Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

PERMETHRIN

InfectoMite 5% w/w cream
InfectoPedicul 0.43% w/v cutaneous solution

UK/W/044/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	15 July 2013
Date of finalisation of PAR	2 August 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	InfectoMite 5% w/w (50mg/g) cream InfectoPedicul 0.43% w/v (430mg/100ml) cutaneous solution
INN (or common name) of the active substance(s):	Permethrin
MAH:	InfectoPharm Arzneimittel und Consilium GmbH
Pharmaco-therapeutic group (ATC Code):	Ectoparasiticides (ATC code: P03AC04)
Pharmaceutical form(s) and strength(s):	50 mg/g cream 430mg/100ml cutaneous solution

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EXECUTIVE SUMMARY

On 20th February 2012, one MAHsubmitted paediatric data for permethrin, in accordance with Article 45 of the Paediatric Regulation. The UK is Rapporteur for this procedure.

Permethrin is a synthetic pyrethroid with oral and contact activity against mites (*Sarcoptes scabei*) and human head lice (*Pediculus capitis*). Permethrin is rapidly absorbed across the insect cuticle. The principal physiological action in susceptible parasites is induction of electrochemical abnormalities across the membranes of excitable cells, leading to sensory hyper-excitability, inco-ordination and prostration. When presented in aqueous base, the ovicidal activity of permethrin is increased by the addition of alcohol.

Permethrin is available as 5% w/w cream/lotion for the treatment of scabies and 1% w/w crème rinse/cutaneous solution/shampoo for the treatment of head lice throughout Europe. In addition, there is a 0.43% w/v cutaneous solution licensed for the treatment of head lice infestations in Germany.

The MAH holds marketing authorisations for Permethrin 5% w/w cream in 8 European countries (AT, CZ, DE, HU, LU, PL, SK, SL) indicated for the treatment of scabies. In addition, a cutaneous solution (430mg permethrin per 100ml alcohol-based solution) is licensed in Germany for the treatment of head lice infestation. All of the MAH's products are authorised for use in adults and in children older than 2 months.

MAH does not hold marketing authorisations in the United Kingdom. There are 6 permethrin containing products licensed in the UK; three 5% w/w cream products for the treatment of scabies and three 1% w/w crème rinse products for the treatment of head lice.
Of note, 5% permethrin creams are licensed from the age of 2 months and 1% crème rinse products from the age of 6 months in the UK.

The data package submitted by the MAH under article 45 of the Paediatric Regulation comprises of 4 documents: a Short Critical Expert Overview of the use of permethrin in children, an updated listing of studies, cited literature and the SmPC for 5% permethrin cream. The SmPC for 0.43% permethrin cutaneous solution was not included in the dossier.

The MAH was asked to submit additional data based on a list of questions agreed by member states at day 85 of the procedure (see section V). The MAH's response dossier was comprehensive and sufficiently addressed all outstanding issues.
The MAH carefully considered and addressed all issues raised in the Day 89 assessment report. The MAH's submitted response package sufficiently addressed all outstanding matters and therefore allowed clear SmPC update recommendations to be made to both 5% permethrin cream and 0.43% permethrin solution products. Although 1% permethrin crème rinse products are licensed in some European MSs for the treatment of head lice infestation in children, no relevant data has been submitted during this paediatric work-sharing procedure and therefore no regulatory conclusions can be drawn regarding these products. Consequently no changes to the SmPC for 1% permethrin solution products are proposed.

RECOMMENDATION

Permethrin is licensed for paediatric use in the treatment of scabies and head lice in many European countries.

5% permethrin cream products have a well established use in children with scabies. The safety and efficacy of permethrin 5% in infants younger than 2 months of age have not been established as there is only very limited data (few case reports) available. 5% permethrin is proven to be safe and effective for the treatment of scabies when used in paediatric subsets > 2 months of age, however close medical supervision is advised in children younger than 2 years of age. Regarding to best clinical practice, application of the 5% permethrin product needs to be head to toe - including the scalp, face and ears - in the paediatric population due to smaller body size. Based on these conclusions relevant updates to section 4.1, 4.2 and 4.4 of the 5% permethrin cream SmPC have been recommended by the rapporteur.

Permethrin has been widely used for the treatment of head lice infestations in children until about 10 years ago, when reports about an increasing number of treatment failure and head lice resistance against permethrin started to emerge in several European countries. Both the prevalence of kdr-like gene mutation and the association between the mutation and treatment resistance varies based on geographical location. In light of this, the rapporteur is of the view that each member state should consider whether to include the following special warning in section 4.4 of the SmPC: *"Head lice resistance against permethrin treatment has been reported depending on geographical location, therefore if live lice are present after the second application, seek medical advice."*
The safety and efficacy of permethrin 0.43% solution in infants younger than 2 months of age have not been established. There is no data available in this paediatric subgroup.

In some European countries (for example NL) permethrin is licensed for short lasting prophylaxis of head lice infestation in persons who have visited schools or other centres at the time of a head lice epidemic. In contrast, in other countries (such as the UK) it is believed that inappropriate application methods, such as permethrin used without detection of live head lice, too short contact time or permethrin applied only once instead of twice 7 days apart, may have contributed to the development of resistance. Therefore the rapporteur is of the view that an update to section 4.2 and 4.4 of the SmPC should be considered at a national level based on already existing licensed indications and local evidence based clinical guidelines.

As parents and carers refer to the package leaflet, this should also be updated accordingly.

Permethrin was proven to be safe in the submitted studies. Adverse events with 0.43% solution were mostly stinging or burning sensations on the scalp or neck. The events were related to the intensity of infestation and the number of bite reactions on the scalp and were attributed to the alcohol content of the product. Paraesthesia, contact dermatitis and urticaria have been reported as adverse events through spontaneous reporting therefore inclusion in section 4.8 of the 0.43% solution SmPC is considered indicated. Furthermore, due to its alcohol content, the 0.43% solution may worsen symptoms of asthma and eczema therefore a relevant safety warning is recommended for inclusion in section 4.4 of the SmPC.

Lastly, although 1% permethrin crème rinse products are licensed in some European MSs for the treatment of head lice infestation in children, no relevant data has been submitted during this paediatric work-sharing procedure and therefore no regulatory conclusions can be drawn regarding these products. Consequently no changes to the SmPC for 1% permethrin solution products are proposed.

Summary of outcome

The rapporteur recommends updates to the SmPCs of all permethrin containing products, however please note that changes in final implemented wording may be needed in sections 4.2, 4.4 and consequently in package leaflets, depending on each member states licensed indications, best medical practice and head lice resistance status. We therefore recommend a type IB variation to be submitted in MSs within 60 days from the publication of this report.

For full detail of the SmPC and PIL wording proposed by the rapporteur please refer to page 42.

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: sections 4.1, 4.2, 4.4. and 5.1

☐ New indication: sections 4.1, 4.2

I. INTRODUCTION

On 20th February 2012, one MAH submitted the following four documents for permethrin, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- Short critical expert overview of the use of permethrin preparations in children
- Updated line listing of studies and literature references
- Cited literature
- German SmPC of 5% cream only

The short critical expert overview summarizes the paediatric information available in German SmPCs for 5% permethrin cream and 0.43% permethrin cutaneous solution.

Three relevant published studies are included in the dossier. One of the submitted studies (Hamm et al 2006) is relevant to 5% permethrin cream use in children with scabies. The MAH states that data from this trial has been assessed during an MR procedure but the publication itself has not been assessed.
Two of the publications (Burow et al 2010, Burgess et al 2010) concern 0.43% permethrin use in paediatric head lice infestations. The MAH claims that both of these trials have already been submitted within a PSUR to a MS but they have not been assessed during the marketing authorisation application.

Rapporteur's Comment

The rapporteur notes that 0.43% w/v permethrin cutaneous solution product is not marketed in the UK. There are three licensed 1% w/w permethrin crème rinse products available on the UK market for the same indication i.e. head lice infestation. In addition there are three 5% w/w permethrin cream products licensed in the UK for the treatment of scabies in adults and children older than 2 months.

The MAH's recommendations for updating the product information

In the MAH's view no action is required concerning the paediatric information contained in the SmPCs and package leaflets of 5% cream since the available data from clinical trials, medical literature and post-marketing surveillance is adequately covered by the currently approved text.

The MAH recommends that section 4.8 of the 0.43% w/v permethrin cutaneous solution SmPC and the corresponding section in the PL should be amended to include paraesthesia, contact dermatitis and urticaria, since these adverse reactions have been observed from spontaneous reports.

II. SCIENTIFIC DISCUSSION

II.1. Information on the pharmaceutical formulation used in the clinical studies

No quality data are discussed by the MAH in the submitted dossier.

Rapporteur's Comment
It appears from the submitted publications that all three studies used MAH's products as study medication.
The submitted 5% cream German SmPC states that cetosteryl alcohol is used as an excipient in 90mg/g concentration. Regarding the European Commission guidance on *'Excipients in the labels and package leaflet of medicinal products for human use' (July 2003; CPMP/463/00)* information for all products containing Cetostearyl alcohol (including cetyl alcohol) should be updated with the following wording: *'May cause local skin reactions (e.g. contact dermatitis)'.* Section 4.4 of the submitted German 5% SmPC sufficiently complies with this guidance. However, several of the UK 5% permethrin products contain potentially irritant excipients (cetostearyl alcohol, propylene glycol, lanolin) and their currently approved UK SmPCs do not follow the above mentioned EU guidance and therefore should be updated. Other member states may also consider similar updates to their local 5% permethrin product information necessary.

The rapporteur is of the view that the MAH should discuss 0.43% permethrin solution's pharmaceutical formulation, including qualitative and quantitative composition, excipients, alcohol content and its potential local inflammatory and irritant effects.

II.2. Non-clinical aspects

The non clinical aspects of permethrin have not been discussed by the MAH.
The submitted SmPC for 5% cream contains the following information in section 5.3:

"5.3 Preclinical safety data
From acute and chronic toxicity studies there is no evidence indicating the occurrence of previously unknown adverse effects in humans.
Furthermore there is no evidence on relevant genotoxic or carcinogenic potential.
In studies on the reproductive toxicity in mice, rats and rabbits after repeated oral administration of permetrin effects were observed only for doses largely exceeding the exposure expected for the topical use of X 5%.
Following the intended use of this active substance a serious harmful effect on aquatic organisms (daphnia and fish) and terrestric organisms (plants) is expected after passage of the sewage treatment plant."

Rapporteur's Comment
The rapporteur does not support the MAH's above statement that *"There is no evidence on relevant carcinogenic potential."* The European Medicines Agency's Committee for Veterinary Medicinal Products summary report on Permethrin (EMEA/MRL/112/96-final, March 1998) states that the International Programme on Chemical Safety (IPCS) classified permethrin as a *possible weak rodent carcinogen*. 3 mice and 2 rat studies were evaluated by the IPCS. The rat studies

gave no indication of carcinogenic potential at up to 250 mg/kg./day or 2500 mg/kg feed. The mouse studies (with doses up to 5000 mg/kg feed) did give some indication of an increased incidence of lung tumours in permethrin-treated mice as compared to concurrent controls. However the incidence of tumours was within the historical control range. The EMA report also states that the carcinogenic potential of permethrin is not a cause for concern.
The currently approved UK 5% permethrin cream SmPC states in Section 5.3: *"Long term studies in rats revealed no evidence of oncogenicity. Similar studies in mice have shown species specific increases in pulmonary adenomas, a common benign tumour of mice of high spontaneous background incidence. In one of these studies, there was an increased incidence of benign liver adenomas and of pulmonary alveolar cell carcinomas only in female mice when permethrin was given in their food for two years (approximately 750 mg/kg bodyweight/day). These findings are not considered to indicate a significant oncogenic potential for permethrin in humans".* The rapporteur is of the view that in light of permethrin's IPCS classification as a weak rodent carcinogen, the above information should be considered for inclusion in Section 5.3 of the SmPC.

According to the above mentioned EMA report permethrin's neurotoxicity has been studied in rats and hens. Structural damage to nerves is only observed following very high doses (400 mg/kg/day for 7 days) of permethrin. The neurotoxic effects diminish with continued exposure and are reversible within a few days.
Recent studies have indicated that early postnatal exposure to permethrin induces behavioural changes, dopaminergic system modulation and oxidative stress in rats. (Nasuti et al 2007). The MAH is asked to discuss permethrin's carcinogenic and developmental neurotoxic effects including the animal findings' clinical relevance.

In summary, the applicant is asked to discuss permethrin's potential carcinogenic and developmental neurotoxic effects and suggest a wording for inclusion in section 5.3 of the SmPC accordingly.

II.3. Clinical aspects

1. Introduction

The MAH's submission is a short summary (6 pages) of relevant paediatric data from the currently approved German SmPCs, rather than a critical assessment or overview of literature data. The MAH did not provide any information about scabies and head lice infestations in the paediatric population and did not discuss permethrin's current status in the treatment of these conditions.

Please note that for clearer understanding, some parts of this section have been divided into two parts by the rapporteur: 5% permethrin cream and 0.43% permethrin cutaneous solution.

2. Clinical overview

a. Pharmacokinetics

The following PK information was included in the submitted 5% permethrin cream SmPC:

*"**5.2 Pharmacokinetic properties***

Investigations with X 5 % in humans revealed an average percutaneous absorption rate of 0.47 ± 0.3 % in healthy subjects and of 0.52 ± 0.3 % in patients.

Pharmacokinetic properties were studied in adult subjects only (6 healthy volunteers and 6 patients with scabies).

Absorbed permethrin is rapidly broken down by esterases as well as hydrolases. After oral administration, peak plasma concentrations are reached in approximately 4 hours. The isomeric mixture is then excreted in the urine in the form of glucuronides, sulfates etc as cis- trans Cl_2CA [(3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid)] and after oxidation to 3 PBA (3-phenoxybenzoic acid). After oral application, up to 6 % is excreted unchanged in the faeces whilst on dermal application, unchanged permethrin is virtually undetectable."

Rapporteur's Comment
The rapporteur supports the MAH's wording for inclusion in section 5.2 of cream 5% SmPC.
In addition, 0.43% permethrin cutaneous solution's PK profile should also be discussed by the MAH and a wording for section 5.2 should be proposed.

b. Clinical efficacy

Permethrin 5% cream

The MAH did not conduct a literature search about permethrin's efficacy in the treatment of scabies in the paediatric population and submitted one published study (Hamm et al 2006). The MAH states that the clinical data published in this paper has been assessed during an MR procedure but the publication itself has not been assessed.

Hamm et al.: Treatment of scabies with 5% permethrin cream: results of a German multicenter study (2006)
A 5 % Permethrin cream formulation was tested in a single-arm multicenter study including adults and children from 3 months of age with proven scabies. On day 0, patients were treated once with Permethrin cream in the study center. Control examinations including dermatoscopy were performed on day 14±2 and on day 28±3. Patients who were not considered cured or who had contact to individuals with untreated scabies received one further treatment with permethrin cream on day 14±2. Itching and local tolerability of the cream were documented in patients'diaries. Side effects were assessed by history, skin inspection and evaluation of patients' notes. About a third of the patients (n = 36, 34%) were children or adolescents. The age range 0 to 6 years contained 15 patients, while the youngest patient was 141 days of age. Cure was achieved in 98 of 103 patients (95%) (combined data of children and adults).
This open-label multicenter study confirmed the high efficacy of 5 % permethrin cream in treating scabies and also demonstrated a marked and continual decrease in itching. The authors claim that a control group was unnecessary in this study, as the infestation with Sarcoptes scabiei would show little, if any, tendency to self-healing over such a short observation period of 28 days. The follow-up of 28 days takes the developmental cycle of the mite into account, 9–14 days in males and 12–21 days in females. Side effects of treatment that could plausibly be attributed to the tested cream were rare. Local tolerability of the cream was good. Often itching was reported; this could generally be explained by scabies itself. History and intensive skin examination found symptoms in 19 patients which might possibly be attributed to the medication. With one exception (moderate itching after application) they consisted of minimal skin symptoms and signs such as prickly sensation, skin dryness, eczema and erythema, as well as headache

in one case. Infants and small children up to 6 years of age tended towards fewer reports of adverse effects in comparison to older children and adults. There was no evidence of special risks in infants and small children.

Rapporteur's Comment

Hamm et al study was carried out with the MAH's 5% permethrin cream product in Germany. The authors claim that the product got approved in Germany in part as a result of this study in 2004.

The study included 106 patients of which 36 were children (34%); 15 of the children were aged between 4 months and 6 years. It is acknowledged that the overall cure rate was 95%, however it is considered a significant limitation of the study that paediatric efficacy data was not analyzed separately.

Regarding tolerability, the authors report that "Infants and small children up to 6 years of age tended towards fewer reports of adverse effects in comparison to older children and adults." The rapporteur is of the view that this observation may be due to the fact that young children are not able to communicate subjective adverse events such as itching, stinging, etc therefore needs careful interpretation.

Itching was rated by the patients on a visual analog scale (scale from 0-100 corresponding to "no itching" up to "unbearable itching"). In children who could not yet make the assessment themselves, their guardian were asked to rate the intensity of itching based on the child's behaviour. The rapporteur is of the view that this leaves room for bias when assessing permethrin's effectiveness in decreasing the intensity of itching in the paediatric population, as the child's behaviour is significantly affected by the disease itself and therefore makes it difficult for the guardian to differentiate between symptoms. Although it is acknowledged that in the overall data analysis itching showed a continuous decline along the 28 day observation period.

In summary, 5% permethrin was proven to be effective and safe in the study population (including 36 children) with scabies.

Of note, the authors (Hamm et al.) included an informative table of *controlled clinical studies evaluating the efficacy of different therapeutic options in scabies* (Table 1.)

Reference	Study design	Cure rate	Significance	Side effects
Taplin et al. 1986 [1]	Single blind, randomized	- Permethrin 91 % - Lindane 65 %	Lindane less effective ($p < 0,025$)	None
Haustein, Hlawa 1989 [14]	Open	- Permethrin 100 % - Lindane 92 % - Benzyl benzoate 100 %	Lindane less effective ($p < 0,025$)	Benzyl benzoate had more frequent early (22 %) and late (42 %) side effects
Schultz et al. 1990 [2]	Single blind, multicenter, randomized	- Permethrin 91% - Lindane 86 %	Not significant ($p = 0,18$)	No significant difference in side effects
Taplin et al. 1990 [5]	Double blind, randomized	- Permethrin 89 % - Crotamiton 60 %	Crotamiton less effective ($p < 0,025$)	None
Amer, el-Gharib 1992 [3]	Randomized	- Permethrin 98 % - Lindane 84 % - Crotamiton 88 %	Lindane and crotamiton less effective ($p < 0,025$)	No significant difference in side effects
Usha, Gopalakrishnan Nair 2000 [18]	Randomized	- Permethrin 98 % - Ivermectin (oral, single dose) 70 % - Ivermectin (oral, 2 doses) 95 %	Single dose ivermectin less effective ($p < 0,001$)	No significant difference in side effects

Furthermore, the rapporteur identified a Clinical Evidence systematic review on scabies treatment (Johnstone et al. 2008) which concluded that topical permethrin is highly effective at increasing clinical and parasitic cure of scabies within 28 days. A Cochrane review by the same authors (Johnstone et al. 2010) evaluated 20 randomized controlled trials involving 2392 participants (3 trials included only adults, 6 included only children, and 11 included both) and concluded that topical permethrin appears to be the most effective treatment of scabies.
In summary, the rapporteur is of the view that permethrin 5% cream is a long established and effective product in the treatment of scabies in children older than 2 months of age. Children under 2 years should be treated under medical supervision.

Of note, the MAH's product (5% cream) is contraindicated in infants less than 2 months of age. Section 4.3 of the German SmPC states: *"X 5% must not be used in newborns and infants less than 2 months of age"*. The UK SmPC gives posology recommendations for children 2 months of age and above, however does not contraindicate permethrin 5% use in infants younger than 2 months. The rapporteur identified several case reports in the literature where 5% permethrin was safely and effectively used in young infants (Salces et al 2009, Baysal et al 2004, Ruiz et al 2004). The MAH is asked to justify the contraindication in this age group.

Permethrin 0.43% cutaneous solution

The MAH did not conduct a literature review about permethrin's efficacy in the treatment of head lice infestations in the paediatric population. Two relevant published trials were submitted in the dossier (Bialek et al 2010, Burgess et al 2010). The MAH claims that these studies have already been submitted within a PSUR to a MS but they have not been assessed during the marketing authorisation application.

- ***Bialek et al. : Permethrin treatment of head lice with knockdown resistance-like gene (2011)***

This paediatric study with permethrin cutaneous solution has been published in German language (Burow et al. 2010) and therefore was not submitted by the applicant. Parts of the data from this trial were recently further published by Bialek et al. in N Engl J Med 2011; 364(4): 386-7.

This was an observational treatment study involving intention-to-treat analysis of data from 150 children (1–15 yr of age, 71% female) enrolled at 12 paediatric private practices across Germany. When pediculosis capitis was diagnosed on the basis of the presence of live lice, 0.5% permethrin lotion was prescribed, as recommended by German health authorities. Treatment was done at home according to the manufacturer's instructions. Cure, defined as absence of living lice (adults or larvae) 16 to 20 days after treatment, was assessed by means of detailed visual inspection during a standardized combing procedure performed by trained personnel. Treatment with permethrin was successful in 142 of 150 children (95%) including 104 of the 112 children whose lice carried the knockdown resistance (kdr)–like gene.
The kdr-like gene is thought to reduce or delay the insecticidal effects of Permethrin, but in this study the presence of the kdr-like gene did not correlate with failure of permethrin treatment. Permethrin treatment was tolerated well in this paediatric population with only minor and self-limited side effects including skin irritation with burning sensation (n=4) or redness (n=2), eye irritation (n=1) and skin pain (n=2).

Rapporteur's Comment
Burow et al study (2010) included a significant number of children (n=150) and 0.5% permethrin treatment was effective in 95% of cases. Bialek et al carried out molecular tests on the head lice collected in the above described study and found that 93% of them carry the knockdown resistance (kdr)-like gene, which is thought to reduce or delay the insecticidal effects of permethrin. Despite this finding, treatment was successful in 104 of 112 (92.8%) children whose lice carried the kdr-like gene. The authors concluded that in the Pediculus capitis populations examined, the kdr-like gene did not correlate with failure of permethrin treatment.

The rapporteur agrees with Bialek et al's conclusion that the kdr-like gene did not correlate with treatment failure in the study population examined in Germany. However, there are several reports available in the literature from other European countries, such as Denmark (Kristensen et al 2006) and France (Durand et al. 2007), which describe strong associations between kdr-like mutations and permethrin resistance. For example, the Danish publication reported that in 17 of 24 head lice samples (71%) tested positive for permethrin resistance, all head lice survived the discriminating permethrin dose and 6 samples (25%) had 3 to 25% dead head lice.

In the UK, several studies have reported lower cure rates and increasing resistance against permethrin over the past decade. Downs et al (1999, 2002) reported 87% failure rate for permethrin treatment and also described a varying prevalence of head lice resistance in many parts of England.

In summary, the rapporteur is of the view that the prevalence of kdr-like gene mutations and its association to permethrin resistance – and therefore permethrin's efficacy - varies greatly with geographical location and therefore each member state should determine permethrin's status in head lice treatment guidelines locally.

- ***Burgess et al.: Clinical trial showing superiority of a coconut and anise spray over permethrin 0.43% lotion for head louse infestation, ISRCTN96469780 (2010)***

A randomised, controlled, parallel group trial involving 100 participants with active head louse infestation was performed in the United Kingdom to investigate the activity of a coconut and anise spray compared with 0.43% permethrin lotion, using two applications of product 9 days apart. The coconut and anise spray was significantly more successful (41/50, 82.0%) cures compared with permethrin (21/50, 42.0%; $p < 0.0001$, difference 40.0%, 95% confidence interval of 22.5% to 57.5%). Per-protocol success was 83.3% and 44.7%, respectively. There were 55 adverse events reported, and 37 participants reported one or more adverse events, 20 in the permethrin lotion group, and 17 in the coconut and anise spray group. Of these, 44 adverse events were recorded in 33 participants in relationship to study treatment. The remainder (11 events) were related to concomitant illness or minor accidents. In the permethrin lotion group, 12 of the 50 participants analysed had a single adverse event, six had two adverse events, one had three adverse events and one had four events (20 participants experiencing an adverse event and 31 adverse events in total). Adverse events related to treatment were mostly stinging or burning sensations on the scalp or neck or both during and after treatment. No subject had a serious adverse event.

The MAH states that cure rate following permethrin treatment in this study from the United Kingdom was low when compared with the data reported by Burow et al. from Germany. It remains to be elucidated whether the permethrin sensitivity of head lice populations in the UK and Germany differ. The MAH claims that since their permethrin products are not licensed in the UK, and treatment efficacy remains high in Germany, no action is needed at this time.

Rapporteur's Comment

85 children and 15 adults were included in the Burgess et al (2010) study, aged 2 to 49 years, median 10 years. The exact number of participants per paediatric subset is not included in the publication. This study found that 29 out of 50 participants (58%) did not respond to treatment using 0.43% permethrin lotion and therefore it was concluded by the authors that the alcohol in the lotion does not appear to improve its effectiveness. In contrast, coconut and anise spray was effective in 82% of cases.

The authors discuss that physiological resistance to insecticide-based products is widespread in Europe and varies not only with the country but also with the region, district, town, or even street. Consequently there are no clear figures indicating the proportion of cases that are likely to experience resistance in a population. The MAH's view about the variation of head lice sensitivity with geographical location is shared by the rapporteur (see comments about Bialek et al study above).

The rapporteur disagrees with the MAH's statement that "since permethrin products of the MAH are not licensed in the UK, and treatment efficacy remains high in Germany, no action is needed at this time", as Article 45 European work-sharing procedures focus on active substances rather than individual products i.e. any European permethrin product is subject to review and data analysis.

0.43% w/v solution is not marketed in the UK. There are three **1% w/w permethrin crème rinse** products licensed in the UK for the treatment of head lice infestation. Posology information is provided in the UK SmPCs for children over 6 months of age and it is stated that the product is "not suitable for children under 6 months of age, unless on the advice of a physician." Based on

UK clinical guidelines (see below), the need for medical supervision in children under 6 months of age is supported by the rapporteur.
Of note, the MAH's product for the same indication (0.43% w/v solution) is contraindicated in children younger than 2 months of age and close medical supervision is advised for children younger than 3 years of age. The rapporteur is of the view that the MAH should justify the recommended age ranges for contraindication and medical supervision.

UK clinical guidelines and formularies recommendations for the treatment of head lice infestations:

The 2011-2012 edition of British National Formulary for Children (BNF-C) in the UK states about permethrin: *"It is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice. Permethrin is also effective against crab lice but it is not licensed for this purpose in children under18 years."* 1% crème rinse products are considered too diluted in use and have insufficient contact time. Dimeticone, Malathion and wet combing methods are recommended by BNF-C as preferred treatment options for head lice infestations.

Furthermore, the very recently published *"Head lice: Evidence-based guidelines based on the Stafford Report 2012 Update"* produced by the UK Public Health Medicine Environmental Group states that "Permethrin is active against head lice but the formulation and licensed methods of application of the current UK products make them unsuitable for the treatment of headlice".

Clinical topic: head lice. NHS Clinical Knowledge Summaries (CKS) states: Permethrin is not recommended because there are concerns that a 10-minute contact time is not long enough for the product to be effective, and because there is evidence of resistance to permethrin in the UK.

The Health Protection Agency's (HPA) latest published guidelines (November 2010) do not recommend permethrin for the treatment of head lice infestations and clearly state in a highlighted box that: "Current recommended products are ones which contain Dimeticone or Malathion". It is also emphasized by the HPA that head lice parasiticidal treatments should only be used in children under the age of six months with medical supervision. HPA advises to carefully follow manufacturers instructions, however warns that the information insert for many of the recommended products do not state that a second application is required. The second application one week after the initial application is a crucial element of treatment. The initial application will kill off the living, moving lice but will not kill all of the eggs. The second application is required as it kills off the immature lice which have 'hatched out' from the remaining viable eggs (but are still too immature to breed themselves).

The British Association of Dermatologists (BAD) patient information leaflet (updated January 2011) lists malathion and synthetic pyrethroids (phenothrin and permethrin) as the most commonly used pediculicides, however states that shampoos which are on the hair for a short time and are diluted with water are less effective than lotions.

Burgess et al (2009) published a Clinical Evidence systematic review of head lice treatment and reported that malathion (98%) was more effective than permethrin (55%) and that studies comparing malathion or permethrin with wet combing have given conflicting results, possibly due to varying insecticide resistance.

In summary, UK clinical guidelines have drifted away from recommending permethrin for the treatment of head lice infestations. This appears to be due to increasing head lice resistance to permethrin and to inappropriate licensed methods of administration of permethrin products. Therefore the rapporteur is of the view that 1% permethrin product information (SmPC and package leaflet) should be updated to reflect the application method advised by national clinical guidelines (see section II.2.c) in order to maximise treatment effectiveness.

Moreover, the rapporteur is of the view that inclusion of a warning about the possibility of head lice resistance depending on geographical location should also be included in section 4.4 of the SmPC.

c. Dosing and method of administration

Permethrin 5% cream

The submitted German 5% permethrin cream SmPC states in section 4.2:

"4.2 Posology and method of administration
Posology
Unless otherwise directed by the physician, the recommended dosage is as follows:

Adults and adolescents over 12 years of age:
Apply up to 30 g of cream (corresponding to one tube of 30 g or ½ tube of 60 g).

Children aged from 6 - 12 years:
Apply up to 15 g of cream (corresponding to ½ tube of 30 g or ¼ tube of 60 g).

Children aged from 2 months - 5 years:
Up to 7.5 g of cream (corresponding to ¼ tube of 30 g or ⅛ tube of 60 g).

X is contraindicated in newborns and infants less than 2 months of age (see section 4.3).
The above dosage information is merely a guide. The actual dose can be adjusted according to the needs of the individual patient and the individual body surface area. For example, some adults might require a larger amount of cream.

Method of administration
For cutaneous use only. The medicinal product must not be swallowed.

Carefully apply a thin layer of cream to the skin (cutaneous use).
Adults and children over 2 years of age should apply the cream uniformly to the whole body including the throat, neck, palms of the hands and soles of the feet. The head and face can be spared unless scabies efflorescences are present in this region.
On application, the areas between the fingers and toes (also under the finger- and toe-nails), the wrists, elbows, armpits, external genitalia and the buttocks should be especially carefully treated.

Children below 2 years:
There is no adequate experience in infants and toddlers. Treatment of children aged 2 months to 23 months should therefore be given only under close medical supervision. In this case, the face, ears and scalp should also be treated. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared. Children should be kept from licking the cream from the hands. If necessary, children should wear gloves.

Instruction on use:
The cream must be left on the skin for at least eight hours, for example, overnight. In order not to endanger the success of treatment, bathing, showering or washing should be avoided during this period. If, by way of an exception, the hands and other parts of treated skin area (buttocks, external genitalia) are washed within the eight hour period, the cream should be reapplied to the

washed area. After at least eight hours, residues of the cream should be removed by showering or washing with soap and water.

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

Note:
Contact persons, especially family members and partners, should undergo a medical examination as soon as possible, and if necessary should be given prompt antiscabies treatment. In the case of close contact with infected persons, or endemic clusters, it can be expedient to treat hitherto symptom-free contacts in order to prevent reinfestations.

In addition, patients should

- *keep their fingernails short and clean them carefully*
- *change wear, bed linen and towels daily over a period of 14 days and wash them at a temperature of at least 60 °C*
- *store items non-washable at a temperature of at least 60 °C (e.g. outer clothing) for some days in a closed plastic bag*
- *vacuum carpets and upholstered furniture thoroughly"*

Rapporteur's Comment
The 2011-2012 edition of British National Formulary for Children (BNF-C) gives the following posology recommendation: *"Apply 5% preparation over whole body including face, neck, scalp and ears; wash off after 8-12 hours; if hands washed with soap within 8 hours of application, they should be treated again with cream; repeat application in 7 days. Note: Manufacturer recommends application to body but to exclude head and neck. However, application should be extended to the scalp, neck face and ears."* This recommendation is in line with the British Association of Dermatologists (BAD) advice to apply treatment to all areas - including the scalp, neck, face and ears - in children as the mites may be anywhere on the skin.

The rapporteur is of the view that the MAH's proposed wording of "*Adults and children over 2 years of age should apply the cream uniformly to the whole body including the* ***throat,*** *neck, palms of the hands and soles of the feet"* should be altered. It is supported that the cream should be applied uniformly to the whole body; however the word 'throat' is misleading - may be understood as oral administration - and therefore should be deleted. Furthermore, the statement of *"The head and face can be spared unless scabies efflorescences are present in this region."* is not supported by the rapporteur as although it may be true in adults, it is not applicable in children due to their smaller body size. Given the difference in adult vs paediatric method of administration and to be in line with European SmPC guidelines the rapporteur proposes to create a separate paediatric subheading in section 4.2. Further separation of the paediatric section to <2 years and >2 years is not supported as the method of administration is identical.
See recommended wording in Section IV, page 25.

Permethrin 0.43% cutaneous solution

The MAH submitted the following information about the product's posology and method of administration:

"Apply enough X solution to soak the hair well. In patients with short hair, 25ml are usually sufficient, while in patients with longer hair 50ml are necessary, in patients with very long or thick hair even more. Dosage in children from 2 months to 3 years of age is limited to 25ml.
According to the SmPC, a single treatment with X is sufficient to eliminate the head lice in most cases (75%) but treatment may be repeated after 8-10 days in case of persisting infestation or reinfestation. After repeated treatment success is achieved in 95-100%"

Rapporteur's Comment
The rapporteur is of the view that the above posology information should be clarified by the MAH and scientific evidence supporting the efficacy of a single application needs to be provided. Furthermore, contact time and maximum dose should also be discussed. The MAH is asked to propose a wording for inclusion in section 4.2 of the SmPC.

The 2011-2012 edition of British National Formulary for Children (BNF-C) gives the following advice on treating head lice in children: *"Head lice infestations (pediculosis) should be treated using lotion or liquid formulations only if live head lice are present. Shampoos are diluted too much in use to be effective. A contact time of 8-12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs. In general, a course of treatment for head lice should be 2 applications of a parasiticidal product 7 days apart to kill lice emerging from any eggs that survive the first application. All affected individuals in a household should be treated at the same time."* Although one 1% Permethrin crème rinse product is listed in BNF-C, there is a note saying: *"Use not recommended, therefore no dose stated (product too diluted in use and insufficient contact time)."*
The British Association of Dermatologists (BAD) patient information leaflet (updated January 2011) also advises that products should be left on for 12 hours before being washed off and 2 applications are needed 7 days apart.
The Department of Health Head Lice treatment advice leaflet (2007) is widely used in UK schools and nurseries and it advises patients "to follow the instructions on the packet carefully, eg as to how long the treatment must remain on the hair to be effective, how often you may apply the product etc." However, all UK licensed 1% permethrin crème rinse/shampoo products' manufacturers' SmPCs recommend 10 minutes contact time and none of them state that a second application is needed in order to achieve successful treatment i.e provide incorrect guidance. The rapporteur is of the view that this product information needs to be updated to be in line with clinical guidelines however no relevant data has been submitted as part of this paediatric work-sharing procedure and therefore no regulatory updates are possible.

As discussed before in this report, head lice resistance against permethrin has developed in several European countries over the past decade partially due to inappropriate use. The rapporteur would like to highlight that using the correct method of administration is crucial both to reduce resistance and to achieve successful treatment of head lice infestations, therefore the rapporteur is of the view that all product information (both SmPC and package leaflet) need to be updated according to best clinical practice. Please note that best clinical practice may vary based on each country's local head lice sensitivity and resistance pattern therefore updates to the SmPC should be considered at a national level.
Furthermore, in some member states – such as in the UK – it is believed that parental overuse of permethrin i.e. prophylactic or 'just-in-case' application, has contributed to the development of significant resistance therefore it is considered important to treat children only if eggs or live head lice have been detected. The rapporteur proposes to include this information as a precaution for use in section 4.4 of the SmPC in member states with significant head lice resistance. However, it is acknowledged that in some European countries permethrin is licensed for prophylactic use, therefore these member states should consider the rapporteur's proposal based on their licensed indications.

d. Clinical safety

The MAH provided segments of sections 4.3, 4.4 and 4.8 of the German SmPCs which were considered relevant to the paediatric population.

Permethrin 5% cream

4.3 Contraindications
X 5 % must not be used in newborns and infants less than 2 months of age.

4.4 Special warnings and precautions for use
There is no adequate experience in infants and toddlers. Treatment of children aged 2 months to 23 months should therefore only be given under close medical supervision.

4.8 Undesirable effects

System Organ Class	***Common*** *(≥1/100 to <1/10)*	***Rare*** *(≥1/10,000 to <1/1,000)*	***very rare*** *(<1/10,000)*	***not known*** *(cannot be estimated from the available data)*
Nervous system disorders	*paraesthesia, skin burning sensation*	*Headache*		
Respiratory, thoracic and mediastinal disorders			*dyspnoea (in sensitive/allergic patients)*	
Gastrointestinal disorders				*Nausea*
Skin and subcutaneous tissue disorders	*pruritus, erythematous rash, dry skin*		*excoriation, folliculitis, skin hypopigmentation*	*Contact dermatitis, urticaria*

Pruritus, erythematous rash, skin tingling, burning or pricking sensation and dry skin can also occur as a result of the disease itself. Pruritus and a postscabies eczema can persist for up to four weeks after the end of treatment. This is caused by a reaction to the killed scabies mites. Emollients and oil baths are recommended as follow-up treatment for dry skin.
Symptoms of contact dermatitis can spread beyond the area of skin treated.
Vomiting was not reported after the use of X 5% but is known in connection with other permethrin-containing drugs.

The MAH states that no specific information on side effects in the paediatric population is given in the SmPC and that there is no evidence of special risks in adolescents, children and infants.

Permethrin 0.43% cutaneous solution

4.3 Contraindications
X is contraindicated in newborns and infants in the first two months of life.

4.4 Special warnings and precautions for use
Treatment of children aged 2 months to 3 years should be given only under close medical supervision because of the lack of adequate data in this age group.

4.8 Undesirable effects
Rare (>=1/10,000 to <1/1,000): Skin irritation (redness), pruritus, skin tingling, burning or pricking sensation Very rare (<1/10,000): Headache, nausea, vomiting, respiratory symptoms and allergic skin reactions.

The MAH claims that no specific information concerning side effects in the paediatric population is given in the SmPC. The MAH is of the view that since head lice infestation is mostly a paediatric disease and the majority of clinical data available for permethrin treatment in this indication has been derived from paediatric studies, the data given in the SmPC can be considered valid for children and adolescents. There is no evidence of special risks in infants and young children.

Rapporteur's Comments
It is noted, that 0.43% product is an alcohol-based solution which may cause significant irritation especially on excoriated scalp. The MAH is asked to provide quality data for 0.43% permethrin solution and discuss its potential inflammatory and irritant effects (refer to section II.1 of this report). Furthermore, the rapporteur is of the view that the MAH should present the potential safety concerns in children with asthma and eczema as symptoms in these patients may be worsened by permethrin.

<u>Postmarketing experience</u>
The MAH only submitted postmarketing information about 0.43% cutaneous solution:

"Continuous post-marketing surveillance of the 0.43% cutaneous solution has identified the following unlisted adverse reactions:

paraesthesia
contact dermatitis
urticaria

No further relevant novel data concerning the paediatric population has been derived from continuous post-marketing surveillance."

The MAH states that these reactions will be added in the SmPCs and package leaflets of the product during an upcoming national variation in a MS.

Rapporteur's Comments
The MAH is proposing to update 0.43% cutaneous solution's SmPC with additional safety information in Section 4.8, however no relevant data has been submitted to support this proposal. The rapporteur acknowledges that a national variation is planned, however it needs to be highlighted that this is a European work-sharing procedure therefore the data supporting the proposed safety information update needs to be available to all member states and therefore the MAH is asked to submit them.

3. Discussion on clinical aspects

Permethrin is licensed for paediatric use for the treatment of scabies and head lice in many European countries.

5% permethrin cream products have a well established use in scabies in children over 2 months of age. 5% permethrin is proven to be safe and effective in this condition, however close medical supervision is advised in children younger than 2 years of age. Regarding to scabies treatment clinical guidelines application of the product needs to be head to toe - including the scalp, face and ears - in the paediatric population.

Permethrin has been widely used for the treatment of head lice infestations in children until about 10 years ago, when reports of increasing number of treatment failures and head lice resistance against permethrin started to emerge in several European countries. Further research into the genetic structure of head louse identified a gene (knockdown resistance like gene; kdr-like gene) possibly responsible for treatment resistance. However, it has been also discovered that both the prevalence of kdr-like gene mutation and the association between the mutation and treatment resistance varies based on geographical location, even within countries.
Consequently head lice treatment clinical guidelines in countries with a high prevalence of resistance - such as the UK - drifted away from recommending permethrin as a first line agent.
Inappropriate application methods, such as short contact time, permethrin used without detection of live head lice or permethrin applied only once instead of twice 7 days apart, may have contributed to the development of resistance in some European countries. However, in some member states - for example in NL – 1% permethrin is licensed for short lasting prophylaxis of head lice infestation in persons who have visited schools or other centres at the time of a head lice epidemic. In light of these divergent views, the rapporteur is of the opinion that member states should consider recommendations based on their national licensed indications, taking into consideration their local products' efficacy, safety and national clinical guidelines.

III. INFORMATION RECEIVED FROM AN EU COMPETENT AUTHORITY

Given that the data package submitted by the MAH in this work-sharing procedure was rather limited and was frequently referencing ongoing procedures submitted at an EU competent authority, the rapporteur contacted the RMS on 26th April 2012 to confirm the regulatory status of MAH's products and to consider the MS's regulatory position prior to circulation the Day 70 assessment report to all member states.
The following comments were received from RMS on 4th May 2012:

"Preclinical
The wording of SmPCs sections 4.6 and 5.3 has been agreed with the MAH in the context of the preparation of a mutual recognition procedure and is adequate in our view. As regards to section 4.6 the UK Assessor seems to agree.
As regards to section 5.3 we are of the opinion that the sentence " Furthermore there is no evidence on relevant genotoxic or carcinogenic potential." is appropriate as well. The incidence of tumours in mice was within the historical control range and the EMA report also states that the carcinogenic potential of permethrin is not a cause for concern. As regards to the aspect developmental neurotoxic effects we support the request to discuss this further.

Rapporteur's comment:
RMS agrees with the MAH's statement in section 5.3 that "there is no evidence of relevant genotoxic or carcinogenic potential". The rapporteur is of the view that although permethrin's carcinogenic potential in animals is not a major concern for humans, in light of permethrin's IPCS classification as a weak rodent carcinogen this information should be considered for inclusion in Section 5.3 of the SmPC. The MAH is asked to discuss permethrin's carcinogenic potential and propose a wording for section 5.3 of the SmPC accordingly.

In addition, the number of documents - previously submitted by the MAH to RMS - were included in the response:

The rapporteur assessed the additional data received from RMS and found relevant information to this work-sharing procedure.

Rapporteur's comment:
0.43% solution product contains a significant amount of ethanol and also propylene glycol which is a known skin irritant, therefore the product's topical inflammatory and irritant effects need to be further discussed by the MAH. Furthermore, compliance with the European Commission guidance on *'Excipients in the labels and package leaflet of medicinal products for human use' (July 2003; CPMP/463/00)* needs to be ensured, thus the following should be included in the SmPC and patient information leaflet: *"Propylene glycol: May cause skin irritation"*

- **0.5% alcoholic permethrin solution, Clinical Overview, July 2008**

Pharmacokinetics

Absorption

Dermal application is the only route of therapeutic administration of permethrin in humans. Formulations used are 5% permethrin dermal creams to treat scabies and mainly 1% hair rinse solutions for head lice. The amount and the rate by which permethrin reaches the systemic circulation may be considered as a measure for its cutaneous bioavailability (BA).
As the cis-isomer of permethrin is considered to be somewhat more toxic in animals and is excreted at a lower rate than the trans-isomer, preparations with a lower proportion of cis-permethrin are used for application in humans, so that the usual cis:trans ratio in most preparations is 25:75.
Permethrin is rapidly metabolised and excreted in urine as inactive metabolites faster than it is absorbed through the skin. For this reason, percutaneous absorption of permethrin was estimated by following the urinary excretion of metabolites; e.g. the major metabolites [cis- and trans-3-(2,2 dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid (CVA)].
Two studies examined the dermal absorption of permethrin in volunteers and patients, see below.

Reference	Dose/ Formulation used/ Body part treated	Conditions/ Subjects	Amount of dose absorbed [% of the dermal dose applied]
Van der Rhee et al., 1989	1.25 g/ 5% cream/ whole body	Scabies patients/ 10 (5F/5M) 23 – 42 years	~ 0.5 [6 mg (3 – 11mg)]
Tomalik-Scharte et al., 2005	3.0 g/ 5% cream/ whole body	Scabies patients/ 6 (3F/3M) 30 years	0.52
	3.0 g/ 5% cream/ whole body	Healthy volunteers/ 6M 29 years	0.47
	0.215 g/ ethanolic solution/ hair of the head	Healthy volunteers/ 6M 27 years	0.35

The relative amount absorbed was independent of the formulation used, of the dose and of the presence of skin lesions. The amount of dose absorbed was low and ranged between 0.35 to 0.52%.

Elimination

The pattern of permethrin metabolites was investigated in the urine of workers employed in indoor pest control. Cis- and trans-CVA and PBCOOH were present in urine following exposure to permethrin. As already pointed out above, permethrin absorbed through the skin is so quickly metabolized that the parent compound has not been detected in plasma with analytical methods available today. Therefore, permethrin has not been identified in human urine.

Rapporteur's comment

0.35% of the ethanolic solution dose applied to the scalp got absorbed in healthy volunteers. In association with permethrin's quick metabolism, this data provides a reassuring transdermal PK profile for 0.43% solution. The MAH is asked to propose a wording for inclusion in section 5.2 of the SmPC.

IV. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 89

The rapporteur considers the submitted data too limited to allow a full assessment on permethrin's paediatric use.

The MAH claims that all of the submitted studies have been assessed in the past by an EU competent authority, as part of MR or PSUR procedures therefore the RMS was contacted by the rapporteur to help achieve consistency in decision making. Information received from the RMS is incorporated in this report (section III)

The rapporteur would like to highlight that this is a European work-sharing procedure therefore all permethrin containing products in all member states are subject to analysis.

It appears that all of the submitted studies used the MAH's products as study medication, however quality data about 0.43% permethrin solution has not been provided. The rapporteur considers this information important in order to sufficiently assess potential inflammatory and irritant effects, such as alcohol use on excoriated scalp. In addition, all SmPCs need to comply with the European guidance on excipient use.

The rapporteur identified an EMA report which states that the ICPS classified permethrin as a possible weak rodent carcinogen. Furthermore, recent animal data suggests that permethrin may have developmental neurotoxic effects. The MAH is asked to further discuss permethrin's carcinogenic and developmental neurotoxic effects and to propose a wording for section 5.3 of the SmPC.

Permethrin is licensed for paediatric use in the treatment of scabies and head lice in many European countries.
5% permethrin cream products have a well established use in scabies in children over 2 months of age. 5% permethrin is proven to be safe and effective in this condition, however close medical supervision is advised in children younger than 2 years of age.
Regarding to best clinical practice, application of the 5% product needs to be head to toe - including the scalp, face and ears - in the paediatric population due to smaller body size. However, this is not reflected in most of the currently approved SmPCs. The MAH is asked to discuss this issue further and revise the wording of section 4.2 accordingly, including a separate paediatric subheading.

It is noted that both of the MAH's products are contraindicated in infants younger than 2 months of age. The rapporteur identified several case reports in the literature where permethrin was safely and effectively used in this paediatric subgroup, therefore the MAH is asked to justify the reasons for contraindication. Of note, the UK SmPCs do not recommend 5% permethrin use under 2 months of age and 1% permethrin use under 6 months of age, however – unlike the MAH's products - there are no age based contraindications in section 4.3 of the SmPC.

Permethrin has been widely used for the treatment of head lice infestations in children until about 10 years ago, when reports about an increasing number of treatment failure and head lice resistance against permethrin started to emerge in several countries. Both the prevalence of kdr-like gene mutation and the association between the mutation and treatment resistance varies based on geographical location. In light of this, the rapporteur is of the view that each member state should consider whether to include the following special warning in section 4.4 of the SmPC: *"Head lice resistance against permethrin treatment has been reported depending on geographical location, therefore if live lice are present after the second application, seek medical advice."*

In some European countries (for example NL) permethrin is licensed for short lasting prophylaxis of head lice infestation in persons who have visited schools or other centres at the time of a head lice epidemic. In contrast, in other countries (such as the UK) it is believed that inappropriate application methods, such as permethrin used without detection of live head lice, too short contact time or permethrin applied only once instead of twice 7 days apart, may have contributed to the development of resistance. Therefore the rapporteur is of the view that an update to section 4.2 and 4.4 of the SmPC should be considered at a national level based on already existing licensed indications and local evidence based clinical guidelines. As parents and carers refer to the package leaflet, this should also be updated accordingly.

The MAH did not provide sufficient information about 0.43% solution posology; therefore is asked to submit missing information such as scientific evidence for efficacy of single application, contact time, maximum dose and to propose a wording for section 4.2 of the SmPC accordingly.

Permethrin was proven to be safe in the submitted studies. Adverse events with 0.43% solution were mostly stinging or burning sensations on the scalp or neck. The events were related to the intensity of infestation and the number of bite reactions on the scalp and were attributed to the alcohol content of the product. The MAH is proposing to include paraesthesia, contact dermatitis and urticaria in section 4.8 of the solution 0.43% SmPC, since these adverse reactions have been observed from spontaneous reports however the supporting data was not submitted. The rapporteur is of the view that although it is claimed that a German national variation is being prepared by the MAH, the safety data should be made available to all member states

Comments were received from four member states at day 85 of the procedure. Three member states supported the rapporteur's conclusions and the request for additional data. Furthermore, one MS highlighted that 1% permethrin crème rinse products are licensed for both the treatment and prophylaxis of head lice infestations. This was taken into consideration by the rapporteur when formulating final conclusions and SmPC wording recommendations. In addition, it was expressed by MS that the MAH's proposal in section 5.3 is agreed, however the Rapporteur's request for additional developmental neurotoxicity data (focusing on clinical aspects) is supported.

V. ADDITIONAL CLARIFICATIONS REQUESTED AT DAY 89

The MAH was requested to provide additional information on the following:

- Currently approved 0.43% cutaneous solution SmPC in English
- Discussion of 0.43% permethrin solution's pharmaceutical formulation, including excipients and the product's potential local inflammatory and irritant effects
- Wording proposal to describe 0.43% permethrin solution's pharmacokinetic properties in section 5.2 of the SmPC
- Discussion of permethrin's carcinogenic and potential developmental neurotoxic effects (and its clinical relevance) with proposed wording for section 5.3 of SmPC
- Justification for contraindication of both products in children younger than 2 months of age
- Discussion of both products recommended method of application with scientific explanation and proposed wording for Section 4.2 of the SmPC
- Supporting data for the proposed safety update in section 4.8 of the 0.43% solution SmPC. Discussion of potential adverse effects, in particular in children with asthma and eczema
- Package leaflet wording proposal for both products

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

1. **Currently approved 0.43% cutaneous solution SmPC in English**

The MAH submitted the currently approved 0.43% cutaneous solution SmPC in English with their suggested changes.

Rapporteur's comment
The applicant submitted the currently approved SmPC wording for 0.43% solution in English. The MAH's recommended changes are discussed later in this report. Issue resolved.

2. Discussion of 0.43% permethrin solution's pharmaceutical formulation, including excipients and the product's potential local inflammatory and irritant effects

The MAH provided details of the pharmaceutical formulation of the 0.43% solution, concluding, a skin irritation potential of the product is not to be expected if used on intact skin. Mild, short-term stinging caused by the ethanol and isopropyl alcohol content might occur in some patients when used on superficially damaged skin.
The MAH has received only six reports of stinging or burning sensation or pain at the application site from the spontaneous reporting. Pruritus, tingling, burning and stinging are listed in the SmPC as rare adverse reactions (≥ 1/10.000 – <1/1.000)
As a positive side effect of the alcoholic basis of the solution, a mild antiseptic effect is to be expected, although this has not been investigated. In head lice patients with superficially damaged skin through scratching, an antiseptic effect would be advantageous.
The SmPC, section 5.1, states that the addition of alcohol to permethrin in this solution is designed to increase the damage to nit contents.
The MAH acknowledges that irritation is possible when the solution comes into contact with the eyes, mucous membranes or open wounds. The MAH proposes the following rewording of the warning that is already given in section 4.4 of the SmPC.

"**4.4 Special warnings and precautions for use**
Due to its alcohol content, X might cause irritations when getting into contact with the eyes, mucous membranes (e.g. nasopharyngeal region, genital area) or open wounds.
When using X, it should be ensured that the solution does not come into contact with these areas. Rinse thoroughly with water in the event of inadvertent contact."

Rapporteur's comment
The MAH provided 0.43% permethrin solution's pharmaceutical formulation and a comprehensive overview of the ingredients' potential irritant effects. In light of the above described information, the rapporteur shares the MAH's conclusion about the solution's potential irritant effects when getting into contact with eyes, mucous membranes or open wounds and considers the proposed wording for section 4.4 acceptable. Issue resolved.

3. Discussion of permethrin's carcinogenic and potential developmental neurotoxic effects (and its clinical relevance) with proposed wording for section 5.3 of SmPC

MAH's response: Permethrin is a synthetic pyrethroid. It is an insecticide mainly used for agricultural purposes. Besides this, its insecticidal potency along with its low toxicity to mammals is also used in antiparasitic medicinal products for human and veterinary use, e.g. for the treatment of scabies or head lice infestations or the impregnation of mosquito nets. In the 5% cream products, it is intended for treatment of scabies, in 0.43% cutaneous solution, it is intended for the treatment of head lice.
According to ICH guideline S1A, testing of carcinogenic potential of a drug substance for human use is only necessary if the drug product is intended to be used for more than 6 month or if there is specific concern (e.g. equivocal genotoxicity results). As both conditions do not apply to permethrin products, carcinogenicity testing is not considered necessary according to this guideline. As permethrin is, however, widely used as a pesticide, a number of carcinogenicity studies have been performed in rats and mice. Based on these studies, the International Programme on Chemical Safety (IPCS) classified permethrin as a possible weak rodent carcinogen [IPCS].

Exposure scenarios
Permethrin 5% cream
The 5% cream is intended to be topically applied on the skin. Two pharmacokinetic studies in human volunteers (intact skin) respectively scabies patients ("damaged skin") revealed an absorption of 0.47% (intact skin) respectively 0.52% ("damaged skin") of the applied permethrin dose, when 5% cream was applied.
The maximum recommended dose for adults is 30 g of 5% cream. This amount of cream contains 1.5 g of permethrin. Assuming absorption of 0.52%, the systemic exposure to permethrin is 7.8 mg. If further a body weight of 50 kg for an adult person is assumed, this corresponds to a dose of 0.156 mg/kg body weight.
The maximum recommended dose for infants aged 2 months to 5 years is 7.5 g cream containing 187.5 mg permethrin. Assuming absorption of 0.52%, the systemic exposure to permethrin is 0.975 mg. If a body weight of 4.0 kg is assumed (worst case: 3% percentile for 2-months old girls), this corresponds to a dose of 0.244 mg/kg body weight.

Permethrin 0.43% cutaneous solution
The maximum amount of 0.43% cutaneous solution which moistens the scalp is 25 ml (for higher volume see below) for adults and children of 2 months or older. With this volume of the solution product, 107,5 mg of permethrin is applied. As the mean absorption of Permethrin from the 0.43% solution applied to the scalp is 0.35%, the maximum systemic dose of permethrin is 0.376. This corresponds to a dose of 0.094 mg/kg if a body weight of 4.0 kg is assumed (worst case: 3% percentile for 2-months old girls).
If more fluid is needed, this is because of longer hair and is not expected to moisten the scalp. Moreover, long hair is only to be taken into account for children weighing more than the 4-kg girl assumed above, therefore the resulting dose per kg body weight is smaller.

Carcinogenic effects
There are three mouse 2-years carcinogenicity studies with permethrin discussed in the IPCS assessment.
In the first study (referred to as "ICI study" in the IPCS assessment), permethrin was administered at dose levels of 250, 1000 and 2500 mg/kg diet. This reveals doses of approximately 30, 125 and 300 mg/kg/day. Minimal liver changes at 1000 and 2500 mg/kg diet were considered to be related to induction of liver microsomal enzymes. No effects were seen on the incidence of unusual tumor types. A slight increase in lung adenomas was observed in males only in the 2500 mg/kg diet group. This difference was significant by the Logrank test at the 5% level but not the 1% level and was not significant by Fisher's exact test. The authors concluded that "A statistically significant difference from controls in one sex in a single dose

group in the analysis of a common tumor type with a high overall incidence should not be considered as a carcinogenic effect unless supported by other evidence. In the case of permethrin no changes were seen in the incidence of carcinoma of the lung in the mouse study".
In the second study (referred to as "FMC II study" in the IPCS assessment), permethrin was administered at dose levels of 0, 20, 500 and 4000 mg/kg diet in males and 0, 20, 2500 and 5000 mg/kg diet in females. This reveals daily oral doses of 0, 2.5, 62.5, and 500 mg/kg body weight (males) respectively 0, 2.5, 312.5 and 625 mg/kg body weight if a daily food consumption of 125g/kg body weight is assumed. In this study, an increased incidence of bronchio-alveolar adenomas was observed in female mice only. The number of female mice with adenomas and/or carcinomas (15/74, 24/72, 35/74, and 44/75 at the four dose levels) revealed a statistically significant dose-response relationship. Male mice did not show this effect. However, some doubt was expressed by the FIFRA Scientific Advisory Panel concerning the conduct of this study.
In the third study (referred to as "BW study" in the IPCS assessment), permethrin doses of 0, 10, 50 and 250 mg/kg body weight were administered. A dose-related trend was observed in females, but not in males, for adenomatous tumours in the lungs. No notable pattern was observed for other neoplasms at any dose level.

No evidence of carcinogenicity was observed in any of the rat studies.

MAH's conclusion on carcinogenic effects of permethrin

The MAH states that permethrin does not exhibit any genotoxic potential.
In rat studies, no evidence of carcinogenicity was observed for Permethrin. Among the three long-term mouse studies, there was evidence of permethrin oncogenicity in the lungs in one strain (CD-1 female only) at the highest dose level (625 mg/kg body weight) only. Although there was a difference between the control and treated groups in terms of lung adenomas in these studies, these differences were not significant when compared with historical control values. The oncogenicity potential, as evaluated by the FIFRA Scientific Advisory Panel, was considered to be very weak.
This very weak oncogenicity potential was found for rodents at doses of 625 mg/kg body weight. This is by a factor of more than 2500 higher than the maximum expected exposure in man. As a genotoxic mechanism of carcinogenicity can be excluded, such a safety margin would be considered as sufficient to exclude a potential risk for the intended use even if the found carcinogenic potential would be relevant for man. The EMA, however, considers the carcinogenic potential to be not a cause for concern.
The conclusion of the U.S. Environmental Protection Agency (Federal Register,1982) and its Scientific Advisory Panel was that permethrin has a low oncogenic potential in mice but none in the rat and that the oncogenic potential for humans was nonexistent or extremely low. The Joint Meeting on Pesticide Residues in 1982 also concluded that the long-term rodent studies on permethrin did not indicate any oncogenic risk to man. And, last not least, in 1999, IPCS concluded that permethrin was "Not carcinogenic to mouse or rat".

The MAH concluded that competent authorities in Europe and the US consider permethrin not to pose a carcinogenic risk to man. The weak effects found in mice are considered as not sufficient to consider permethrin as a rodent carcinogen. It is unquestioned that these effects are not relevant to man. And finally, they occur at dose levels far above the maximum exposure levels expected in man. Therefore, a carcinogenic risk for the use of permethrin is not to be expected.

Developmental neurotoxicity of permethrin

Pyrethroids are known to be neurotoxins. Permethrin belongs to the type I pyrethroids, characterized by toxic signs that progress from increased sensitivity to external stimuli, to a fine tremor, to a gross whole body tremor and prostration, to death. Structural basis for these effects

is distal damage to peripheral nerves caused by primary interaction of the pyrethroids with a sodium channel. These effects, however, occur at near-lethal doses (Aldridge). The neurotoxicity no effect level for a single dose of permethrin was 200 mg/kg (US EPA). This is by a factor of more than 800 higher than the maximum expected systemic exposure to permethrin according to the exposure scenario. The neurotoxic effects are reversible after discontinuation of dosing with pyrethroids.
Nasuti et al. (2007) have treated male rat pups from postnatal day 6 to 15 by gavage with permethrin at doses of 34.05 mg/kg and investigated neurotoxic effects of permethrin on postnatal days 21 and 35. They reported increased locomotion in the open field test on day 35, but not on day 21. Other parameters of the open field test like rearing, grooming, and number of centre entries or time spent in the centre were not affected by permethrin treatment. Further, on day 35 a set of biochemical and biophysical parameters was investigated. The results are summarized in Table 1.

Table 1. Biochemical and biophysical parameters investigated after previous permethrin treatment [19]

Parameter	Effect if compared to control
striatal dopamine level	decreased
3,4-dihydroxyphenylacetic acid	no change
3-methoxy-4-hydroxyphenylacetic acid level	increased
gluthatione peroxidase activity	increased
superoxid dismutase activity	decreased
Protein carbonyl group formation in lipid extracts	increased
"oxidation index" lipid extracts	no change
Plasma membrane fluidity on striatum	no change
fluorescence anisotropy of DPH in	no change
generalized polarization (GP340) of Laurdan in striatum cells	no change
generalized polarization (GP340) of Laurdan in lipid extracts	no change
GSH level in striatum cells	decreased
Protein carbonyl group formation in erythrocytes	no change
"oxidation index" in erythrocytes	increased
erythrocyte plasma membrane fluidity	no change
superoxide anion formation during monocyte respiratory burst	decreased

This study may be very important for basic research of pyrethroid toxicity, for a sound risk assessment with view on human exposure; however, it suffers from some experimental flaws:
- It is a very small study. Guideline studies on developmental toxicity require at minimum a number of 16 litters per dose group; the present study worked with 10 litters per group.
- Some of the biochemical investigations have been made on only 6 animals per group, which is very few for a rodent study.
- Historical control data (which are very important for interpretation of developmental studies due to the limited statistical power) are not available. It can therefore not be decided, whether an effect found in this study is a real effect or if it is just an unusual value within the natural range.
- Only behaviour parameters and biochemical/biophysical parameters have been investigated. No information is provided on morphological effects.

Due to these flaws, the MAH considers that conclusions made by the authors can only be very vague. In spite of these flaws, however, the study gives a hint towards a potential for

developmental neurotoxicity in rats. These effects, however, occurred at 34.05 mg/kg/day, which is by a factor of 140 higher than the maximum expected human exposure (not to mention the difference between single dose exposure and repeated dose administration). In another study, permethrin was administered to parental (F0) animals and behavioural endpoints of motor reflexes, motor coordination, and activity were evaluated in F1 progeny. Significant differences in the development of reflexes, swimming ability, and open field activity were evident in the offspring for the 9.8 and 19.6 mg/kg/d dose groups compared to the control group. The NOEL obtained in this study for the effects of permethrin on the development of the F1-progeny was 4.9 mg/kg/d. This is by a factor of 20 higher than the maximum expected human exposure.
The auditory startle response amplitude was investigated after administration of 0, 30, 60, or 120 mg/kg permethrin to 21-day-old rats. Although an increase of startle response amplitude was observed, this increase was neither dose related nor statistically significant. Moreover, the lowest dose was by a factor of more than 120 higher than the maximum expected human exposure.

MAH's conclusion on developmental neurotoxicity of permethrin

Permethrin is not only a neurotoxin at near lethal doses. There is also evidence that it can cause developmental neurotoxicity if peri- or postnatal offspring is exposed to permethrin (although this evidence is limited). All studies that revealed such effects, however, were performed with multiple administrations at high dose levels which were by a factor of 20 or more above the expected maximum human exposure. Moreover, except the study of Sheets et al, all studies were performed with multiple dosing, whereas the intended clinical use is a single administration which may be repeated once within a range of one to two weeks. Sheets stated that infants and children are not more sensitive to lower doses of pyrethroids than adults. It is therefore reasonable to conclude that the potential of permethrin to cause developmental neurotoxicity in laboratory animals will not be relevant for the clinical use of the 5% cream or the 0.43% cutaneous solution.

MAH's overall conclusion

Due to the above discussed aspects of permethrin's potential carcinogenic and neurodevelopmental effects, the MAH is of the view that no changes are necessary for section 5.3 of the respective SmPCs. The non-clinical aspects of permethrin are sufficiently covered by the current texts.

Currently approved SmPCs state in section 5.3:

5.3 Preclinical safety data

From acute and chronic toxicity studies there is no evidence indicating the occurrence of previously unknown adverse effects in humans. Furthermore, there are no evidence on relevant genotoxic or carcinogenic potential.
In studies on the reproductive toxicity in mice, rats, and rabbits after repeated oral administration of permethrin effects were observed only at doses largely exceeding the exposure expected for the topical use of X 5%.
Following the intended use of this active substance a serious harmful effect on aquatic organisms (daphnia and fish) and terrestric organisms (plants) is expected after passage of the sewage treatment plant."

Rapporteur's comment

The MAH provided a comprehensive overview of currently available data on permethrin's carcinogenic and potential developmental neurotoxic effects.

The MAH states: “Among the three long-term mouse studies, there was evidence of permethrin oncogenicity in the lungs in one strain (CD-1 female only) at the highest dose level (625 mg/kg body weight) only. This is by a factor of more than 2500 higher than the maximum expected exposure in man. As a genotoxic mechanism of carcinogenicity can be excluded, such a safety margin would be considered as sufficient to exclude a potential risk for the intended use even if the found carcinogenic potential would be relevant for man.” The rapporteur considers the MAH has provided sufficient justification that permethrin does not appear to pose a significant carcinogenic risk to humans.

The MAH has also provided sufficiently information on permethrin’s potential developmental neurotoxicity and concluded: “All studies that revealed such effects, however, were performed with multiple administrations at high dose levels which were by a factor of 20 or more above the expected maximum human exposure. It is therefore reasonable to conclude that the potential of permethrin to cause developmental neurotoxicity in laboratory animals will not be relevant for the clinical use of the 5% cream or the 0.43% cutaneous solution.” The rapporteur supports the MAH’s conclusions.

In summary, both issues of carcinogenicity and developmental neurotoxicity are considered resolved by the rapporteur and no relevant changes to section 5.3 of the SmPC are deemed necessary.

4. Wording proposal to describe 0.43% permethrin solution’s pharmacokinetic properties in section 5.2 of the SmPC

MAH’s response: The German 0.43% cutaneous solution SmPC states in Section 5.2:

“**5.2 Pharmacokinetic properties**
Following application of approximately 50 ml X to the haircovered scalp (215 mg permethrin), an average of 0.23% of the applied dose (maximum 0.39%, minimum 0.16%) was excreted in the urine of 6 subjects within the first 48 hours.
Mean total cumulative urinary excretion after a total of 168 hours of exposure time was 0.35% (between 0.26% and 0.53%) of the applied amount. Absorbed permethrin is rapidly cleaved by esterases or hydrolases. When orally administered, the peak plasma concentration is reached after about 4 hours. The isomeric mixture is then excreted in the urine in the form of glucuronides, sulfates etc. as cis- trans Cl2CA [(3-(2,2-dichlorovinyl)-2,2- dimethylcyclopropane-1-carboxylic acid)] and, after oxidation to 3 PBA (3-phenoxybenzoic acid). After oral application, up to 6% is excreted unchanged in the faeces whilst on dermal application, unchanged permethrin is virtually undetectable.”

Rapporteur’s comment
The MAH provided the previously missing pharmacokinetic information on 0.43% solution. The currently approved SmPC wording is considered sufficient and no changes are deemed necessary. Issue resolved.

5. Justification for contraindication of both products in children younger than 2 months of age

MAH’s response: The diagnosis of scabies or pediculosis in newborns and infants younger than 2 months of age is rare in developed countries, and consequently no publication could be

identified of prospective trials or case series in this age group. Only a few case reports have been published which do not present sufficient evidence to establish the safety and efficacy of permethrin treatment in this age group.
The contraindication of both products in children younger than 2 months of age was established during the national MA procedures in 2003 and 2004, respectively. At that time, it was common regulatory practice, at least in some MSs, to set a contraindication for certain paediatric age groups if the available evidence for efficacy or safety in the respective age groups was not sufficient.
Since the revision of the SmPC guideline in 2005, patient populations not studied in the clinical trial programme should be mentioned in a precaution in section 4.4 and not in the contraindication section (4.3) unless a safety issue can be predicted. Lack of data alone should not lead to a contraindication.
In the light of the current version of the SmPC guideline (September 2009) and the current QRD templates, the MAH recommends to replace the contraindication by appropriate statements in the sections 4.2, 4.4 and 5.1 of both products' SmPCs as follows:

"Section 4.2
Paediatric population
The safety and efficacy of X in children under 2 months of age have not been established.
Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Section 4.4
Paediatric population
The safety and efficacy of X in children under 2 months of age have not been established.

Section 5.1
Paediatric population
Newborns and infants:
The safety and efficacy of permethrin in newborns and infants under 2 months of age have not been established since no data are available from prospective trials or larger case series. A limited number of case reports in the treatment of children under 2 months of age presenting with scabies do not suggest specific safety concerns for the use of topical permethrin in this age group, but no definite conclusion can be drawn."

Rapporteur's comment
The MAH explained the origin of contraindication in children younger than 2 months of age and proposed a revised wording following more recent regulatory guidelines.

The rapporteur agrees with the MAH that very limited data are available about the use of permethrin in infants < 2 months of age. The only available information consists of 3 case reports describing 3 infants with scabies. These data are considered not robust enough to warrant inclusion in section 5.1 of the SmPC. Furthermore, the proposed wording for section 4.2 does not need to be repeated in section 4.4 according to the 2009 SmPC guidelines. In summary, the following SmPC wording is recommended for both permethrin products (5% cream and 0.43% solution):

"**Section 4.2**
Paediatric population
The safety and efficacy of X in children under 2 months of age have not been established. No data are available."

In light of the above clarification of paediatric age groups in which the products are indicated, the rapporteur recommends the following wording for inclusion in section 4.1 of the SmPCs:

5 % permethrin cream
"**4.1 Therapeutic indications**
Permethrin 5% cream is indicated for the treatment of scabies in adults and children > 2 months of age."

0.43% permethrin solution
"**4.1 Therapeutic indications**
Permethrin 0.43% is indicated for the treatment of head lice infestations in adults and children > 2 months of age."

c)
In addition, given that only limited amount of data is available in children younger than 2 years of age with 5% permethrin cream, the MAH recommended the following wording for inclusion in section 4.2 and 4.4 of the relevant SmPC:

"There is no adequate experience in infants and toddlers. Treatment of children aged 2 months to 23 months should therefore only be given under close medical supervision."

Similarly, there is limited experience available with the use of 0.43% cutaneous solution in children less than 3 years of age. The MAH recommended the following wording for inclusion in section 4.2 and 4.4 of the SmPC:
"Only limited experience is available with X in children aged 2 months to 3 years. Therefore treatment must be given only under close medical supervision in this age group."

The rapporteur considers the MAH's wording about the need for medical supervision for 0.43% solution more appropriate and recommends bringing the 5% cream SmPC wording in line with this: "Only limited experience is available with X in children aged 2 months to 23 months. Therefore treatment must be given only under close medical supervision in this age group."

For the rapporteur's final SmPC wording recommendations please refer to section VIII (page 42).

6. Discussion of both products recommended method of application with scientific explanation and proposed wording for Section 4.2 of the SmPC

5% cream

MAH's response: The MAH supports the rapporteur's statement that the word 'throat' can be misleading in the currently approved SmPC of the 5% cream. The MAH is of the view that the word throat in the English version of the SmPC of the 5% cream should be deleted. The MAH also supports the rapporteur's view to create a separate paediatric subheading in section 4.2 and to delete the statement of "The head and face can be spared unless scabies efflorescences are present in this region", as far as the paediatric treatment recommendation is concerned.

The MAH's proposals for the 5% cream SmPC section 4.2 are (updates in bold):
"4.2 Method of administration
Paediatric population
The safety and efficacy of X in children under 2 months of age have not been established.

Children should apply the cream uniformly to the whole body, including the palms of the hands, soles of the feet, neck, face, ears, and scalp. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared. Children should be kept from licking the cream from the hands. If necessary, children should wear gloves.
There is no adequate experience in infants and toddlers. Treatment of children aged **up** to 23 months should therefore be given only under close medical supervision."

Permethrin 0.43% cutaneous solution

The MAH acknowledges that medical guidelines may differ between the member states. The guideline issued by the German Society for Paediatric Infectious Diseases (Deutsche Gesellschaft für Pädiatrische Infektiologie, DGPI) recommends a contact time of 30-45 minutes for alcoholic permethrin solutions for treatment of head lice infestation, thus supporting the method of administration of the MAH's product. The guideline further states that a second treatment after 8-10 days may not be necessary according to literature data. The DGPI makes reference to a German study (Bialek et al. 2005) where no lice were found in 94% of patients after a single treatment. Recommendations for treatment of head-lice infestation may also vary because of different pharmaceutical forms, i. e. alcoholic solution in Germany versus aqueous suspension (cream rinse) in the UK.

As already discussed by the rapporteur, a recent German study supports the current posology and method of application of the product. An overall cure rate of 95% was observed when it was prescribed in private practices and was applied at home according to the directions and recommendations given in the patient information leaflet. This result is further supported by another German multicenter observational study published in 2005 by Bialek et al. which followed the same protocol as in the study of Burow et al (2010). This study was already assessed by the NCA during the MA application. It comprised 193 patients in the safety population and 191 patients in the efficacy population, respectively. Patients or care-givers were advised to perform the treatment according to the instructions in the package leaflet. A control visit was scheduled for day 8. If lice or hatchable lice eggs were still detected on visual inspection at day 8, a second treatment was prescribed. The final visit was scheduled for day 15. Treatment success (no live lice detectable by intensive combing performed by trained personnel) was achieved in 94% of patients on day 8 after a single application of the solution. Overall treatment success was 98% at the final visit on day 15.

Concerning the maximum dose, no systematic data are available for this well established product. The data from the observational studies performed in Germany suggest that 150ml are usually sufficient to treat even adults with long and thick hair (unpublished data on file).

MAH's overall conclusion:

These clinical data and German guideline support the method of application recommended in the SmPC of the 0.43% including the recommendation to repeat to treatment after 8 to 10 days in the case of persistent or recurrent infestation.
The MAH supports the rapporteur's notion that best clinical practice may vary based on each country's local head lice sensitivity and resistance pattern therefore updates to the SmPC should be considered at a national level. The MAH is of the view that the recommended method of administration of the 0.43% solution is well established and has been proven safe and effective in clinical studies. The MAH therefore does not consider that changes are necessary in the SmPC and package leaflet concerning the contact time or the number of recommended applications.
Nevertheless, the MAH proposes a rewording of section 4.2 of the SmPC taking into account the recommendations of the rapporteur. A maximum dose of 150ml is proposed for adults and

children 4 years of age and older. The maximum dose for children from 2 months to 3 years of age is already given in the SmPC (25ml).
The MAH also supports the rapporteur's view that prophylactic treatment with permethrin might contribute to parasite resistance. The SmPC of the 0.43% contains a warning in section 4.2 stating that *"Prophylactic treatment with X cannot reliably prevent infestation with lice and is therefore not appropriate."*
The rapporteur's proposal to include a warning in section 4.4 of the SmPC in member states with significant resistance is supported by the MAH. However, this should be decided on a national level based on their licensed indications, as suggested by the rapporteur.

Permethrin 1% Cream Rinse
The MAH cannot comment on the treatment recommendations of the 1% cream rinse, since no data are available and the MAH's of the cream rinse products in the UK do not participate in this work sharing.

Rapporteur's comment
The MAH sufficiently addressed the issues identified in the method of administration of the 2 marketed products' (5% cream and 0.43% solution).

Permethrin 5% cream:
The MAH agreed the rapporteur's recommendation regarding the method of administration and sufficiently clarified the paediatric age groups. Section 4.2 of the MAH's revised SmPC already correctly states that *"The safety and efficacy of X in children under 2 months of age have not been established";* therefore the rapporteur does not consider repetition of this information under the "Method of administration" subheading necessary.

Permethrin 0.43% cutaneous solution:
The MAH submitted the 0.43% permethrin solution SmPC in English which includes a sufficiently detailed description of the method of administration in the paediatric population. This administration guidance is based on scientific data and a national guideline and therefore is considered acceptable by the rapporteur. Furthermore, the MAH added the maximum recommended doses. Issue resolved.

As previously discussed in this paediatric work-sharing procedure report, product information (SmPC and PIL) needs to be updated according to best clinical practice, however this may differ based on each member states' local head lice sensitivity and resistance pattern. Therefore updates to section 4.2 Method of administration subheading of the SmPC should be considered at national level.

Permethrin 1% crème rinse
It is acknowledged that the participating MAH cannot comment on the treatment recommendations for the 1% cream rinse permethrin products as it is not marketed by them. No relevant data regarding the use of this product in the paediatric population has been submitted as part of this European paediatric work-sharing procedure. It is therefore concluded by the rapporteur that no regulatory actions are possible.

7. **Supporting data for the proposed safety update in section 4.8 of the 0.43% solution SmPC. Discussion of potential adverse effects, in particular in children with asthma and eczema**

MAH's response: As stated in the MAH's Short Critical Expert Overview on Paediatric Data for Permethrin, the update on adverse reactions to the product information of the 0.43% cutaneous solution was due to spontaneous reports of adverse events from consumers and healthcare providers to the MAH. Since marketing authorisation of the 0.43% cutaneous solution the following spontaneous reports were received by the MAH:

- 4 reports of paraesthesia
- 2 reports of urticaria
- report of contact dermatitis

These adverse events were assessed as at least possibly related to treatment with the solution. These adverse reactions are known for other permethrin formulations and were already listed in the respective SmPC of the 5% cream. Thus, they were considered to be also relevant for the solution product based on even only a very limited number of spontaneous reports. The frequency of the reactions was defined as "unknown" since no data were available concerning their incidence with the concrete pharmaceutical formulation of the 0.43% solution. A national variation was filed to include these adverse reactions into the SmPC and the package leaflet.

The MAH provided quality data for 0.43% permethrin solution including a discussion on its potential inflammatory and irritant effects in its response document. Regarding the potential safety concern of the use of permethrin in children with asthma and eczema, the MAH performed a literature research and could not identify any relevant data in support of the mentioned safety concern. The following statement is included in section 4.4 of the SmPC of another cream product
"X crème rinse may be used as normal in asthmatics, however contact your doctor or pharmacist before commencing treatment if you have any particular concerns". Moreover, warnings for asthmatics are currently included in product information in the U.S. as well as in Switzerland. In the MAH's pharmacovigilance database there was one case report with asthma identifiable that concerned a female adult with a history of mild asthma and who reported severe asthma after the application of the 0.43% solution. This case was classified as serious by the reporter but lacked medical confirmation.

Although there was no association identifiable from the scientific literature, in light of the plausible increased irritating effect of alcoholic vapours from the 0.43% cutaneous solution to asthmatics and of similar inclusion in product information in the U.S. and in Switzerland, the MAH supports the view of the rapporteur to include a warning regarding asthma in section 4.4. The following wording is proposed by the MAH:

"4.4 Special warnings and precautions for use
Due to its alcohol content, X might cause irritations when getting into contact with the eyes, mucous membranes (e.g. nasopharyngeal region, genital area) or open wounds.
When using X, it should be ensured that the solution does not come into contact with these areas. Rinse thoroughly with water in the event of inadvertent contact.
X may worsen symptoms of asthma or eczema."

Rapporteur's comment
The MAH provided sufficient background information for the proposed updates in section 4.8 of the SmPC. Issue resolved.

The MAH also addressed the potential safety concerns in children with asthma and eczema. The recommended relevant wording in section 4.4 of the SmPC is considered acceptable by the rapporteur. Issue resolved.

8. Package leaflet wording proposals for both products

The MAH submitted package leaflet wording proposals for both products. Updates and changes are printed in bold.

PACKAGE LEAFLET: Information for the user 5 % cream
Permethrin
[…]
2. WHAT YOU NEED TO KNOW BEFORE YOU USE X
Do not use X:
- If you are allergic to Permethrin, other pyrethrins or any of the other ingredients of this medicine (listed in section 6)
~~- In newborns and infants less than 2 months of age.~~
Warnings and precautions:
Talk to your doctor or pharmacist before using X.
- If you are treating infants **– see below in the section "Children up to 23 months of age"**
~~X may only be used under close supervision by a doctor in children aged 2 months up to 23 months.~~
- If you are known to be allergic to chrysanthemums or other compositae - you should only use X after speaking to your doctor.

Warning:
For cutaneous use only! Do not swallow this medicine.

Avoid contact with eyes or mucous membranes (inside the nose or throat, genital region) or open wounds.

X is harmful to all types of insects and also to animals living in water e. g. fish. Take care that X does not get into aquaria or terraria.

X contains paraffins. These excipients of the cream can reduce the efficiency and hence the reliability of latex products (e. g. condoms, diaphragms) used at the same time.

X may worsen symptoms of asthma or eczema.

Children up to 23 months of age
Do not use X in newborns and infants less than 2 months of age, unless your doctor tells you so. There is no adequate experience in infants and toddlers. Treatment to children ~~aged 2 months~~ up to 23 months of age should only be given under close medical supervision.

[…]

X contains cetostearyl alcohol and sorbic acid which may cause local skin irritation (e. g. contact dermatitis).

3. HOW TO USE X

Always use X exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Carefully apply a thin layer of cream to the skin (see "How and when should you use X?").
Adults and adolescents over 12 years of age:

Apply up to 30 g of cream (corresponding to one tube of 30 g or ½ tube of 60 g)

Children aged from 6 - 12 years:
Apply up to 15 g of cream (corresponding to ½ tube of 30 g or ¼ tube of 60 g)

Children aged from 2 months - 5 years
Apply up to 7.5 g of cream (corresponding to ¼ tube of 30 g or ⅛ tube of 60 g)

Newborns and infants under 2 months of age
There is only limited amount of data available in this age group and no dose can be recommended (see also section 2 under "warnings and precautions").

The above information is merely a guide. The dose can be adjusted according to the needs of the individual patient and the individual body surface area. For example, some adults require a larger amount of cream.

How and when should you use X?
X is for cutaneous use only.
Take care not to allow the cream to get into the eyes or come into contact with mucous membranes (inside the nose or throat, genital region) or open wounds. If accidental contact occurs, rinse thoroughly with water.
Adults **~~and children over 2 years of age~~** should apply the cream to the whole body including the **~~throat~~**, neck, palms of the hands and soles of the feet. The head and face can be spared unless this area includes places affected by scabies (itch mites).
When applying the cream, the areas between the fingers and toes (also under the finger- and toe-nails), the wrists, elbows, armpits, external genitalia and buttocks should be especially carefully treated.

Children **~~below 2 years:~~**
Children should apply the cream uniformly to the whole body, including the palms of the hands, soles of the feet, neck, face, ears, and scalp. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared.
Keep your child from licking the cream from the hands. If necessary, children should wear gloves.
There is no adequate experience in infants and toddlers. Treatment to children **up to the age ~~aged 2 months to~~** of 23 months should therefore only be treated under close medical supervision. **~~In this case, the face, ears and scalp should also be treated.~~**

Elderly
Elderly patients (over 65 years) should use the cream in the same way as adults **~~and children over 2 years of age,~~** but in addition, the face, ears and scalp should also be treated. Care should be taken to avoid applying the cream to areas of skin around the eyes.

How long should you use X?
One application of X is usually sufficient.
Leave the cream on the skin for at least eight hours, for example, overnight. Avoid bathing, showering or washing during this period, because this could endanger the success of treatment. If, by way of an exception, you have to wash your hands within the eight hour period, then reapply the cream to the hands and wrist area. The same applies if you have to wash other parts of treated skin (buttocks, external genitalia).
After at least eight hours, take a shower or wash the skin with soap and water.
Provided these instructions for use are followed, a single application is generally sufficient for successful treatment. However, in cases of persistent or renewed infestation, it may be necessary to repeat the treatment after 14 days.

[…]

4. POSSIBLE SIDE EFFECTS
Like all medicines, X can cause side effects, although not everybody gets them.

If severe hypersensitivity reactions occur, please consult a doctor immediately! In this case you must not use X any more.
Common: may affect up to 1 in 10 people
Itching (pruritus), reddening of the skin or unusual sensations on the skin (paraesthesias) such as tingling, pricking, skin burning sensation as well as dry skin are common. However, such symptoms can also occur as a result of the disease itself. Moisturisers and oil baths are recommended as follow up treatment for dry skin. The itching and a skin rash (post-scabies eczema) may persist for up to four weeks after the end of treatment. This is caused by a reaction to the killed scabies mites. If after using X you have the impression that the disease is persisting, please speak to your doctor before applying it again.

Rare: may affect up to 1 in 1,000 people
Headache can occur rarely.

Very rare: may affect up to 1 in 10,000 people
Very rarely, skin lesions (excoriations), inflammation of the hair follicles (folliculitis) and reduced skin pigmentation have been reported at the time X is used.
Sensitive/allergic persons have reported breathing difficulties at the time substances from the pyrethrin group were being used.

Not known: frequency cannot be estimated from the available data
Intolerability reactions may occur on the skin (contact allergy reactions) that are expressed as itching, reddening, blisters or nettle rash (urticaria). These reactions may also spread beyond the area of skin treated.
Nausea may appear. Vomiting was not reported after the use of X but is known in connection with other permethrin-containing drugs.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

PACKAGE LEAFLET: Information for the user 0.43% cutaneous solution

Permethrin
[…]
2. WHAT YOU NEED TO KNOW BEFORE YOU USE X
Do not use X:
- If you are allergic to Permethrin, other pyrethrins or any of the other ingredients of this medicine (listed in section 6) .
~~**- In newborns and infants under 2 months of age.**~~

Warnings and precautions:
Talk to your doctor or pharmacist before using X.
- If you are treating infants – see below in the paragraph "Children up to 3 years of age"
- If you are known to be allergic to chrysanthemums or other compositae - you should only use X after speaking to your doctor.

Treatment should only be initiated if eggs or live lice have been detected.

For cutaneous use only! Do not swallow this medicine.
Due to its alcohol content, X is flammable.

Due to its alcohol content, X might cause irritations when getting into contact with eyes or mucous membranes (inside the nose or throat, genital region) or open wounds. **Always make sure that the solution does not come into contact with these areas.** In case of accidental contact rinse with water thoroughly.

X may worsen symptoms of asthma or eczema.

Children ~~2 months of age~~ up to 3 years
Do not use X in newborns and infants less than 2 months of age, unless your doctor tells you so. There is no adequate experience in infants and toddlers. Treatment to children ~~aged 2 months~~ up to 3 years of age should only be given under close medical supervision.

[…]

X contains propylene glycol which may cause local skin irritation.

3. HOW TO USE X
Always use X exactly as described below or as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
One single application of X is generally sufficient.
For treatment, the hair must be saturated well with the solution. The amount required for this depends on the hair volume: around 25 ml is sufficient for short hair; about 50 ml is required for longer hair, or even more for very long and thick hair **(up to 150ml in adults and children 4 years of age and older).**
Children up to 3 years
In children aged over 2 months up to 3 years, a maximum dose of 25 ml must be respected.
There is only limited data on the use of X in newborns up to the age of 2 months and no dose can be recommended (see also section 2 under "warnings and precautions").
Prior to administering X, the hair is washed with shampoo (but without conditioner) and rubbed. Use a fresh and light towel on your shoulders for an easy detection of falling lice. X is massaged evenly into the still damp hair, ensuring that the hair near the scalp is particularly well covered with X, as most lice and louse eggs are located here. Long and particularly thick hair should be separated and treated strand by strand.
X must only be used undiluted and should not be used with shampoo, soap or other cleaning products.
X should be left to act on the uncovered scalp hair for 30–45 minutes; it should then be rinsed out with clear, warm water.
Prior to drying the hair, all resistant louse eggs adhering to hairs should be combed out with a special louse or nit comb. Dry your hair with a fresh towel.
To ensure optimal efficacy, the hair must not be washed with hair-washing agents (shampoo) for the first three days following the use of X (rinsing out with water is permitted). The active substance will then remain on the hair and will continue to eradicate larvae hatching from the eggs even after treatment, or the egg contents will be severely damaged.
Checks for any re-infestation with head lice should be made as frequently as possible, but by the 5th day after treatment as a minimum. Head and body lice are easily transmitted from individual to individual; it is strongly recommended that checks be carried out among all contact persons within the family and in children communities.
When these directions for use are observed, therapeutic success is generally achieved with as little as one single application. However, it may become necessary to repeat treatment after 8 to 10 days in the case of persistent or recurrent infestation.
Concomitant treatment of all community members (school class, nursery groups) is often expedient in stubborn epidemics, even if not all members are presenting with symptoms
In case of infestations of body lice the respective areas are to be treated accordingly. Adhere to the precautions.
If you have the impression that the effect of X is too strong or too weak, talk to your doctor or pharmacist.

[…]

4. POSSIBLE SIDE EFFECTS
Like all medicines, X can cause side effects, although not everybody gets them.
The following frequency categories are underlying the adverse drug reactions:
Rare**:** may affect up to 1 in 1.000 people
Very rare: may affect up to 1 in 10.000 people
Not known: frequency cannot be estimated from the available data
Rarely: Rarely skin irritations (redness) or itching have been observed which may manifest as tingling, pricking, and skin burning sensation. However, such symptoms can also occur as a result of the disease itself.

Very rarely**:** Headache, nausea and vomiting can occur very rarely; breathing difficulty (respiratory complaints) and hypersensitivity reactions (allergic reactions) have been reported in close temporal relation to the application of active substances of the pyrethrine group.
Unknown**:** Unusual sensations on the skin (paraesthesias) such as tingling, pricking, skin burning sensation in one or more areas of the body may occur. Intolerability reactions may occur on the skin (contact dermatitis) that are expressed as itching, reddening, blisters or nettle rash (urticaria).
If severe hypersensitivity reactions occur, please consult a doctor immediately! In this case you must not use X any more.
If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not mentioned in this information leaflet.

Rapporteur's comment
The rapporteur considers the MAH's packet leaflet proposal for 5% cream acceptable.

The rapporteur does not consider the wording "There is only limited data on the use of X in newborns up to the age of 2 months and no dose can be recommended (see also section 2 under "warnings and precautions")" in section 3 of the 0.43% solution package leaflet necessary as it has been previously stated that do not use the product in infants < 2months of age unless your doctor tells you so. The rest of the 0.43% permethrin solution PIL wording proposal is considered agreeable.

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Permethrin is licensed for paediatric use in the treatment of scabies and head lice in many European countries.
5% permethrin cream products have a well established use in children with scabies. The safety and efficacy of permethrin 5% in infants younger than 2 months of age have not been established as there is only very limited data (few case reports) available. 5% permethrin is proven to be safe and effective for the treatment of scabies when used in paediatric subsets > 2 months of age, however close medical supervision is advised in children younger than 2 years of age. Regarding to best clinical practice, application of the 5% permethrin product needs to be head to toe - including the scalp, face and ears - in the paediatric population due to smaller body size. Based on these conclusions relevant updates to section 4.1, 4.2 and 4.4 of the 5% permethrin cream SmPC have been recommended by the rapporteur.

Permethrin has been widely used for the treatment of head lice infestations in children until about 10 years ago, when reports about an increasing number of treatment failure and head lice resistance against permethrin started to emerge in several European countries. Both the prevalence of kdr-like gene mutation and the association between the mutation and treatment resistance varies based on geographical location. In light of this, the rapporteur is of the view that each member state should consider whether to include the following special warning in section 4.4 of the SmPC: *"Head lice resistance against permethrin treatment has been reported depending on geographical location, therefore if live lice are present after the second application, seek medical advice."*
The safety and efficacy of permethrin 0.43% solution in infants younger than 2 months of age have not been established. There is no data available in this paediatric subgroup.

In some European countries (for example NL) permethrin is licensed for short lasting prophylaxis of head lice infestation in persons who have visited schools or other centres at the time of a head lice epidemic. In contrast, in other countries (such as the UK) it is believed that

inappropriate application methods, such as permethrin used without detection of live head lice, too short contact time or permethrin applied only once instead of twice 7 days apart, may have contributed to the development of resistance. Therefore the rapporteur is of the view that an update to section 4.2 and 4.4 of the SmPC should be considered at a national level based on already existing licensed indications and local evidence based clinical guidelines.
As parents and carers refer to the package leaflet, this should also be updated accordingly.

Permethrin was proven to be safe in the submitted studies. Adverse events with 0.43% solution were mostly stinging or burning sensations on the scalp or neck. The events were related to the intensity of infestation and the number of bite reactions on the scalp and were attributed to the alcohol content of the product. Paraesthesia, contact dermatitis and urticaria have been reported as adverse events through spontaneous reporting therefore inclusion in section 4.8 of the 0.43% SmPC is considered indicated. Furthermore, due to its alcohol content, the solution product may worsen symptoms of asthma and eczema therefore a relevant safety warning is recommended for inclusion in section 4.4 of the SmPC.

Lastly, although 1% permethrin crème rinse products are licensed in some European MSs for the treatment of head lice infestation in children, no relevant data has been submitted during this paediatric work-sharing procedure and therefore no regulatory conclusions can be drawn regarding these products. Consequently no changes to the SmPC for 1% permethrin solution products are proposed.

The rapporteur recommends the following updates to permethrin product SmPCs however please note that alterations in wording may be needed in sections 4.2, 4.4 and consequently in package leaflets, depending on each member states licensed indications, best medical practice and head lice resistance status.

Final SmPC recommendations

a) Permethrin 5% cream

4.1 Therapeutic indications

Permethrin 5% cream is indicated for the treatment of scabies in adults and children > 2 months of age.

4.2 Posology and method of administration

Posology
Unless otherwise directed by the physician, the recommended dosage is as follows:

Adults and adolescents over 12 years of age:
Apply up to 30 g of cream (corresponding to one tube of 30 g or ½ tube of 60 g).

Paediatric population
Children aged from 6 - 12 years:
Apply up to 15 g of cream (corresponding to ½ tube of 30 g or ¼ tube of 60 g).

Children aged from 2 months - 5 years:
Up to 7.5 g of cream (corresponding to ¼ tube of 30 g or ⅛ tube of 60 g).

The safety and efficacy of X in children under 2 months of age have not been established. No data are available.

Method of administration
For cutaneous use only. The medicinal product must not be swallowed.
Carefully apply a thin layer of cream to the skin (cutaneous use).
Adults should apply the cream uniformly to the whole body including the neck, palms of the hands and soles of the feet. The head and face can be spared unless scabies efflorescences are present in this region.
On application, the areas between the fingers and toes (also under the finger- and toe-nails), the wrists, elbows, armpits, external genitalia and the buttocks should be especially carefully treated.

Paediatric population
Children should apply the cream uniformly to the whole body, including the palms of the hands, soles of the feet, neck, face, ears, and scalp. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared. Children should be kept from licking the cream from the hands. If necessary, children should wear gloves.
Only limited experience is available with X in children aged 2 months to 23 months. Therefore treatment must be given only under close medical supervision in this age group.

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

[…]

4.3 Contraindications
Hypersensitivity to the active substance permethrin or other substances of the pyrethrin group or to any of the excipients listed in section 6.1. In such cases treatment should be switched to a chemically different antiscabies agent.

4.4 Special warnings and precautions for use
In the case of hypersensitivity to chrysanthemums or other compositae, treatment should only be given if strictly indicated.
When using X 5%, care should be taken not to allow the cream to get into the eyes or come into contact with mucous membranes (e.g. nasopharyngeal space, genital area) or open wounds.

Paediatric population
Only limited experience is available with X in children aged 2 months to 23 months. Therefore treatment must be given only under close medical supervision in this age group.

For cutaneous use only!
This medicinal product contains cetostearyl alcohol and sorbic acid which may cause local skin reactions (e.g. contact dermatitis). Note : if applicable to the product's composition.
X 5% is harmful to all types of insects and also for aquatic forms of life (fishes, daphnia, algae). Contamination of aquaria and terraria is to be avoided.
Note: The excipients of the cream (liquid paraffin, white soft paraffin) can reduce the functioning and hence the reliability of latex products (e.g. condoms, diaphragms) used at the same time.

4.8 Undesirable effects

System Organ class	**common** (≥1/100 to <1/10)	**rare** (≥1/10,000 to <1/1,000)	**very rare** (<1/10,000)	**not known** (cannot be estimated from the available data)

Nervous system disorders	Paraesthesia, skin burning sensation	headache		
Respiratory, thoracic and mediastinal disorders			Dyspnoea (in sensitive/allergic patients)	
Gastrointestinal disorders				nausea
Skin and subcutaneous tissue disorders	pruritus, erythematous rash, dry skin		Excoriation, folliculitis, skin hypopigmentation	contact dermatitis, urticaria

5.1 Pharmacodynamic properties

[…]
Paediatric population
Newborns and infants:
The safety and efficacy of permethrin in newborns and infants under 2 months of age have not been established since no data are available from prospective trials or larger case series. A limited number of case reports in the treatment of children under 2 months of age presenting with scabies do not suggest specific safety concerns for the use of topical permethrin in this age group, but no definite conclusion can be drawn.

5.2 Pharmacokinetic properties
Investigations with the 5 % cream in humans revealed an average percutaneous absorption rate of 0.47 ± 0.3 % in healthy subjects and of 0.52 ± 0.3 % in patients.
Pharmacokinetic properties were studied in adult subjects only (6 healthy volunteers and 6 patients with scabies).
Absorbed permethrin is rapidly broken down by esterases as well as hydrolases. After oral administration, peak plasma concentrations are reached in approximately 4 hours. The isomeric mixture is then excreted in the urine in the form of glucuronides, sulfates etc as cis- trans CI2CA [(3- (2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid)] and after oxidation to 3 PBA (3- phenoxybenzoic acid). After oral application, up to 6 % is excreted unchanged in the faeces whilst on dermal application, unchanged permethrin is virtually undetectable.

5.3 Preclinical safety data
From acute and chronic toxicity studies there is no evidence indicating the occurrence of previously unknown adverse effects in humans. Furthermore there is no evidence on relevant genotoxic or carcinogenic potential. In studies on the reproductive toxicity in mice, rats and rabbits after repeated oral administration of permethrin effects were observed only for doses largely exceeding the exposure expected for the topical use of the 5% cream. Following the intended use of this active substance a serious harmful effect on aquatic organisms (daphnia and fish) and terrestric organisms (plants) is expected after passage of the sewage treatment plant.

b) Permethrin 0.43% solution

4.1 Therapeutic indications
Permethrin 0.43% is indicated for the treatment of head lice infestations in adults and children > 2 months of age.

4.2 Posology and method of administration

Posology
One single application of X is generally sufficient. Apply enough X solution to soak the hair well. In patients with short hair, 25ml are usually sufficient, while in patients with longer hair 50ml are necessary, in patients with very long or thick hair even more (up to 150ml in adults and children 4 years of age and older).

Paediatric population
The safety and efficacy of X in children under 2 months of age have not been established. No data are available.
Dosage in children from 2 months to 3 years of age is limited to 25ml.

Method of administration
For external use only. This medicinal product must not be swallowed.
Prior to administering X, the hair is washed and rubbed. X is massaged evenly into the still damp hair, ensuring that the hair near the scalp is particularly well covered with X, as most lice and louse eggs are located here. Long and particularly thick hair should be separated and treated strand by strand. X should be left to act on the uncovered scalp hair for 30–45 minutes; it should then be rinsed out with clear, warm water. Prior to drying the hair, all resistant louse eggs adhering to hairs should be combed out with a louse or nit comb.
To ensure optimal efficacy, the hair must not be washed with hair-washing agents (shampoo) for the first three days following the use of X (rinsing out with water is permitted).
The active substance will then remain on the hair and will continue to eradicate larvae hatching from the eggs even after treatment, or the egg contents will be severely damaged.
Checks for any reinfestation with head lice should be made as frequently as possible, but by the 5th day after treatment as a minimum.
Head and body lice are easily transmitted from individual to individual; it is strongly recommended that checks be carried out among all contact persons within the family and in children communities.
When these directions for use are observed, therapeutic success is generally achieved (in approximately 75% of cases) with as little as one single application. However, it may become necessary to repeat treatment after 8 to 10 days in the case of persistent or recurrent infestation.
Following repeated treatment, the success rate is 95 - 100%.
Prophylactic treatment with X cannot reliably prevent infestation with lice and is therefore not appropriate. However, concomitant treatment of all community members (school class, nursery groups) is often expedient in stubborn epidemics, even if not all members are presenting with symptoms.
Short-term and strict on-label treatment is required to counteract the selection of resistant lice.
Treatment should therefore be restricted to one single application, in addition to any repeat treatment that may be required.

4.3 Contraindications
In cases of known hypersensitivity to permethrin or other active substances of the pyrethrine group, X should not be used and a chemically different anti-lice agent should be selected.

4.4 Special warnings and precautions for use (Note : if applicable based on product's composition)
Treatment should only be initiated if eggs or live lice have been detected.

(In member states with significant resistance rates of head lice, the following sentence should be added:

"Head lice resistance against permethrin treatment has been reported depending on geographical location, therefore if live lice are present after the second application, the patient should seek medical advice.")

Due to its alcohol content, X might cause irritations when getting into contact with the eyes, mucous membranes (e.g. nasopharyngeal region, genital area) or open wounds.
When using X, it should be ensured that the solution does not come into contact with these areas. Rinse thoroughly with water in the event of inadvertent contact.

X may worsen symptoms of asthma or eczema.

Due to its alcohol content, X is inflammable.
Propylene glycol may cause skin irritation.

In cases of hypersensitivity to chrysanthemums or other members of the Composite family (daisy family), care should be taken when assessing the indication for treatment.

Paediatric population
Only limited experience is available with X in children aged over 2 months up to 3 years. Therefore, treatment must be performed only under close specialist supervision in this age group.

4.8 Undesirable effects

Organ class	**Rare (≥ 1/10,000 - <1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known (cannot be estimated from the available data)**
Nervous system disorders	Headache		Paraesthesia
Respiratory, thoracic and mediastinal disorders		Respiratory complaints	
Gastrointestinal disorders		Nausea, vomiting	
Skin and subcutaneous tissue disorders	Skin irritation (erythema), pruritus, tingling, burning or stinging	Allergic skin reactions	Contact dermatitis, urticaria

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
[…]
Paediatric population
Newborns and infants:
The safety and efficacy of permethrin in newborns and infants under 2 months of age have not been established since no data are available from prospective trials or larger case series. A limited number of case reports in the treatment of children under 2 months of age presenting with scabies do not suggest specific safety concerns for the use of topical permethrin in this age group, but no definite conclusion can be drawn.

5.2 Pharmacokinetic properties
Following application of approximately 50 ml X to the hair-covered scalp
(215 mg permethrin), an average of 0.23% of the applied dose (maximum 0.39%, minimum 0.16%) was excreted in the urine of 6 subjects within the first 48 hours. Mean total cumulative urinary excretion after a total of 168 hours of exposure time was 0.35% (between 0.26% and 0.53%) of the applied amount. Absorbed permethrin is rapidly cleaved by esterases or hydrolases. When orally administered, the peak plasma concentration is reached after about 4 hours. The isomeric mixture is then excreted in the urine in the form of glucuronides, sulfates etc. as cis- trans CI2CA [(3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid)] and, after oxidation to 3 PBA (3-phenoxybenzoic acid). After oral application, up to 6% is excreted unchanged in the faeces whilst on dermal application, unchanged permethrin is virtually undetectable.

5.3 Preclinical safety data
From acute and chronic toxicity studies there is no evidence indicating the occurrence of previously unknown adverse effects in humans. Furthermore there is no evidence on relevant genotoxic or carcinogenic potential. In studies on the reproductive toxicity in mice, rats and rabbits after repeated oral administration of permethrin effects were observed only for doses largely exceeding the exposure expected for the topical use of X.
Following the intended use of this active substance a serious harmful effect on aquatic organisms (daphnia and fish) and terrestric organisms (plants) is expected after passage of the sewage treatment plant.

c) Permethrin 1% solution

No change.

Final package leaflet recommendations

a) Permethrin 5 % cream

PACKAGE LEAFLET: Information for the user

[…]

2. WHAT YOU NEED TO KNOW BEFORE YOU USE X

Do not use X:
- If you are allergic to Permethrin, other pyrethrins or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions:
Talk to your doctor or pharmacist before using X.
- If you are treating infants – see below in the section “Children up to 23 months of age”
- If you are known to be allergic to chrysanthemums or other compositae - you should only use X after speaking to your doctor.

Warning:
For cutaneous use only! Do not swallow this medicine.

Avoid contact with eyes or mucous membranes (inside the nose or throat, genital region) or open wounds.

X is harmful to all types of insects and also to animals living in water e. g. fish. Take care that X does not get into aquaria or terraria.

Note: if applicable to product’s composition: X contains paraffins. These excipients of the cream can reduce the efficiency and hence the reliability of latex products (e. g. condoms, diaphragms) used at the same time.

X may worsen symptoms of asthma or eczema.

Children up to 23 months of age
Do not use X in newborns and infants less than 2 months of age, unless your doctor tells you so. There is no adequate experience in infants and toddlers. Treatment to children up to 23 months of age should only be given under close medical supervision.

[…]

Note: if applicable to product's composition: X contains cetostearyl alcohol and sorbic acid which may cause local skin irritation (e. g. contact dermatitis).

3. HOW TO USE X

Always use X exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Carefully apply a thin layer of cream to the skin (see "How and when should you use X?").
Adults and adolescents over 12 years of age:
Apply up to 30 g of cream (corresponding to one tube of 30 g or ½ tube of 60 g)

Children aged from 6 - 12 years:
Apply up to 15 g of cream (corresponding to ½ tube of 30 g or ¼ tube of 60 g)

Children aged from 2 months - 5 years
Apply up to 7.5 g of cream (corresponding to ¼ tube of 30 g or ⅛ tube of 60 g)

Newborns and infants under 2 months of age
There is only limited amount of data available in this age group and no dose can be recommended (see also section 2 under "warnings and precautions").

The above information is merely a guide. The dose can be adjusted according to the needs of the individual patient and the individual body surface area. For example, some adults require a larger amount of cream.

How and when should you use X?
X is for cutaneous use only.
Take care not to allow the cream to get into the eyes or come into contact with mucous membranes (inside the nose or throat, genital region) or open wounds. If accidental contact occurs, rinse thoroughly with water.
Adults should apply the cream to the whole body including the neck, palms of the hands and soles of the feet. The head and face can be spared unless this area includes places affected by scabies (itch mites). When applying the cream, the areas between the fingers and toes (also under the finger- and toe-nails), the wrists, elbows, armpits, external genitalia and buttocks should be especially carefully treated.

Children
Children should apply the cream uniformly to the whole body, including the palms of the hands, soles of the feet, neck, face, ears, and scalp. Parts of the skin around the mouth (because the cream could be licked off) and the eyes should be spared.
Keep your child from licking the cream from the hands. If necessary, children should wear gloves.
There is no adequate experience in infants and toddlers. Treatment to children up to the age of 23 months should therefore only be treated under close medical supervision.

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

How long should you use X?
One application of X is usually sufficient.
Leave the cream on the skin for at least eight hours, for example, overnight. Avoid bathing, showering or washing during this period, because this could endanger the success of treatment. If, by way of an exception, you have to wash your hands within the eight hour period, then reapply the cream to the hands and wrist area. The same applies if you have to wash other parts of treated skin (buttocks, external genitalia).
After at least eight hours, take a shower or wash the skin with soap and water.
Provided these instructions for use are followed, a single application is generally sufficient for successful treatment. However, in cases of persistent or renewed infestation, it may be necessary to repeat the treatment after 14 days.

[…]

4. POSSIBLE SIDE EFFECTS
Like all medicines, X can cause side effects, although not everybody gets them.
If severe hypersensitivity reactions occur, please consult a doctor immediately! In this case you must not use X any more.
Common: may affect up to 1 in 10 people
Itching (pruritus), reddening of the skin or unusual sensations on the skin (paraesthesias) such as tingling, pricking, skin burning sensation as well as dry skin are common. However, such symptoms can also occur as a result of the disease itself. Moisturisers and oil baths are recommended as follow up treatment for dry skin. The itching and a skin rash (post-scabies eczema) may persist for up to four weeks after the end of treatment. This is caused by a reaction to the killed scabies mites. If after using X you have the impression that the disease is persisting, please speak to your doctor before applying it again.

Rare: may affect up to 1 in 1,000 people
Headache can occur rarely.

Very rare: may affect up to 1 in 10,000 people
Very rarely, skin lesions (excoriations), inflammation of the hair follicles (folliculitis) and reduced skin pigmentation have been reported at the time X is used.
Sensitive/allergic persons have reported breathing difficulties at the time substances from the pyrethrin group were being used.

Not known: frequency cannot be estimated from the available data
Intolerability reactions may occur on the skin (contact allergy reactions) that are expressed as itching, reddening, blisters or nettle rash (urticaria). These reactions may also spread beyond the area of skin treated.
Nausea may appear. Vomiting was not reported after the use of X but is known in connection with other permethrin-containing drugs.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

b) 0.43% permethrin cutaneous solution

PACKAGE LEAFLET: Information for the user

[…]
2. WHAT YOU NEED TO KNOW BEFORE YOU USE X
Do not use X:
- If you are allergic to Permethrin, other pyrethrins or any of the other ingredients of this medicine (listed in section 6) .

Warnings and precautions:
Talk to your doctor or pharmacist before using X.
- If you are treating infants – see below in the paragraph “Children up to 3 years of age”
- If you are known to be allergic to chrysanthemums or other compositae - you should only use X after speaking to your doctor.

Treatment should only be initiated if eggs or live lice have been detected.

For cutaneous use only! Do not swallow this medicine.
Due to its alcohol content, X is flammable.

Note: if applicable to product’s composition: Due to its alcohol content, X might cause irritations when getting into contact with eyes or mucous membranes (inside the nose or throat, genital region) or open

wounds. Always make sure that the solution does not come into contact with these areas. In case of accidental contact rinse with water thoroughly.

X may worsen symptoms of asthma or eczema.

Children up to 3 years
Do not use X in newborns and infants less than 2 months of age, unless your doctor tells you so. There is no adequate experience in infants and toddlers. Treatment to children up to 3 years of age should only be given under close medical supervision.

[…]

Note: only if applicable to product's composition: X contains propylene glycol which may cause local skin irritation.

3. HOW TO USE X
Always use X exactly as described below or as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
One single application of X is generally sufficient.
For treatment, the hair must be saturated well with the solution. The amount required for this depends on the hair volume: around 25 ml is sufficient for short hair; about 50 ml is required for longer hair, or even more for very long and thick hair (up to 150ml in adults and children 4 years of age and older).

Children up to 3 years
In children aged over 2 months up to 3 years, a maximum dose of 25 ml must be respected.

Prior to administering X, the hair is washed with shampoo (but without conditioner) and rubbed. Use a fresh and light towel on your shoulders for an easy detection of falling lice. X is massaged evenly into the still damp hair, ensuring that the hair near the scalp is particularly well covered with X, as most lice and louse eggs are located here. Long and particularly thick hair should be separated and treated strand by strand.
X must only be used undiluted and should not be used with shampoo, soap or other cleaning products.
X should be left to act on the uncovered scalp hair for 30–45 minutes; it should then be rinsed out with clear, warm water.
Prior to drying the hair, all resistant louse eggs adhering to hairs should be combed out with a special louse or nit comb. Dry your hair with a fresh towel.
To ensure optimal efficacy, the hair must not be washed with hair-washing agents (shampoo) for the first three days following the use of X (rinsing out with water is permitted). The active substance will then remain on the hair and will continue to eradicate larvae hatching from the eggs even after treatment, or the egg contents will be severely damaged.
Checks for any re-infestation with head lice should be made as frequently as possible, but by the 5th day after treatment as a minimum. Head and body lice are easily transmitted from individual to individual; it is strongly recommended that checks be carried out among all contact persons within the family and in children communities.
When these directions for use are observed, therapeutic success is generally achieved with as little as one single application. However, it may become necessary to repeat treatment after 8 to 10 days in the case of persistent or recurrent infestation.
Concomitant treatment of all community members (school class, nursery groups) is often expedient in stubborn epidemics, even if not all members are presenting with symptoms
In case of infestations of body lice the respective areas are to be treated accordingly. Adhere to the precautions.
If you have the impression that the effect of X is too strong or too weak, talk to your doctor or pharmacist.

[…]

4. POSSIBLE SIDE EFFECTS
Like all medicines, X can cause side effects, although not everybody gets them.
The following frequency categories are underlying the adverse drug reactions:

Rare**:** may affect up to 1 in 1.000 people
Very rare: may affect up to 1 in 10.000 people
Not known: frequency cannot be estimated from the available data
Rarely: Rarely skin irritations (redness) or itching have been observed which may manifest as tingling, pricking, and skin burning sensation. However, such symptoms can also occur as a result of the disease itself.
Very rarely**:** Headache, nausea and vomiting can occur very rarely; breathing difficulty (respiratory complaints) and hypersensitivity reactions (allergic reactions) have been reported in close temporal relation to the application of active substances of the pyrethrine group.
Unknown**:** Unusual sensations on the skin (paraesthesias) such as tingling, pricking, skin burning sensation in one or more areas of the body may occur. Intolerability reactions may occur on the skin (contact dermatitis) that are expressed as itching, reddening, blisters or nettle rash (urticaria).
If severe hypersensitivity reactions occur, please consult a doctor immediately! In this case you must not use X any more.
If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not mentioned in this information leaflet.

c) Permethrin 1% solution

No change.

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA

MAH	Name of the medicinal product	Strength	Pharmaceutical form	Active substance
Infectopharm Arzneimittel GmbH	Infectomite 5%	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectopedicul	430 mg/100 ml	cutaneous solution	Permethrin
Infectopharm Arzneimittel GmbH	Infectoperm 5%	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % Creme	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krem	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krém	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 1 x 30 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 1 x 60 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 10 x 30 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 2 x 30 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 5 x 30 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 2 x 60 g	50 mg/g	cream	Permethrin

Infectopharm Arzneimittel GmbH	Infectoscab 5 % krema, 5 x 60 g	50 mg/g	cream	Permethrin
Infectopharm Arzneimittel GmbH	Infectoscab 5%	50 mg/g	cream	Permethrin

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