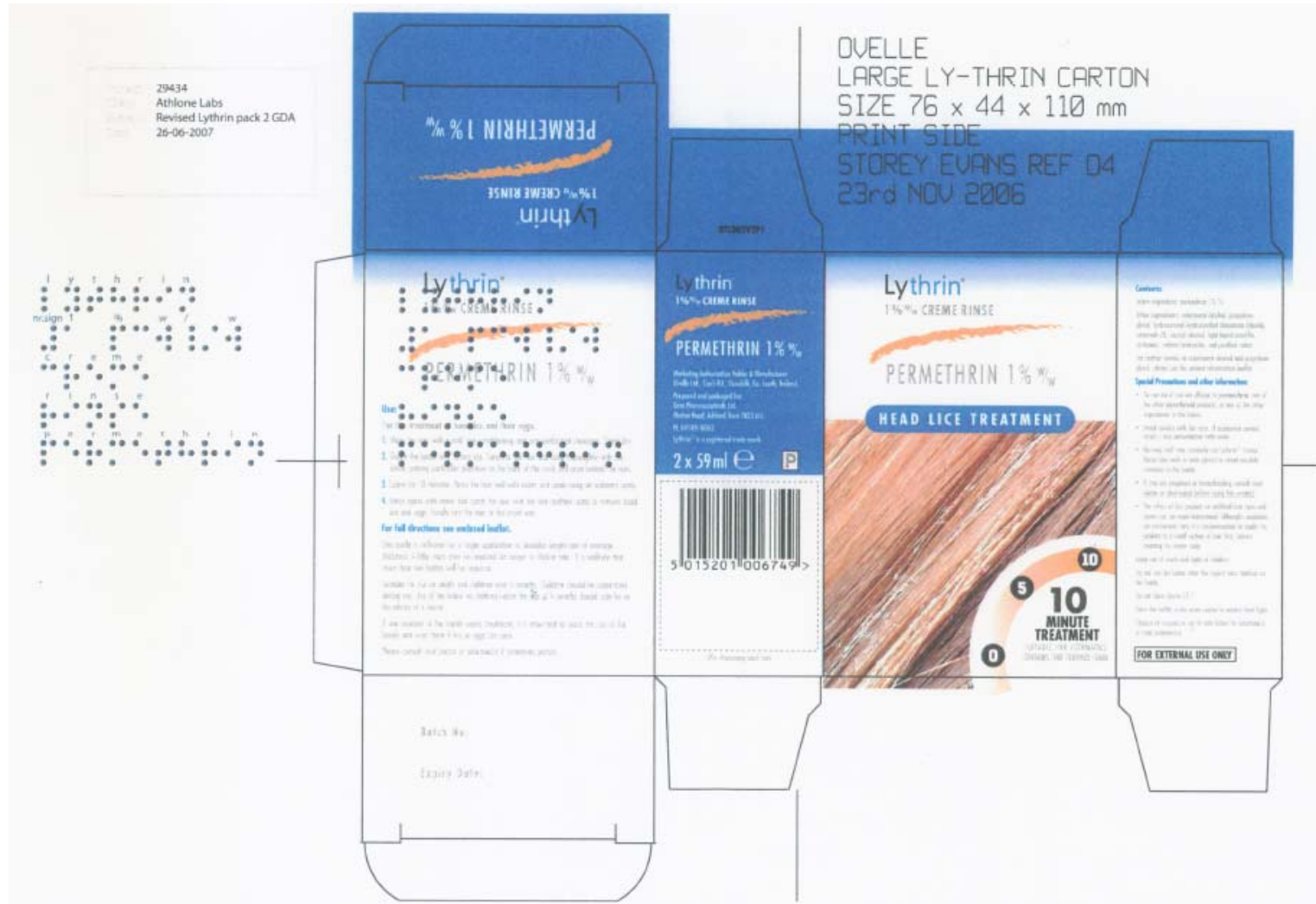
10
MINUTE
TREATMENT
SUITABLE FOR ASTHMATICS
CONTAINS FINE TOOTHED COMB

LABELLING

Carton for pack size 1 x 59ml



Carton for pack size 2 x 59ml – with braille



Bottle label

Use: For the treatment of head lice and their eggs.

1. Wash the hair with a mild non-conditioning and non-irritating shampoo, towel dry.
2. Shake the bottle well before use. Saturate the hair and scalp thoroughly with the lotion, paying particular attention to the back of the neck and area behind the ears.
3. Leave for 10 minutes. Rinse the hair well with water and comb using an ordinary comb.
4. Rinse again with water and comb the hair with the fine toothed comb to remove dead lice and eggs. Finally dry the hair in the usual way.

For full directions see enclosed leaflet.

One bottle is sufficient for a single application to shoulder length hair of average thickness. A little more may be required for longer or thicker hair. It is unlikely that more than two bottles will be required. Suitable for use on adults and children over 6 months of age. Children should be supervised during use. Use of the lotion on children below the age of 6 months should only be on the advice of a doctor. If any member of the family needs treatment, it is important to check the rest of the family and treat them if lice or eggs are seen. Please consult your doctor or pharmacist if symptoms persist.

Special Precautions and other information:

- Do not use if you are allergic to permethrin, any of the other pyrethroid products, or any of the other ingredients in the lotion.
- Avoid contact with the eyes. If accidental contact occurs, rinse immediately with water.
- Nursing staff who routinely use Lythrin® Crème Rinse may wish to wear gloves to avoid possible irritation to the hands.
- If you are pregnant or breastfeeding consult your doctor or pharmacist before using this product.
- The effect of this product on artificial hair dyes and perms has not been determined. Although complaints are extremely rare, it is recommended to apply the product to a small section of hair first, before treating the entire scalp.

Keep out of reach and sight of children. Do not use the lotion after the expiry date marked on the bottle. Do not store above 25°C. Store the bottle in the outer carton to protect from light. Dispose of unused or out of date lotion by returning it to your pharmacist.

FOR EXTERNAL USE ONLY 0102032V2P1

Lythrin®
1% w/w CRÈME RINSE

PERMETHRIN 1% w/w

HEAD LICE TREATMENT

10 MINUTE TREATMENT

Contents:

Active ingredient: permethrin 1% w/w

Other ingredients: octocryl alcohol, propylene glycol, hydroxyethyl hydroxyethyl ammonium chloride, octocryl-20, benzyl alcohol, light liquid paraffin, carboxymethyl cellulose, and purified water.

For further details on octocryl alcohol and propylene glycol, please see the patient information leaflet.

Marketing Authorisation Holder & Manufacturer: Ovale Ltd., Cow's Rd., Durrish, Co. Louth, Ireland.

Prepared and packaged for:
Kent Pharmaceuticals Ltd., Winton Road, Ashford, Kent TN23 4LL.

PL 04149/0003

Lythrin® is a registered trade mark.

59 ml e