Permethrin 5% w/w Dermal Cream

2.5 Clinical Overview

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Document status: Modification of Final prepared on 11.12.2018

Date of Preparation: 22.01.2020

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Abbreviations

3PBA	3-phenoxybenzoic acid
4′-OH-PBA	4′OH-phenoxybenzoic acid
4'-OH-PBacid	3-(4'-hydroxyphenoxy)benzoic acid
AAP	American Academy of Pediatrics
AChE	acetylcholinesterase
AE	adverse effect
AIDS	acquired immune deficiency syndrome
BB	benzyl benzoate
CDC	Centers for Disease Control and Prevention
CEPA	Californian Environmental Protection Agency
CHMP	Committee for Medicinal Products for Human Use
Cl2CA	*cis*/*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid
CVA	*cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
DCCA	3-(2,2 dichlorovinyl)-2,2-dimethyl-(1-cyclopropane) carboxylic acid
DEET	N,N-diethyl-m-toluamide
EU	European Union
FDA	Food and Drug Administration
GBHC	gamma benzene hexachloride
IARC	International Agency for Research on Cancer
ICH	International Conference on Harmonisation
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
MA	marketing authorisation
mITT	modified intention-to-treat
NfG	Note for Guidance
NS	non-significant
PBacid	3-phenoxybenzoic acid
PBPK	physiologically based pharmacokinetic model
PP	per protocol
SAE	serious adverse effect
TEAE	treatment emergent adverse events
UK	United Kingdom
US	United States
VAS	visual analogue scale
WHO	World Health Organization

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2.5.1 Product Development Rationale

Permethrin [(±)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate] is a synthetic chemical, a member of the family of pyrethroids. Permethrin was first licensed in 1985 by the US Food and Drug Administration (FDA), and has been used since as an insecticide, acaricide, and insect repellent. It is a first-line treatment for scabies in the United Kingdom (UK), the United States (US), and Australia [redacted]). It is also effective against crab lice and head lice. Permethrin is on the World Health Organization's (WHO) List of Essential Medicines, the most important medications needed in a basic health system (*19th WHO Model List of Essential Medicines, 2015*). Permethrin 5% w/w Dermal Cream is indicated for the treatment of scabies in adults and children > 2 months of age, and crab lice in adults.

Scabies is an intensely itchy parasitic infection of the skin caused by the mite *Sarcoptes scabiei* var *hominis* ([redacted]). It is a common public health problem with an estimated global prevalence of 300 million cases ([redacted] Crusted scabies is a more severe form of the disease ([redacted]). Crusted scabies is also called Norwegian scabies because the condition was first described in Norway in the mid-19th century. Crusted scabies is different from traditional scabies, as there seems to be a problem with the immune response to the mites allowing for the infestation of an individual with hundreds of thousands of the mites. Crusted scabies usually affects people with a compromised immune system and is observed most frequently in the elderly, mentally or physically disabled, and in patients with acquired immune deficiency syndrome (AIDS), lymphoma, or other conditions that decrease the effectiveness of the immune response ([redacted]. In these cases, spread of infection may occur during brief contact or via contaminated objects. Because the mite is very small and is usually not directly visible, initial diagnosis is based on the signs and symptoms. The standard conclusive diagnostic technique consists of mites' identification by microscopic examination of scales obtained by skin scraping ([redacted] Infestation begins when pregnant female mites are transferred from the skin of an infested person to the skin of an uninfested person ([redacted] The disease manifestations are mediated through inflammatory and hypersensitivity reactions to mites and mite products [redacted] Infestation is accompanied by intense itching, papular rash, and emotional disturbance from the concept of arthropod infestation ([redacted]).

There are three types of lice that infest humans: head louse (*Pediculus humanus capitis*), body louse (*Pediculus humanus corporis*), and crab or pubic louse (*Phthirus pubis*). The crab louse is feeding exclusively on blood ([redacted]).

Crab louse is usually found in the person's pubic hair ([redacted]). This human ectoparasite is adapted to a sedentary life style on pubic hair, and sometimes on eyelashes and body hair, not often leaving the infested body. They are usually transmitted during sexual contact, and have been associated with other sexually transmitted diseases ([redacted] . All lice infestations are diagnosed by identification of live adult lice, and viable eggs (nits) on the hair shafts in the specific body regions giving them their names ([redacted]). Empty egg cases attached to hair shafts are not diagnostic of an active infection.

Effective control of scabies and crab lice requires treatment of affected patients, their close contacts, and environmental fomites ([redacted]). Delayed or missed diagnosis, improper application of medication, inadequate treatment, or poor compliance may have serious consequences. Permethrin is indicated for the treatment and prevention of head lice and scabies in exposed individuals ([redacted]). Permethrin formulations include a prescription-only 5% strength for scabies and an over-the-counter 1% strength for lice. Permethrin acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated ([redacted] Delayed repolarization and paralysis of the pests leading to death are the consequences of this disturbance. Although the methodological quality of trials vary [redacted] a meta-analysis suggests that topical permethrin is the most effective intervention against scabies ([redacted]). Treatment with most scabicidal medications calls for treating with an initial dose and re-treating 7 days later; however, the biological basis for when it is optimal to re-treat has not been documented.

This clinical overview of permethrin takes into account that the medicinal product the Marketing Authorisations (MA) will be applied for, Permethrin 5% Cream of [redacted] is therapeutically equivalent with an original medicinal product Lyclear Dermal Clear (Permethrin 5%) Cream of Stiefel Laboratories (Ireland) Limited, Belgium containing permethrin as active substance, a drug product that is already marketed in many European Union (EU) and non-EU countries for more than 10 years.

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According to Article 10, 1(a)(iii) of Directive 2001/83/EC, the applicant is not required to provide the results of pharmacological and toxicological tests or the results of clinical trials if the concerned medicinal product is essentially similar to a product which has been authorised within the Community for not less than ten years and is marketed in the Member State for which the application is made ("Generic" application). Therefore, the nonclinical testing strategy can be found in the dossier of the original product which is at the disposal of the competent Authority concerned and for which a MA has been granted. Therefore, the Applicant's product development rationale was focused on

development of a drug product that complied with the accepted definition of essential similarity, namely to contain the same drug substance that is bioequivalent with the cited Reference Product. The primary requirement, apart from compliance with all current and applicable regulatory requirements, International Conference on Harmonisation (ICH) requirements, and Note for Guidance (NfG) and other Committee for Medicinal Products for Human Use (CHMP) guidance, was to ensure that the product demonstrated equivalent therapeutic efficacy, had a similar impurities / related substances profile to the cited Reference Product, and used recognised excipients, thereby ensuring an equivalent efficacy and safety profile to the Reference Product.

The present overview provides critical evaluation of clinical data on the efficacy and tolerability of permethrin together with the results of a bioequivalence study demonstrating that Permethrin 5% Cream of [redacted], [redacted] is bioequivalent to Lyclear Dermal (Permethrin 5%) Cream, MA holder is Omega Pharma Ltd., UK. All efficacy and safety data discussed here were retrieved from publicly available literature.

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2.5.2 Overview of Biopharmaceutics

2.5.2.1 Overview of Reference Formulation and Similarity

A randomized, double-blind, multicentric, parallel group, comparative clinical study of Permethrin 5% cream of [redacted] Test) vs Permethrin 5% cream of Medgenix Benelux NV (Belgium) (Reference) was carried out for the treatment of scabies (*Clinical Study Report ECTS/19/002*).

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The primary objective of the study was to compare clinical effectiveness (with clinical endpoint) of Permethrin 5% Cream of [redacted] (Test) vs Permethrin 5% Cream of Medgenix Benelux NV (Belgium) (Reference) for the treatment of Scabies. The secondary objective was to evaluate and compare the safety and tolerability of Permethrin 5.0% w/w Cream of [redacted] (Test Product) with Permethrin 5.0% w/w Cream manufactured by Medgenix Benelux NV (Belgium) (Reference Product) for the treatment of scabies. Subjects reported to the study site for following visits:

- Visit-1: Screening, Day -5 to 1 (Up to 5 days of randomization), Randomization & Hospitalization Check in Day 1, Check out Day 2
- Visit-2: Evaluation visit: Day 7 ± 1 day
- Visit-3: Follow up Visit: Day 14 ± 2 days
- Visit-4: End of study Visit: Day 28 ± 2 days

After informed consent process and completion of all screening assessments, and once all the inclusion/exclusion criteria were met, the eligible subjects were enrolled in the study. Subjects with confirm diagnosis of scabies were consider qualified for inclusion in this study. Clinical diagnosis was done by presence of scabies severity, subjective assessment and objective assessment based on VAS score. Dermoscopic and microscopic examination was also done for the confirmation of presence of viable mites. Urine pregnancy test for female subjects was performed during screening visit.

Screening and randomization considered as Visit-1, which could be either on same day or on different day. On day of randomization, subjects were instructed to report in the evening for hospitalization. Hospitalised subjects were asked to take bath and pat dry the skin with clean towel. The investigational product (IP) whether test or reference was provided to subject randomly in 1:1 respectively with blinding and informed subjects to apply one tube (Permethrin 5% cream, 30 gm) (or more, if required)

topically on the entire surface of skin of the body from neck to toe, particularly areas between fingers and toes, under the arms, under the fingernails and toenails, writs, external genitalia, buttocks which is clean, dry and cool and as per instruction given to him/her. Study medication was dispensed by the site staff to qualified subjects. After application, site reaction and eye irritation were evaluated immediately and after 1 hr of the IP application. IP was allowed to remain in contact with the skin for at least 8 to 14 hours overnight. Next day morning, an assessment of eye irritation and application site reaction was performed.

Subjects were instructed to take post-dose bath with warm water not earlier than 8 hours after application. Each subject was instructed on how to prevent re-infection after check out from hospital. Subject diary was provided to each subject to record side effects and concomitant medication detail. Subjects were trained via detailed and translated instructions in the subject diary on how to record detail of side effects and concomitant medication. All subjects were instructed to complete the subject diary if any side effect found or any concomitant medication taken. All close family members of the subject were also given standard treatment for scabies to prevent re-infection at home.

After check out from hospital, follow up visit was performed on day 7 (Visit 2) and day 14 (Visit 3) and end of study visit was performed on day 28 (Visit 4).

Physical examination was done during screening, at each evaluation, and at follow visit until the end of study. At each visit, subjects were carefully monitored for all adverse events. Vital signs (like blood pressure, pulse, respiratory rate and oral body temperature) were measured at pre-dose and post dose and at each visit until the end of study. Subjective and objective assessment was done at each follow up visit after randomization until the end of study including dermoscopic and microscopic examination. Application site reaction (such as erythema-redness, edema-swelling, pruritus-itching, rash, burning/stinging, pain, numbness, tingling) was assessed at each evaluation and follow up visit until the end of study.

Overall, [redacted] subjects were screened and randomised in the study. Subjects no. 0103, 0109, 0110, 0227, 0229, 0230, 0235 & 0237 received single study medication after randomization number and return for at least one post-baseline evaluation visit but did not completed the study hence, these subjects were considered for statistical analysis for mITT population but not considered for PP population and Subjects no. 0139 & 0207 did not visited the study site after received the randomization number hence, they were not considered for statistical analysis for PP population & mITT population as per protocol & SAP.

The primary endpoint was as follows:

- Proportion of responder during the 28 ± 2 days compared between treatments. The responder defined as patients with no scabies remaining and at least 50% improvement in the VAS score for pruritus.

There were four secondary variables:

- Dermoscopy & confirmation of absence of mites, eggs/ova and/or mite feces by Microscopy.
- Reported reduction or absence of pruritus (itching).
- Clinical visual reduction or absence of scabietic lesions.
- Percentage reduction in VAS scores for pruritus.

Safety endpoints were:

- Spontaneously reportable and directly observable adverse events including local skin irritation to application site after first application until post treatment follow-up.
- Eye irritation.

Statistical analysis was performed on the data to determine clinical effectiveness (with clinical endpoint) of test formulation to the reference formulation by [redacted]. Statistical analysis was performed by SAS® (software version 9.4) to compare the proportion of responder on the 28 ± 2 days between two treatments (Test vs Reference). In primary analysis, the following criteria were considered:

1) Patients with no scabies remaining.
2) At least 50% improvement in the VAS scores for pruritus.
3) During the treatment duration of 28 ± 2 days, if subject satisfy criteria 1 and 2 at any visit then subject was to be considered as responder and to be discontinue from the study considering study completion status 'Yes'.

Based on the above definition subjects were to be identified as responder and non-responder and both the treatments were compared based on the frequency of the responder from the total number of subjects. Fisher's exact test was used to check equivalence in proportion of responder during the 28 ±2 days between Permethrin 5% Cream of [redacted] and Permethrin 5% cream of Medgenix Benelux NV (Belgium). Five (5%) level of significance was used. As additional information, 90% confidence interval with yate's correction was provided for the difference in the proportion of responder during 28 ±2 days between both the groups. Summary of scabies score was provided visit wise with descriptive statistics and analysis of mean change in severity score of scabies from baseline to Day 14 and Day 28 was provided for mITT and PP population. As additional information, dermoscopic

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and microscopic outcome and 50% improvement in pruritus VAS scale for evaluation of the responders and non-responders was also performed and presented.

In secondary analysis, the following criteria were considered:

1) Dermoscopy & microscopy: confirmation of absence of mites, eggs/ova and/or mite feces by Microscopy.
2) Subject assessed: Reported reduction or absence of pruritus (itching).
   Reduction or absence of pruritus was summarized and listed by visit and treatment.
   The reduction was summarized also using shift tables.
3) Clinical Visual reduction or absence of scabietic lesions.
   Reduction or absence of scabietic lesions was summarized and listed by visit and treatment. The reduction was analyzed between treatments using change from baseline in total number of scabietic lesions using ANCOVA with baseline as covariate and the treatment is effect. The change from baseline was summarized visit wise. The within treatment comparison was performed using paired t-test.
4) Percentage reduction in VAS scores for pruritus.
   Reduction or absence of scabietic lesions was summarized and listed by visit and treatment. The reduction was analyzed between treatments using change from baseline in number of scabietic lesions using ANCOVA with baseline as covariate and the treatment is effect. The change from baseline was summarized visit wise. The within treatment comparison was performed using paired t-test.

Statistical analysis was done on PP and mITT population. Results are summarized in Tables 1-8 below.

Table 1 Analysis for proportion of responder on no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study (PP population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted]) n (%)	p-value
Responder	[redacted] (58.97%)	[redacted] 51.22%)	0.5090

Non-Responder	[redacted] (41.03%)	[redacted] (48.78%)	

Table 2 90% confidence interval of responder on no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study (PP population)

	Test [redacted]) n (%)	Reference [redacted]) n (%)	90% Confidence Interval
Responder	23 (58.97%)	21 (51.22%)	(-12.99, 28.50)
Non-Responder	16 (41.03%)	20 (48.78%)	

Table 3 Analysis for proportion of responder on no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study (mITT population)

	Test (N=[redacted] n (%)	Reference (N=[redacted] n (%)	p-value
Responder	[redacted] (54.76%)	[redacted](54.35%)	1.0000
Non-Responder	[redacted] (45.24%)	[redacted] (45.65%)	

Table 4 90% confidence interval of responder on no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study (mITT population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted] n (%)	90% Confidence Interval
Responder	[redacted] (54.76%)	[redacted] (54.35%)	(-19.34, 20.17)
Non-Responder	[redacted] (45.24%)	[redacted] (45.65%)	

For Tables 1 to 4, responder is defined as subjects with no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study.

Table 5 Analysis for proportion of responder on Dermoscopy and Microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study (PP population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted] n (%)	p-value
Responder	[redacted] (97.44%)	[redacted] (95.12%)	1.0000
Non-Responder	[redacted] (2.56%)	[redacted] (4.88%)	

Table 6 90% confidence interval of responder on Dermoscopy and Microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study (PP population)

	Test (N[redacted]) n (%)	Reference (N=[redacted] n (%)	90% Confidence Interval
Responder	[redacted] 97.44%)	[redacted] (95.12%)	(-7.11, 11.74)
Non-Responder	[redacted] (2.56%)	[redacted] (4.88%)	

Table 7 Analysis for proportion of responder on Dermoscopy and Microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study (mITT population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted] n (%)	p-value
Responder	[redacted] (92.86%)	[redacted] (95.65%)	0.6664
Non-Responder	[redacted] (7.14%)	[redacted] (4.35%)	

Table 8 90% confidence interval of responder on Dermoscopy and Microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study (mITT population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted] n (%)	90% Confidence Interval
Responder	[redacted](92.86%)	[redacted] (95.65%)	(-13.27, 7.68)

Table 8 90% confidence interval of responder on Dermoscopy and Microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study (mITT population)

	Test (N=[redacted]) n (%)	Reference (N=[redacted]) n (%)	90% Confidence Interval
Non-Responder	[redacted] (7.14%)	[redacted] (4.35%)	

For Tables 5 to 8, responder is defined as subjects with dermoscopy and microscopy evaluation and at least 50% improvement in the VAS scores for pruritus at the end of study.

Safety results

The number of application was once only on randomization day in both groups. Overall, exposure duration and actual application of study treatment were similar in both groups. None of the subject required redosing as there was no reinfection found in any of the subject during evaluation visit of Day 7.

No serious adverse event (SAE) was reported during the study. Ten adverse events (AEs) were reported in [redacted] subjects during the study. All the AEs were reported after randomization and referred as treatment emergent adverse events (TEAE). Among the 10 TEAEs, 5 TEAEs were reported in [redacted] subjects (9.09%) receiving test product and [redacted] TEAEs were reported in [redacted] subjects (8.70%) receiving reference product. Reported TEAEs were mild in severity. The adverse events in any treatment group were eye burning immediately after the application and 1 hr after application and skin burning. Most of the reported TEAEs were possibly related to study drug and were recovered/resolved.

Mean value of each vital sign (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and body temperature) was comparable in the both treatment groups. All the other values were within clinically acceptable limits. There was no such difference for the rest of reported application site reaction across the treatment groups. Overall, incidence of application site reaction was comparable across the treated groups at end of study visit.

2.5.2.2 Comparative *In Vitro* Release Characteristics

N/A

2.5.2.3 Comparative *In Vivo* Release Characteristics

N/A

2.5.2.4 Conclusions on Biopharmaceutics and Essential Similarity

Based on results summarized in Table 1, there is no statistically significant difference observed ($p > 0.05$) between Test and Reference product in terms of responder on no scabies remaining and at least 50% improvement in the VAS scores for pruritus at the end of study (PP population). Hence, Permethrin 5% Cream of [redacted] (Test) and Permethrin 5% cream of Medgenix Benelux NV (Belgium) (Reference) were concluded as therapeutically equivalent.

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2.5.3 Clinical Pharmacology

2.5.3.1 Pharmacokinetics

2.5.3.1.1 Absorption

Permethrin is virtually insoluble in water (< 0.00495 to 0.18 mg/L at 20 °C) and is readily soluble in all solvent (> 250 g/L at both 20°C and 30°C). The molecule is highly lipophilic with a log P_{ow} of 4.67 ± 0.01 at 25°C and is absorbed slowly through the skin, which usually prevents systemic toxicity. The percutaneous absorption of permethrin is generally lower in humans than other mammalian species ([redacted]; [redacted] The Burroughs Wellcome Co submission for approval by regulatory agencies in several countries included the results of 11 clinical trials of Nix and Elimite conducted between 1977 and 1984, in which the two permethrin-containing products were applied to the skin of human volunteers and the percutaneous absorption measured ([redacted]). More than 100 volunteers were included in these studies and exposures ranged from single applications to weekly treatments over 8 weeks. No quantifiable levels of intact permethrin were found in plasma or urine after treatments. The maximum percutaneous absorption from 5% permethrin cream (Elimite) calculated by measurements of CVA in urine was 2.08% of the applied dose, and the mean percentage absorbed was less than 1%. Based on these studies, a dermal absorption rate of 2% was assumed for humans by the Medical Toxicology and Worker Health and Safety Branches of the Department of Pesticide Regulation of Californian Environmental Protection Agency (CEPA) in their risk characterization of permethrin [redacted]

Because of the concern for potential neurotoxic effects (central nervous system excitation, convulsions) in the treatment of scabies, percutaneous absorption of 1% lindane lotion and 5% permethrin cream was compared as alternative scabicides [redacted]). *In vitro* percutaneous absorption of the two products was identical in guinea pig skin; however, human skin was 20-fold more permeable to lindane than to permethrin. *In vivo* guinea pig blood and brain levels of lindane were fourfold greater than permethrin levels (Fig. 1). In conclusion, the risk for toxic effects, as assessed by systemic exposure during overuse conditions, is projected to be 40 to 400 times lower for 5% permethrin cream than for 1% lindane lotion.

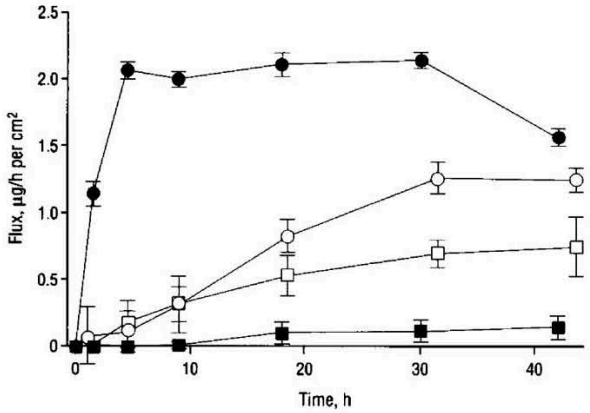

Figure 1 *In vitro* rate of penetration profiles for lindane and permethrin in guinea pig and human skin. Values are means measured from two guinea pigs and three human donors (at least two determinations for each donor and animal). The applied dose was 10 µL of each product (100 µg of lindane, 465 µg of permethrin). Bars indicate SEs. □ Guinea pig skin, 5% permethrin; ○ Guinea pig skin, 1% lindane; ■ Human pig skin, 5% permethrin; ● Human skin, 1% lindane.

Dermal absorption of permethrin in human skin has been studied *in vitro* [redacted] Dermatomed skin from human cadavers was mounted in flow-through diffusion cells, and ^{14}C-labeled cis-permethrin (10 and 100 nM) was applied in acetone to the skin. Fractions of receptor fluid were collected every 4 h. At 24 h, the skins were washed to remove unabsorbed chemical. In human skin, 2% of the dose of permethrin was detected in the receptor fluid for both dose levels at 24 h (Fig. 2). About 70% of the dose was removed by the skin wash and 22–25% remained in the skin.

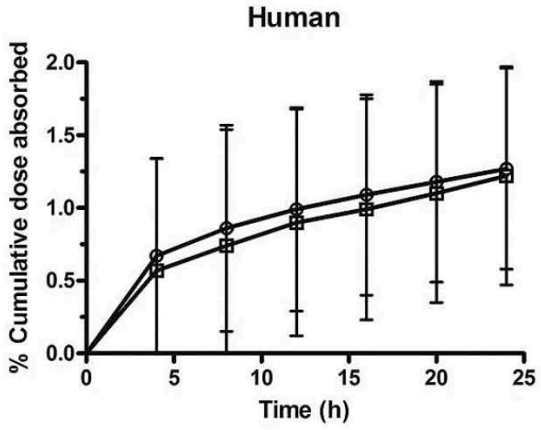

Figure 2 Cumulative percent of the dose of [^{14}C]-permethrin detected in receptor fluid over 24 h after application to human skin. Doses of [^{14}C]-permethrin were 10 (□), and 100 (○) nM and were applied in acetone. Data represents mean ± SD, n = 3.

Similar observation was made when ^{14}C-permethrin in ethanol solution was applied to freshly excised human skin in an *in vitro* test system predictive of skin absorption in humans ([redacted] Twenty-four hours after application, the radiolabel recovered from dermis and receptor fluid was summed to determine percent absorption. At doses of approximately 2.25, 20, and 200 µg/cm^2 permethrin, values of 1, 3, and 2%, respectively, were obtained for percutaneous absorption (Table 9).

Table 9 Disposition of radioactivity, expressed as percent of applied radioactive dose, following topical application of radiolabelled permethrin to excised human skin

Item	Permethrin dose (µg/cm^2)		
	2.25	20	200
Skin decontamination	85 ± 6	79 ± 9	79 ± 7
Epidermis	3.1 ± 1.1	3.8 ± 1.6	2.0 ± 1.1
Dermis	1.1 ± 1.1	2.5 ± 3.7	2.0 ± 1.7
Receptor fluid	0.23 ± 0.10	0.20 ± 0.09	0.10 ± 0.04
Total recovery [a]	97 ± 1	96 ± 2	96 ± 3
Percutaneous absorption [b]	1.3 ± 1.1	2.7 ± 3.6	2.1 ± 1.7

Values are mean ± 1 SD of 9 replicates. Application area was 0.8 cm^2, and application volume was 5 µL.
[a] Total recovery includes small amounts of radioactivity recovered from decontamination of cells. [b] (Receptor fluid + dermis).

To assess the human tolerance, absorption, and persistence of permethrin when used against human lice, ten adult volunteers (four men, six women) were treated with 15-40 mL of permethrin (25:75) (1%) head louse solution ([redacted]). Their hair was allowed to dry naturally and then washed with baby shampoo. Urine samples were collected at 0-24, 24-48, 120-144, and 336-360 hr to measure dermal absorption. Permethrin excretion during the first 24 hr was only about 1% of the applied dose, while the cumulative maximum over 14 days was only about 5.5 mg.

The systemic exposure of permethrin and the duration of residence in the human body were determined following topical administration ([redacted] . The study consisted of three parts. In six young healthy men (Part 1), 50 ml of an ethanolic solution containing 215 mg permethrin (cis/trans: 25/75) was administered to the hair of the head. In another six young healthy men (Part 2) and in six male or female scabies patients (Part 3), 60 g of cream containing 3 g permethrin was administered to the skin of the whole body. Urine was collected up to 168 h post-dose. Urinary excretion of the main metabolite of permethrin, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (CVA) and its conjugates were measured using a gas chromatography/electron capture detection method. Pharmacokinetics were similar in

all study conditions. The time of maximal urinary excretion rate was 12.3, 20.0 and 14.6 h, terminal elimination half-life was 32.7, 28.8 and 37.8 h and urinary recovery of the metabolite reached 0.35, 0.47 and 0.52 % of the permethrin dose, respectively, in Parts 1, 2 and 3 (means).

Ten scabies patients (five men and five women) had about 25 g (range, 21-32 g) of a 5% permethrin cream applied to the skin of the whole body, with the exception of the head and neck ([redacted]). Dermal absorption of permethrin was calculated from the quantity of conjugated and nonconjugated cis- and trans- CVA metabolites of permethrin determined in the urine. In samples of urine collected by seven patients one and two days after application of the permethrin cream, 414 and 439 µg mean total CVA were found, respectively. The mean total CVA in the urine of three patients who collected their urine in the same container for two days was 1435 µg. The urinary concentration of trans-CVA varied during the first 48 h from 0.11 to 1.07 µg/mL and that of the cis-isomer from 0.02 to 0.21 µg/mL CVA was still detectable in the urine of three patients after a week and in the urine of one the patients, reported to be an alcoholic, after two weeks. The absorption of permethrin over the first 48 h after application was estimated from the urinary CVA excretion levels to be 6 mg (range, 3-11 mg), i.e., 0.5% of the dose applied.

Among approximately 350 people who were individually dusted against body lice with 30-50 g of powders containing 2.5 or 5.0 g/kg permethrin (cis:trans, 25:75), the mean amount of permethrin absorbed during the first 24 h after treatment was estimated to be 14 µg/kg among 19 of the subjects using the powder containing 2.5 g/kg permethrin and 39 µg/kg among 15 of the subjects using the 5 g/kg powder. No residue was found in samples of urine taken 30 and 60 days after treatment [redacted]).

The estimated *in vivo* human dermal absorption factors ranged from 1.4% to 5.7% using the rat and human *in vitro* dermal absorption data with the rat *in vivo* dermal absorption data. Based on the rat *in vivo* study, the increase in absorption at 120 hours indicated that radiolabel (permethrin) remaining in the skin after washing at 24 hours was bioavailable. Therefore, 5.7% should be considered as the estimated human dermal absorption factor for risk assessment purpose ([redacted]).

2.5.3.1.2 Distribution

There have been no studies conducted on the distribution of permethrin in the tissues of primates, including humans. Although there is some information on the distribution of permethrin in tissues of mammals, the majority of this information has been obtained in rodents. Pyrethroids are lipophilic molecules that generally undergo rapid absorption and distribution following ingestion by mammals ([redacted] . Unless isolated in

lipid depots, they are quickly metabolized and eliminated from the body. In the rat, *cis* permethrin is retained longer than its more metabolically labile *trans* isomer.

The amount of the permethrin in the tissues is of some importance even at concentrations that are lower than the concentrations necessary to produce neurotoxicity. Studies using human skin fibroblast androgen receptors have demonstrated that nonsteroidal compounds, including permethrin, can interact competitively with human androgen receptors and the sex hormone binding globulin ([redacted]). Those studies provide a mechanism by which chronic exposure of humans to pesticides containing nonsteroidal compounds might result in endocrine disturbances relating to androgen action.

2.5.3.1.3 Metabolism

Because permethrin is neurotoxic and carcinogenic in laboratory animals at high doses, an understanding of its metabolic fate after absorption, regardless of the route, is useful. It is most likely that the liver is quantitatively the most important site for permethrin biotransformation. Given what is known about the similarities in biotransformation enzymes in animals and humans, it is also likely that the metabolic pathway operant in animals will be present in humans ([redacted]).

The proposed metabolic pathway for *cis*- and *trans*-permethrin include five principle sites of metabolic actions in both permethrin isomers (ester cleavage, oxidation at the *trans*- and *cis*-methyl of the geminal dimethyl group of the acid moiety, and oxidation at 2'- and 4'- position of the phenoxy group) ([redacted]). Conjugation of the resultant carboxylic acids, alcohols, and phenols with glucuronic acid, glycine, and sulfuric acid occur to varying extent. *cis*-Permethrin is more stable then *trans*-permethrin, and the *cis* isomer yielded four faecally excreted ester metabolites that resulted from hydroxylation at the 2'- or 4'-position of the phenoxy-group or at the *trans*- or *cis*-methyl group on the cyclopropane ring. The ester cleaved metabolites are extensively excreted into the urine whereas the metabolites retaining an ester bond were found only in the faeces. The major metabolite from the acid moiety of both isomers was *cis*/*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (Cl2CA) in free (1-8%) and glucuronide (14-42%) forms. Other significant metabolites were *trans*-OH-Cl2CA (1-5%) and *cis*-OH-Cl2CA in the free (3-5%), lactone (0-4%) and glucuronide (1-2%) forms. On the other hand, the alcohol moiety released after cleavage of the ester bond of both isomers was converted mainly to the sulphate of 3-(4'-hydroxyphenoxy) benzoic acid (4'-OH-PBacid) (29-43% of the dose) and 3-phenoxybenzoic acid (PBacid) in the free (1-10%) and glucuronide (7-15%) forms. Other significant metabolites of the alcohol moiety were PBalc, PBacid-glycine and the sulphate of 3-(2'-hydroxyphenoxy) benzoic acid

(2'-OH-PBacid). [1RS,*trans*]- and [1RS,*cis*]-permethrin showed no significant differences in metabolic fate in the rat from [1R,*trans*]- and [1R,*cis*]-permethrin, respectively.

The metabolism of *cis*-permethrin in human hepatic microsomes are solely the result of oxidative processes ([redacted]). With *trans*-permethrin, hydrolysis was slightly greater and lower than oxidation in human hepatic microsomes, respectively.

Percentage metabolism of *cis*- and *trans*-permethrin by human P450 isoforms is shown in Table 10.

Table 10. Percentage metabolism of *cis*- and *trans*-permethrin by human P450 isoforms

Isoform	*cis*-Permethrin	*trans*-Permethrin
CYP1A1	13.3 ± 3.8	27 ± 2.6
CYP1A2	22 ± 2.6	24.3 ± 2.1
CYP2B6	NS	NS
CYP2C8	19.3 ± 2.3	18.3 ± 2.5
CYP2C9*1	39.3 ± 2.9	NS
CYP2C9*2	NS	22.6 ± 2.1
CYP2C9*3	NS	NS
CYP2C19	83.3 ± 4.5	89.7 ± 0.6
CYP3A4	25 ± 9.6	NS

NS – Non-significant difference. The percentage metabolism of pyrethroids by human P450s was assessed by a one-sample t-test. Values that were not significantly different from 0 were labelled NS ($p < 0.05$).

A physiologically based pharmacokinetic (PBPK) model of deltamethrin disposition was modified to describe permethrin kinetics in the rat and human ([redacted] Unlike formulated deltamethrin, which consists of a single stereoisomer, permethrin is formulated as a blend of *cis*- and *trans*-diastereomers. Time courses were assessed for *cis*-permethrin and *trans*-permethrin in several tissues (brain, blood, liver, and fat) in the rat following oral administration of 1 and 10 mg/kg permethrin (*cis*/*trans*: 40/60). Hepatic intrinsic clearance of *cis*- and *trans*-permethrin in rat and human microsomal fractions determined from individual isomers and as part of 40:60 *cis*/*trans* blend is show in Fig. 3.

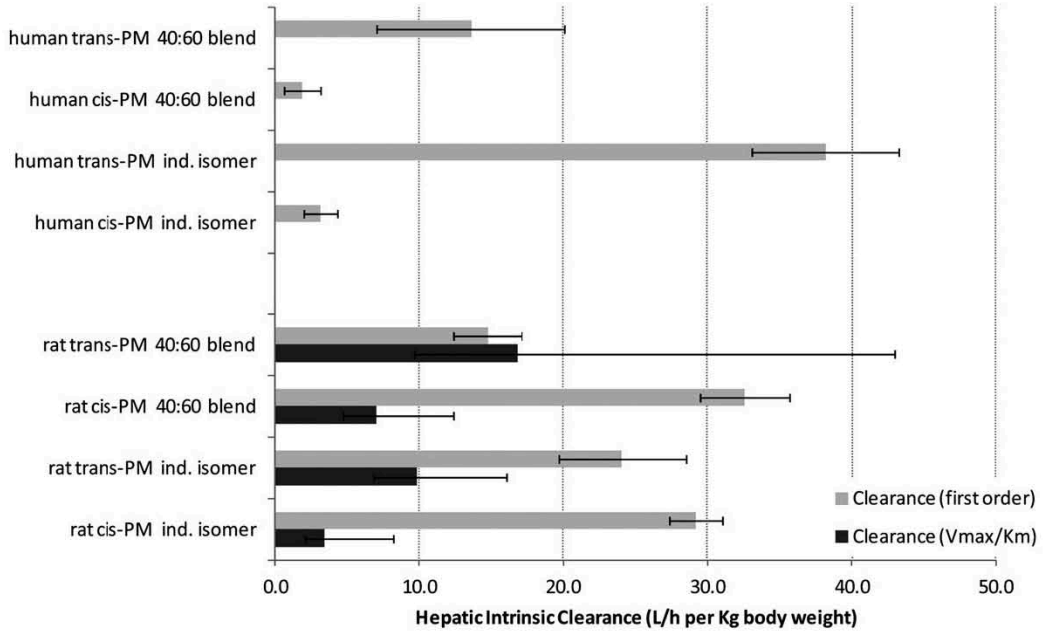

Figure 3. Clearance of *cis*- and *trans*-permethrin in rat and human microsomal fraction determined from individual isomers and as part of 40:60 *cis*/*trans* blend. Clearance rates were determined by the half-life approach ([substrate] << Km) or the Michaelis-Menten constants ($V_{max}/_{Km}$).

Urinary metabolites accounted for 35–60% of the oral dose of permethrin. In contrast, urinary metabolites accounted for 0.1–1.2% of the applied dermal dose.

Neither permethrin nor its hydroxyl derivatives (Fig. 4a) are eliminated in urine. However, hydrolysis of *cis*- and *trans*-permethrin (Fig. 4c) renders phenoxybenzoic acid (3-PBA) and *cis*- or *trans*-3-(2,2 dichlorovinyl)-2,2-dimethyl-(1-cyclopropane) carboxylic acid (*trans*-DCCA), each of which is excreted in urine. Hydroxylation by

cytochrome P450 (Fig. 4b) at the carbon proximal to the ester results in ester cleavage, rendering 3-PBA and DCCA.

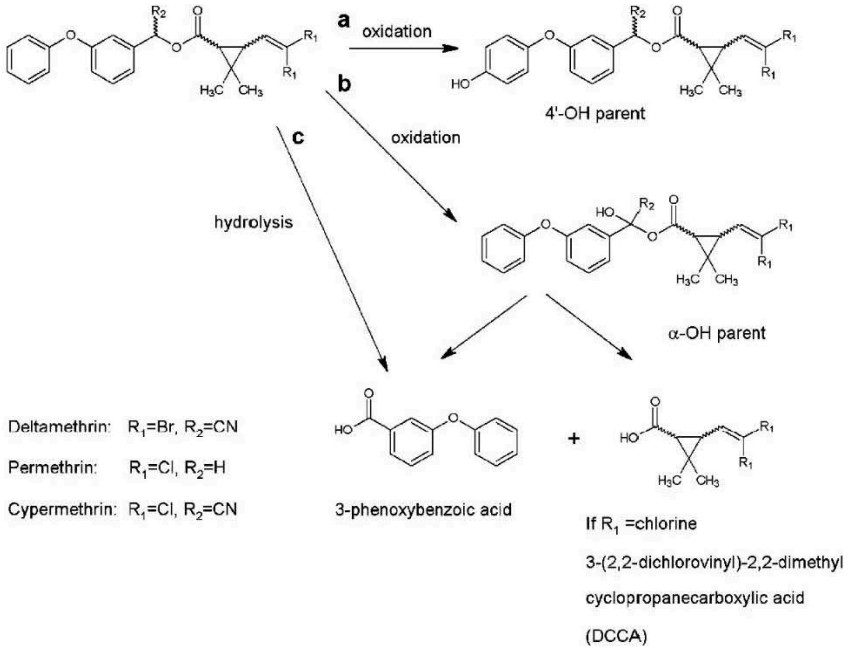

Figure 4. Metabolic clearance of permethrin [1RS, 3RS:1RS, 3RS (*cis/trans*)], cypermethrin [RS- α-cyano; 1RS, 3RS; 1RS, 3SR (*cis/trans*)], or deltamethrin-[1R; *cis*; alpha S]. Oxidation via cytochrome P450 yields hydroxyl derivatives (a) of the parent compound (e.g., 4-hydroxy permethrin). An important pathway for urinary metabolite of *cis* isomers, oxidation leads to ester cleavage products following hydroxylation at the carbon proximal to the ester (b) Hydrolysis (c), via carboxylesterases, yields a dichlorovinyl acid (permethrin, cypermethrin) or dibromovinyl acid (deltamethrin) and phenoxybenzyl alcohol. (*Tornero-Velez et al., 2012*).

2.5.3.1.4 Elimination

The metabolites are primarily 3-phenoxybenzyl alcohol and its oxidation products, which are rapidly excreted in urine. The other hydrolysis products are dimethyl or dichlorovinyl acids, which are partially hydroxylated and rapidly excreted. In radiolabel experiments, no accumulation of the parent compounds or of their metabolites was observed ([redacted] .

Two human volunteers, who consumed about 2 and 4 mg of permethrin (25:75), respectively, excreted 18-37% and 32-39% of the administered dose, detected as the metabolite $C_{12}CA$, after acid hydrolysis of their urine collected over 24 hr ([redacted])

2.5.3.2 Pharmacokinetics in Special Populations

2.5.3.2.1 Renal Impairment

No data can be retrieved on how renal function may affect the elimination of permethrin. However, only about 0.3% to 2% of the topically applied dose of ^{14}C-labelled permethrin is excreted in urine. Since topical permethrin is metabolized in the liver and excreted in the urine as inactive metabolites, there does not appear to be an increased risk of toxic reactions in patients with impaired renal function when used as labelled ([redacted]).

2.5.3.2.2 Hepatic Impairment

No data can be retrieved on how hepatic function may affect the elimination of permethrin. However, permethrin is a neurotoxin that is metabolized in the liver to inactive metabolite. As a result, impaired liver function may interfere with detoxicating metabolic processes.

2.5.3.2.3 Age

Clinical studies of permethrin cream, 5% did not identify sufficient numbers of subjects aged 65 and over to allow a definitive statement regarding whether elderly subjects respond differently from younger subjects ([redacted]). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. This drug is known to be substantially excreted by the kidney. However, since topical Permethrin is metabolized in the liver and is excreted in the urine as inactive metabolites, there does not appear to be an increased risk of toxic reactions in patients with impaired renal function when used as labelled.

2.5.3.2.4 Gender

No gender related data could be retrieved on permethrin pharmacokinetics.

2.5.3.3 Clinically Relevant Pharmacokinetic Interactions

No data can be retrieved on clinically relevant pharmacokinetic interactions in humans. The possibility for enhancement of permethrin transdermal absorption by N,N-diethyl-m-toluamide (DEET) has been reported using the hairless mouse skin as a barrier membrane ([redacted]). Subchronic dermal application of DEET and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum ([redacted]). These results suggest that DEET used in combination with permethrin might serve to facilitate the absorption of permethrin through the skin, and these observations may be of relevance in human applications.

2.5.3.4 Pharmacodynamics

2.5.3.4.1 Pharmacology and Mode of Action (Primary Pharmacodynamics)

Pyrethroids can be classified into two types based on the signs of toxicity to mammals ([redacted] and to cockroaches ([redacted]): Type I and Type II compounds. 1R- *cis*- and 1R- *trans*-permethrin belong to Type I. Permethrin is a neurotoxin; it interacts with a fraction of the voltage-dependent sodium channels in excitable membranes that produce a prolongation of the inward sodium current during excitation, in which the channels remain open much longer than normal ([redacted]). Delayed repolarization results in paralysis of the nerves in the exoskeletal respiratory muscles of the parasite leading to death. Membrane depolarization might also result in enhanced neurotransmitter release and eventually blockage of excitation. Although postsynaptic neurotransmitter responses can be suppressed by pyrethroids, doses must be higher than those that produce effects on sodium channels ([redacted]). Electrophysiological recordings from dosed cockroaches reveal trains of cercal sensory spikes and, sometimes, spike trains from the cercal motor nerves and the central nervous system. The signs of poisoning caused by Type I pyrethroid compounds are restlessness, incoordination, hyperactivity, prostration, and paralysis ([redacted] .

Pyrethroid containing products including permethrin were tested ([redacted]). S*arcoptes scabiei* var suis mites were collected from experimentally-infected pigs. The study was performed in triplicate under room conditions and the mites were inspected under a stereomicroscope at intervals (5, 10, 15, 20, 25, 30, 40, 50, 60 min, 2, 3, 4, 5 and 24 h) after exposure to the products. The median survival time was 50 ± 30.4 min and 120 ± 309 min when mites were exposed to permethrin 4 % and 0.6%, respectively.

The efficacy of a 65% permethrin spot-on formulation against the dog louse, *Trichodectes canis* de Greer 1778, was studied ([redacted]). Fourteen dogs naturally infested with *T. canis* were evenly and randomly allocated to treatment with 65% permethrin administered at the label dose rate of 1 or 2 ml per dog or to an untreated control group. Louse counts were performed on Days 0 (pretreatment), 7, 14, 21, and 28. Lice were eliminated from all dogs treated with the 65% permethrin spot-on within 7 days after treatment, and no subsequent reinfestations due to hatching of eggs were observed during the 28-day evaluation period. Untreated control dogs were subsequently treated with the 65% permethrin spot-on after the initial phase was completed and lice populations were evaluated as previously described. All lice were cleared from these dogs by Day 7, and there were no signs of reinfestation.

2.5.3.4.2 Secondary Pharmacodynamics

The pyrethroid class can modulate the dopaminergic system by up-regulation of dopamine transporter ([redacted]) and by marked increase in dopamine turnover ([redacted]). Permethrin is a potent inhibitor of the mitochondrial complex I ([redacted] Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with permethrin ([redacted]).

2.5.3.4.3 Safety Pharmacology

Permethrin is neurotoxic at high doses ([redacted]). It produces a variety of clinical neurotoxic effects in animals. Some of those effects are tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait; reversible axonal injury occurs at high doses. These symptoms are universal for pyrethroids. Few data are available on the neurotoxic effects of pyrethroids in humans - especially for permethrin.

Nerve conduction studies and interviews of 23 laboratory technicians involved with several pyrethroids in field trials, formulation, or other laboratory work showed no evidence of nerve impairment associated with exposure to permethrin ([redacted]). Symptoms of facial paraesthesia and occasional pruritic rashes were reported among those workers, but symptoms were not clearly related to permethrin.

Systemic symptoms that occurred in the most serious accidental cases were mainly digestive, including epigastric pain, nausea, and vomiting ([redacted]

2.5.3.4.4 Clinically Relevant Pharmacodynamic Interactions

Synergic interaction between pesticides has been widely documented in animals, however, the physiological mechanisms by which an insecticide synergizes another remains unclear ([redacted]). No data could be retrieved on clinically relevant pharmacodynamic interactions in humans.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.4 Overview of Efficacy

2.5.4.1 Efficacy in treatment of scabies

Several clinical trials for the treatment of human ectoparasites have demonstrated the efficacy of permethrin in eradicating the organisms. In clinical studies of over 3500 patients, permethrin was effective. The only expected adverse drug experience associated with permethrin was local irritative symptoms, which ranged in frequency from 2.1% to 5.9% ([redacted]). Many of these symptoms were thought to be the result of the lice infestation. In a 2010 Cochrane review of interventions for treating scabies, randomized controlled trials of drug treatments for scabies were identified ([redacted] and twenty-two small trials involving 2676 people were included. One trial was placebo controlled, 18 compared two or more drug treatments, three compared treatment regimens, and one compared different drug vehicles. A 5% topical preparation was used in each permethrin trial. The number of applications ranged from one (3 trials) to two (2 trials) to two consecutive overnight applications repeated after 14 days (1 trial). Topical permethrin appeared more effective than oral ivermectin (140 participants, 2 trials), topical crotamiton (194 participants, 2 trials), and topical lindane (753 participants, 5 trials). Permethrin also appeared more effective in reducing itch persistence than either crotamiton (94 participants, 1 trial) or lindane (490 participants, 2 trials). No difference was detected between the synthetic permethrin and a natural pyrethrin-based topical treatment (40 participants, 1 trial), and between permethrin and benzyl benzoate (53 participants, 1 trial). The authors conclude that topical permethrin appears to be the most effective treatment for scabies.

In a 2018 Cochrane review, the efficacy and safety of topical permethrin and topical or systemic ivermectin for treating scabies in people of all ages were compared ([redacted]). Fifteen studies (1896 participants) comparing topical permethrin, systemic ivermectin, or topical ivermectin met the inclusion criteria. Treatments with one to three doses of ivermectin or one to three applications of permethrin may lead to little or no difference in rates of complete clearance after four weeks' follow-up (illustrative cures with 1 to 3 applications of permethrin 93% and with 1 to 3 doses of ivermectin 86%; RR 0.92, 95% CI 0.82 to 1.03; 581 participants, 5 studies; *low-certainty evidence*). Reporting of adverse events in the included studies was suboptimal. No withdrawals due to adverse events occurred in either the systemic ivermectin or the permethrin group (*moderate-certainty evidence*). The authors concluded that for the most part, there was no difference detected in the efficacy of permethrin compared to

systemic or topical ivermectin. Overall, few and mild adverse events were reported. Their confidence in the effect estimates was mostly low to moderate. Poor reporting was considered a major limitation. In another systematic review and meta-analysis of randomized controlled trials, the authors concluded that oral ivermectin is less effective than topical permethrin ([redacted]).

In a systematic review and network meta-analysis of 52 randomized controlled trials including 9917 patients, it was found that permethrin (the reference treatment) had a significantly higher cure rate than sulfur, malathion, lindane, crotamiton, and benzyl benzoate ([redacted]). Combination permethrin plus oral ivermectin was ranked highest in terms of cure.

Permethrin resistance in other ectoparasites, such as head lice, is increasing ([redacted]). This suggests that its emergence in scabies mites is a real possibility. In 1994, before widespread permethrin treatment was introduced, all mites were killed within 30 min of *in vitro* exposure to permethrin. By the year 2000, however, 35% of mites were alive after 3 h of exposure and a significant proportion remained alive overnight.

A randomized controlled trial was conducted to compare the efficacy of 5% Permethrin with 10% Crotamiton in 160 patients of scabies (*Rao et al, 2019*). Treatment was effective in 81.3% patients being treated with 5% Permethrin and 53.8% in 10% Crotamiton group. Comparison of treatment showed superiority of 5% Permethrin over 10% Crotamiton ($p = 0.001$). There was no effect of age and gender on this outcome difference.

Permethrin 5% dermal cream was compared in an investigator-blinded, randomized study against lindane 1% lotion for the treatment of microscopically confirmed scabies ([redacted]). Eleven of 23 patients treated with permethrin cream were cured in 2 weeks (48%). Only two patients had scabies 1 month after a single treatment with this product, giving a cure rate of 91%. One of these two patients was considered to have a reinfestation. Only three of twenty-three (13%) patients treated with 1% lindane lotion were free of scabies 2 weeks after a single treatment and fifteen of twenty-three (65%) were cured at 1 month. The higher cure rate at 1 month seen with permethrin cream was significant ($p < 0.025$).

The efficacy of topical permethrin cream was compared with oral ivermectin in the treatment of scabies ([redacted]). Eighty-five consecutive patients were randomized into two groups. Forty patients and their family contacts received 200 µg/kg of ivermectin, and another 45 patients and their family contacts received a single overnight topical application of 5% permethrin cream. Patients were followed up at intervals of 1, 2, 4, and 8 weeks. A single dose of ivermectin provided

a cure rate of 70%, which increased to 95% with two doses at a 2-week interval. A single application of permethrin was effective in 97.8% of patients. One (2.2%) patient responded to 2 applications at a 2-week interval. Permethrin-treated patients recovered earlier. During the trial, a single application of permethrin was superior to a single dose of ivermectin. Two doses of ivermectin were as effective as a single application of permethrin.

The efficacy of topical permethrin was compared with topical lindane in the treatment of scabies in a double-blind, randomized study ([redacted]). All consecutive patients with scabies were randomized into two groups. One group and their family contacts received 5% permethrin cream, and the other group and their family contacts were treated with topical 1% lindane cream. Subsequently, patients were followed up at 2- and 4-week post-treatment. Of the 99 patients enrolled in the study, 52 patients were treated topically with 5% permethrin cream, and 47 patients received 1% lindane cream. Permethrin provided an improvement rate of 84.6% after two weeks, whereas lindane was effective only in 48.9% of patients. Permethrin 5% cream was significantly more effective in the treatment of scabies in comparison with lindane in this study.

Three treatment modalities were compared for safety, efficacy, and economy in scabies ([redacted]) in a prospective, randomized, comparative clinical trial conducted in 103 participants randomly allocated to three groups. The first group received benzyl benzoate (BB) 25% lotion; the second group received permethrin 5% cream; whereas the third group received tablet ivermectin 200 µg/kg as a single dose. Permethrin decreased pruritus by 76% at the end of one week and had significantly better cure rate than ivermectin.

The efficacy of oral ivermectin was compared with commonly used topical antiscabies drugs including topical permethrin 5% cream ([redacted]). This study was conducted in four groups including 60 patients in each group by simple random sampling. Treatment given in each group was: Group 1: ivermectin (200 µg/kg body weight) oral in a single dose, Group 2: topical permethrin 5% cream single application, Group 3: topical gamma benzene hexachloride (GBHC) lotion 1% single application and Group 4: topical benzyl benzoate (BB) lotion 25% single application. All patients were followed for improvement in terms of severity of disease and severity of pruritus at the end of the first week and sixth week. Efficacy of ivermectin, permethrin, GBHC and BB lotion considering improvement in severity of pruritus as parameter were 85%, 90%, 75% and 68.33%, respectively at the second follow-up. Similarly, considering improvement in severity of lesion, results were 80%, 88.33%, 71.66% and 65% respectively at the second follow up. Topical permethrin (5%) was more effective as compared to topical BB lotion and topical GBHC lotion ($p<0.05$, significant) but

statistical difference between efficacy of topical permethrin and oral ivermectin was non-significant (p>0.05).

The efficacy of topical permethrin was compared to oral ivermectin in treatment of scabies in a quasi-experimental study ([redacted]). One hundred-twenty patients of scabies were enrolled and randomly divided in 2 groups of 60 each. Topical 5% permethrin whole body application for 10-12 hours and oral ivermectin (200 µg/kg) were applied in Groups A and B, respectively. Response to treatment was judged on decrease in severity of pruritus, nonappearance of new lesions and absence of burrows. Mean age in Group A (permethrin) was 29.45+9.72 years and in Group B (ivermectin) was 31.45+12.78 years. In both groups, 66.7% patients showed complete cure.

In an open-label, randomized, comparative, parallel clinical trial, the efficacy and safety of topical permethrin, oral ivermectin, and topical ivermectin were compared in the treatment of uncomplicated scabies ([redacted]). Three-hundred fifteen patients were randomly allocated to three groups. The first group received permethrin 5% cream as single application, the second group received tablet ivermectin 200 µg/kg as single dose, and the third group received ivermectin 1% lotion as single application. The primary efficacy variable was clinical cure of lesions. At the end of the first week, cure rate was 74.8% in the permethrin group, 30% in the oral ivermectin group, and 69.3% in the topical ivermectin group ($P < 0.05$). At the end of the second week, the cure rate was 99% in the permethrin group, 63% in the oral ivermectin group, and 100% in topical the ivermectin group ($P < 0.05$). At the end of third week, 100% cure rate was observed in permethrin and topical ivermectin group while 99% in oral ivermectin group.

In an open label randomized comparative study conducted in 210 patients randomly allocated to two groups cost effectiveness of topical permethrin versus oral ivermectin was compared ([redacted]). The first group received permethrin 5% cream as single application, the second group received tablet ivermectin 200 µg/kg as single dose. If there were no signs of cure, the same intervention was repeated at each follow up. At the end of the first week, cure rate was 74.8% in the permethrin group, 30% in the oral ivermectin group. At the end of the second week, cure rate was 99% in the permethrin group, 60% in the oral ivermectin group. At the end of third week, 100% the cure rate was observed in permethrin while 99% in the oral ivermectin group. Topical permethrin was more cost effective than oral ivermectin in treatment of uncomplicated scabies.

The efficacy and safety of permethrin 5% lotion were compared with oral ivermectin for the treatment of scabies ([redacted]). Sixty patients with scabies were enrolled, and randomized into two groups. The first group and their family contacts

received 5% permethrin cream twice with a one-week interval, and the other received a single dose of oral ivermectin. Treatment was evaluated at intervals of 2 and 4 weeks. A single dose of ivermectin provided a cure rate of 62.4%, which increased to 92.8% with 2 doses at a 2-week interval. Treatment with two applications of permethrin with a one-week interval was effective in 96.9% of patients. Permethrin-treated patients recovered earlier. Two applications of permethrin with a one-week interval are more effective than a single dose of ivermectin. Two doses of ivermectin are as effective as a single application of permethrin.

2.5.4.2 Efficacy in treatment of crab lice

Several clinical trials for the treatment of human ectoparasites have demonstrated the efficacy of permethrin in eradicating the organisms in humans. Summaries of clinical trials were reviewed, in which 1% permethrin cream rinse was used to treat body lice (650 subjects), head lice (3,041 subjects), and crab lice (56 subjects), and 5% permethrin dermal cream was used to treat scabies (2,068 subjects) and crab lice (28 subjects) ([redacted]). All trials demonstrated the efficacy of permethrin against human ectoparasites.

Quality of evidence comparing one treatment of pediculosis pubis with another is not available, and most of the recommendations are based on studies on the treatment of head lice ([redacted]). Moreover, due to resistance in head lice, some results may be inapplicable in pubic lice or vice versa. The possibility of resistance to some of the therapies should be considered if the infestation persists, and a different pediculicide should be applied. The recommended regimen for permethrin is to apply 5% cream on wet hair, wash out after 10 minutes (level of evidence IV; grade C recommendation).

Phthiriasis palpebrarum is an ectoparasitosis in which *Phthirus pubis* infests the eyelashes. A case of unilateral phthiriasis palpebrarum with crab louse has been reported ([redacted]). A 45-year-old man presented with conjunctival hyperaemia and moderate itching associated with irritation, and crusty excretions of the eyelashes in the left eye. Careful slit-lamp examination revealed many lice and nits in left eye and mild conjunctival hyperaemia. No abnormality was found in the right eye. On dermatologic examination, only one louse was found at the pubic area. The patient was treated effectively with petrolatum jelly and 1% permethrin shampoo. At the end of the first week, no louse or nit was present on eyelashes and pubic area.

In a 2010 Cochrane review of interventions for treating headlice, randomised trials (published and unpublished) or trials using alternate allocation were identified, which compared pediculicides with the same and different formulations of other pediculicides, and pediculicides with physical methods ([redacted] . Two studies

comparing permethrin with its respective vehicles showed a higher cure rate for the active ingredient than the vehicle. Another study comparing synergised pyrethrins with permethrin showed their effects to be equivalent. The authors conclude that permethrin, synergised pyrethrin and malathion were effective in the treatment of head lice.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.5 Overview of Safety

2.5.5.1 Adverse Events Characteristic of Pharmacological Class

The acute toxicity of synthetic pyrethroid insecticides has been studied extensively ([redacted] . Toxicity is highly dependent on stereochemical structure, with each geometric and/or optical isomer possessing its individual toxic potency. Most products, however, are mixtures of isomers. Occupational exposure to pyrethroids may occur through dermal contact and inhalation of dust and sprays ([redacted] . While inhalation is the main route of exposure in industrial workers, the skin is the main route of exposure in workers applying the compounds in agriculture or public health.

When pyrethroids were introduced in China at the beginning of the 1980s, Chinese cotton growers were not adequately informed about the health risk related to the use of these compounds, and handled them without taking any precautions ([redacted]). As a consequence, in the 1980s, the well-known outbreaks of acute deltamethrin and fenvalerate poisoning described in the literature occurred. Since 1988, no clinical case of occupational pyrethroid poisoning has been reported.

Exposure of the general population may occur by inhalation, skin contact with products, by eating foods containing residues of pyrethroids applied as pesticides or veterinary drugs, or through accidental swallowing or drinking of pyrethroid products. Recent studies carried out in the EU and the US have shown detectable amounts of pyrethroid metabolites in urine samples from the general population ([redacted]). No evidence of adverse effects has been reported for such levels of exposure.

Symptomatic acute cases generally follow accidental overexposure or lack of care in handling the compounds at the workplace, whereas accidental ingestion of high doses is the main cause of poisonings for the general population. Acute poisoning very rarely poses a life-threatening risk to the exposed subjects, but severe poisonings and even potential for causing mortality may arise if concentrated formulations are swallowed [redacted] . In occupational poisonings, the initial symptoms are skin burning, itching or dizziness. These sensations reported in exposed subjects might not be the result of skin reactions, but signs of peripheral nerve involvement ([redacted]; [redacted] About half of the occupational patients develop abnormal facial sensitization (paraesthesia); in the case of swallowing, the main symptoms are epigastric pain, nausea and vomiting ([redacted] . The prognosis of acute occupational poisonings from pyrethroids is usually good, without any chronic or long-term consequence. In follow-up studies, the affected workers showed a complete recovery.

The nervous system is the target organ of the toxic action of pyrethroids, but the effects on the respiratory tract can also be observed, such as massive haemorrhages and oedema of the lungs following inhalation at concentrations above or near lethal concentrations ([redacted]

2.5.5.2 Adverse Events of Permethrin

There are few human studies with permethrin. However, exposures to natural pyrethrins have been associated with dermal, pulmonary, and allergic responses. The allergic responses have been attributed to impurities in the permethrin. Most of the studies of synthetic pyrethroids involved workers applying the chemicals for fly control ([redacted]. Medical examinations, including extensive neurological and electrophysiological examinations, of these individuals failed to demonstrate any abnormality. Skin sensations and paraesthesia have been reported in workers heavily exposed to dermally applied permethrin. These symptoms develop shortly after exposure (with a latent period as short as 30 min), peak by 8 hr, and disappear by 24 hr. Other symptoms that have been reported include numbness, itching, tingling, and a burning sensation. Specific studies of human liver changes have not been conducted, although extensive medical investigations of workers exposed to permethrin did not reveal any clinical chemistry changes (serum enzymes) that would suggest liver toxicity.

In a systematic review, potentially relevant articles were identified through a search of electronic databases, which included all studies of pesticide exposure and human cancer. Eighteen articles were selected, including six identified from the list of references of other articles. The authors concluded, permethrin exposure does not seem to entail a risk of cancer in humans ([redacted]

In a 2010 Cochrane review of interventions for treating scabies, randomized controlled trials of drug treatments for scabies were identified ([redacted]). Twenty-two small trials involving 2676 people were included. No serious adverse events were reported. A number of trials reported skin reactions in participants randomized to topical treatments. There were occasional reports of headache, abdominal pain, diarrhoea, vomiting, and hypotension.

Little information exists on workers who manufacture permethrin. In a study of six Swedish forestry workers who handled seedlings immersed in a 2% aqueous solution of permethrin ([redacted]), airborne permethrin concentrations ranged from 0.01 to 0.09 mg/m^3. No adverse effects of those exposures were noted. In another study of 87 Swedish nursery workers who were studied 1-2 months after the planting season, symptoms of itching and burning skin and respiratory and eye irritation were reported. Symptoms were twice as prevalent among workers exposed to a permethrin mixture of *cis*/*trans* isomers in a ratio of 25:75 than to a mixture of 40:60;

skin and respiratory irritation was reported by 63% of those exposed to a *cis*/*trans* ratio of 25:75 and by 33% of those exposed to a ratio of 40:60. In addition, increased nasal secretions were noted among 13% of those exposed to the 25:75 mixture.

Staff involved with bagging, mixing, or spraying a 5% preparation of permethrin (*cis*/*trans* ratio, 25:75) in Nigeria were evaluated with a questionnaire and urinalysis ([redacted] Although substantial exposures and absorption occurred, as shown by urinary excretion studies, no adverse health effect could be attributed to permethrin exposures in this group.

Among 17 civilian volunteers exposed to 1% permethrin (*cis*/*trans* ratio, 25:75) via skin patches for up to 9 days, two complained of mild erythema and skin irritation ([redacted]).

A group of 10 male volunteer soldiers wore uniforms impregnated with an aqueous solution of 0.2% permethrin (*cis*/*trans* ratio, 25:75) ([redacted] . They were evaluated after 48 hr for their levels of permethrin exposure and for symptoms of toxicity. Their average exposure to permethrin was 3.8 mg/day, and none complained of skin irritation or other health problems.

The production of skin paraesthesia by various pyrethroids, including permethrin, has been examined in human volunteers ([redacted] . Permethrin (0.13 mg/cm^2) was applied on five occasions to 4 cm^2 of an ear lobe; the other lobe had distilled water applied. Evaluation at 48 hr showed that all pyrethroids, including permethrin, produced altered skin sensation. Paraesthesia typically developed within 30-60 min of application, was maximal within 8 hr, and slowly disappeared within 24 hr. The changes caused by permethrin were substantially less than those caused by pyrethroids that contained an α-cyano group.

A Draize repeat insult patch test was performed with 184 subjects who represented both sexes, ranged in age from 18 to 80, and were from all races ([redacted]). A 40% permethrin solution (technical-grade permethrin, 92.5%, and ethanol, 95%) was used. A dose of 0.2 mL was applied to the upper arm or back of each subject and placed beneath an occluded patch 3 times per week for 3 weeks. Two weeks after the induction period, a challenge application was made on a previously untreated site and was removed 72 hr later. Responses were recorded at 96 hr. None of the 184 test subjects showed evidence of allergic contact dermatitis. However, several subjects described a transient burning, stinging, or itching sensation.

Permethrin can induce skin sensations and paraesthesia in exposed workers, which develop after a latent period of approximately 30 min, peak by 8 h and disappear within 24 h. Numbness, itching, tingling, and burning are symptoms frequently reported [redacted]).

2.5.5.2.1 Cardiovascular effects

Examination of 199 workers engaged for 0.5 to 4.5 months in dividing and packaging pyrethroids revealed no aberrations in heart function ([redacted]).

2.5.5.2.2 Respiratory effects

Examination of 199 workers engaged for 0.5 to 4.5 months in dividing and packaging pyrethroids revealed no aberrations in respiratory function ([redacted]

2.5.5.2.3 Nervous System Effects

Permethrin is neurotoxic at high doses; however, there are few data available on the neurotoxic effects of pyrethroids in humans - especially for permethrin. Initial systemic symptoms that occurred in the most serious cases were mainly digestive, including epigastric pain, nausea, and vomiting ([redacted]). Additional systemic symptoms in humans include burning, itching, or tingling sensation of the face, epigastric pain, anoxemia, nausea, vomiting, dizziness, headache, fatigue, convulsions, and coma. Nerve conduction studies and interviews of 23 laboratory technicians involved with several pyrethroids in field trials, formulation, or other laboratory work showed no evidence of nerve impairment associated with exposure to permethrin ([redacted]). Symptoms of facial paraesthesia and occasional pruritic rashes were reported among those workers, but symptoms were not clearly related to permethrin.

2.5.5.2.4 Gastrointestinal effects

After accidental ingestion of pyrethroids, the initial symptoms were mainly digestive, such as epigastric pain, nausea, and vomiting, and developed within 10 min to 1 h [redacted]).

2.5.5.2.5 Hepatobiliary effects

Specific studies of human liver changes have not been conducted; however, extensive medical investigations of workers exposed to permethrin did not reveal any clinical chemistry changes (serum enzymes) that would suggest liver toxicity ([redacted]

2.5.5.2.6 Renal effects

Examination of 199 workers engaged for 0.5 to 4.5 months in dividing and packaging pyrethroids revealed no aberrations in renal function ([redacted]). Since topical permethrin is metabolized in the liver and excreted in the urine as inactive metabolites, there does not appear to be an increased risk of toxic reactions in patients with impaired renal function when used as labelled ([redacted]).

2.5.5.2.7 Haematological effects

Examination of 199 workers engaged for 0.5 to 4.5 months in dividing and packaging pyrethroids revealed no aberrations in blood ([redacted]).

2.5.5.2.9 Dermatological effects

Forestry workers exposed to wettable powders of permethrin (*trans*:*cis* = 75:25) experienced itching, burning sensations, and blisters ([redacted] These symptoms occurred at a frequency of approximately 10% in a group of 139 unprotected persons using only gloves occasionally.

2.5.5.3 Effects in Population Sub – Groups

2.5.5.3.1 Pregnancy

There are limited data on the use of permethrin containing medication in pregnancy; however, the amount of permethrin absorbed systemically following a whole body application is extremely low. According to the European guideline for the management of pediculosis pubis, permethrin appears to be safe in pregnancy (level of evidence III; grade B recommendation) ([redacted] .

2.5.5.3.2 Lactation

Because less than 2% is absorbed after topical application, rapid metabolism to inactive metabolites and safe application directly on infants' skin, topical permethrin products are acceptable in nursing mothers ([redacted] . Extensive exposure, such as from agricultural use or malaria control might have long-term health concerns because residues can be found in breastmilk ([redacted]

2.5.5.3.3 Paediatric

Only limited experience is available with permethrin containing dermal cream in children aged 2 months to 23 months ([redacted]). Therefore, treatment must be given only under close medical supervision in this age group. The American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention (CDC), and other clinicians consider topical permethrin 5% the scabicide of choice because of its safety and efficacy profile relative to other available agents ([redacted], [redacted] . Seven scabies patients under two months of age were treated with permethrin 5% cream ([redacted]). Topical therapy was repeated up to three times in four patients due to incomplete resolution or recurrence of skin lesions. Permethrin therapy was well tolerated in all seven infants, even when conducted several times.

2.5.5.3.4 Geriatric

Clinical studies of permethrin cream (5%) did not identify sufficient numbers of subjects aged 65 and over to allow a definitive statement regarding whether elderly subjects respond differently from younger subjects ([redacted]). Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

2.5.5.3.5 Gender

No data on gender related differences could be retrieved in terms of safety of permethrin use.

2.5.5.3.6 Racial

No data on race related differences could be retrieved in terms of safety of permethrin use.

2.5.5.4 Overview of Adverse Events of Permethrin

The frequency of treatment-related signs and symptoms are listed in Table 11. (*Lyclear SPC, Omega Pharma, 2014*).

Table 11. The frequency of treatment-related signs and symptoms with permethrin

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	Urticaria

The 1% permethrin cream rinse for head lice is available over the counter under the brand name NIX (*NRC US, 1994*). This product has been more thoroughly tested than any pediculicide ever introduced. More than 21,000 patients have been followed under

controlled conditions, including 18,000 monitored during post-marketing surveillance. The overall reported adverse events were approximately 2.5 per 1,000 patients, which is extremely low for any topical medication. These events include reports of pruritus, which is difficult to evaluate because pediculosis (head lice) is a pruritic condition.

2.5.5.5 Overdose

2.5.5.5.1 Experience and Symptoms

There are no reports of overdosage with dermal cream products containing permethrin 5%. Application of a full tube of cream to a 2 month old would result in a dose of approximately 350 mg/kg to skin (*Lyclear SPC, Omega Pharma, 2014*). It is unlikely that such a dose would cause overt signs of systemic toxicity even if 100% of the permethrin were absorbed. It is possible that excessive application of dermal cream products containing permethrin 5% will result in localised adverse reactions or more severe skin reactions. The clinical signs of acute poisoning become evident within 2 hr of overexposure to permethrin and are targeted to the central nervous system; symptoms are incoordination, ataxia, hyperactivity, convulsions, and, finally, prostration, paralysis, and death ([redacted] .

2.5.5.5.2 Treatment

Symptomatic treatment is indicated should hypersensitivity-type reactions occur. In the event of accidental ingestion of the contents of dermal cream products containing permethrin 5% by a child, gastric lavage should be considered if consultation is within 2 hours of ingestion (*Lyclear SPC, Omega Pharma, 2014*).

2.5.5.6 World Wide Marketing Experience

In an observational, epidemiological safety study, public health departments dispensed permethrin or another pediculicide, counselled about treatment in the customary methods, and followed each patient between 7 and 14 days after treatment via return visit or telephone call to identify any subsequent adverse clinical events ([redacted] Classified by pediculicide exposure, 18 950 patients received permethrin. Of all treatments, 49 adverse events occurred. The following five adverse events were considered medically important.

Case Pl: A 16-year-old girl with no previous history of allergy experienced breathing difficulty while her sister was being treated with permethrin. The episode subsided after the girl left the treatment room.

Case P2: A 34-year-old woman with a history of drug allergies experienced mild nausea and moderate to severe shortness of breath that lasted about 4 hours. The patient had been taking Inderal® (propranolol) (12 mg daily).

Case P3: A 10-year-old girl with a history of asthma and food allergies experienced arm shaking and stuttering that lasted less than a minute and did not recur. The patient did not require a medical visit. She had used the pediculicide A-200 on two occasions, 10 days and 6 days before treatment with permethrin.

Case P4: A 35-year-old woman (mother of P3) with a history of food allergies experienced two incidents of arm shaking for about 40 seconds and some skin irritation. The patient did not have a medical visit for these events. The Health Department physician stated that the arm shaking was probably due to the patient's steady use of her arms in applying 10-minute massages to three individuals on the same day.

Case PS: A 23-year-old woman with no previous allergy history experienced a swollen face beginning 1 day after treatment and lasting 1 week. She required medical treatment. The patient reported that the adverse event could have been caused by a new facial soap and that she did not attribute it to the permethrin treatment.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.6 Benefits and Risks Conclusions

2.5.6.1. Global Assessment of Efficacy

Permethrin is a neurotoxin that acts on the nerve cell membrane to disrupt the sodium channel current, by which the polarization of the membrane is regulated, and thereby kills mites and lice. Delayed repolarization and paralysis of the pests are the consequences of this disturbance. Permethrin is a first-line treatment for scabies and is effective against crab lice and head lice. Permethrin was first licensed in 1985 by the US FDA, and is on the WHO's List of Essential Medicines, the most important medications needed in a basic health system. Permethrin formulations include a prescription-only 5% w/w cream and lotion preparation strength for scabies and an over-the-counter 1 % w/w rinse for lice. The estimated *in vivo* human dermal absorption factors of permethrin from various solutions (acetone, ethanol) and preparations (crème, lotion) ranged from 1.4% to 5.7% using the rat and human *in vitro* dermal absorption data with the rat *in vivo* dermal absorption data. Based on the rat *in vivo* study, the increase in absorption at 120 hours indicated that radiolabel (permethrin) remaining in the skin after washing at 24 hours was bioavailable. Therefore, 5.7% should be considered as the estimated human dermal absorption factor for risk assessment purpose. Several clinical trials for the treatment of human ectoparasites have demonstrated the efficacy of permethrin in eradicating the organisms. A 5% topical preparation was used in each permethrin trial. The number of applications ranged from one (3 trials) to two (2 trials) to two consecutive overnight applications repeated after 14 days (1 trial). Topical permethrin appeared more effective than oral ivermectin (140 participants, 2 trials), topical crotamiton (194 participants, 2 trials), and topical lindane (753 participants, 5 trials). Permethrin also appeared more effective in reducing itch persistence than either crotamiton (94 participants, 1 trial) or lindane (490 participants, 2 trials). While the cited publications do not contain specific data on the exact composition of the various dosage forms of potentially differing viscosities, the efficacy was demonstrated with each cream preparation. Likewise, a double blind, multicentre, randomized, parallel group, active-controlled clinical study conducted by the Applicant to compare the efficacy and safety of Permethrin 5% cream of [redacted] (Test) with Permethrin 5% cream of Medgenix Benelux NV (Belgium) (Reference) in subjects with scabies demonstrated that the test treatment was at least as effective as the reference treatment.

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In a 2010 Cochrane review of interventions for treating scabies, twenty-two randomized controlled trials of drug treatments for scabies were identified including

2676 people. The authors concluded that topical permethrin appeared to be the most effective treatment for scabies. With one or two applications of 5% permethrin cream, the cure rate varies between 66.7% 97.8% of patients. Clinical trials continue to confirm the efficacy of permethrin for the treatment of scabies and crab lice. Notwithstanding, permethrin resistance in ectoparasites, such as head lice, is widespread. This suggests that its emergence in scabies mites is a real possibility, though clinical resistance of scabies mites to permethrin is yet to be documented. In 1994, before widespread permethrin treatment was introduced, all mites were killed within 30 min of in vitro exposure to permethrin. By the year 2000, however, 35% of mites were alive after 3 h of exposure and a significant proportion remained alive overnight. Overall, topical permethrin still appears to be the most effective treatment for scabies. In a 2018 Cochrane review, the efficacy and safety of topical permethrin and topical or systemic ivermectin for treating scabies in people of all ages were compared. Fifteen studies (1896 participants) comparing topical permethrin, systemic ivermectin, or topical ivermectin were analyzed. The authors concluded that for the most part, there was no difference detected in the efficacy of permethrin compared to systemic or topical ivermectin. Poor reporting was considered a major limitation. In another systematic review and meta-analysis of randomized controlled trials, the authors concluded that topical permethrin is more effective than oral ivermectin.

2.5.6.2. Global Assessment of Safety

Pyrethroids are highly lipophilic and are absorbed slowly through the skin, which usually prevents systemic toxicity. The estimated *in vivo* human dermal absorption factors ranged from 1.4% to 5.7% using the rat and human *in vitro* dermal absorption data with the rat *in vivo* dermal absorption data. Based on the rat *in vivo* study, the increase in absorption at 120 hours indicated that radiolabel (permethrin) remaining in the skin after washing at 24 hours was bioavailable. Therefore, 5.7% should be considered as the estimated human dermal absorption factor for risk assessment purpose.

Several clinical trials for the treatment of human ectoparasites have demonstrated the efficacy of permethrin in eradicating the organisms while demonstrating low toxicity to humans. In clinical studies of over 3500 patients, the only expected adverse drug experience associated with permethrin was local irritative symptoms, which ranged in frequency from 2.1% to 5.9%. Many of these symptoms were thought to be the result of the lice infestation.

Toxicity is highly dependent on stereochemical structure, each geometric and/or optical isomer possessing its individual toxic potency. Animal studies indicate that IV or PO *cis*-permethrin is more than 10-fold more toxic than the *trans* isomer and 2-5-fold more

toxic than the 40:60 *cis/trans* isomer mix used in the majority of toxicity studies. Most products, however, are mixtures of isomers. Occupational exposure to pyrethroids may occur through dermal contact and inhalation of dust and sprays. While inhalation is the main route of exposure in industrial workers, the skin is the main route of exposure in workers applying the compounds in agriculture or public health. Exposure of the general population may occur by inhalation, skin contact with products, by eating foods containing residues of pyrethroids applied as pesticides or veterinary drugs, or through accidental swallowing or drinking of pyrethroid products. Recent studies carried out in the EU and the US have shown detectable amounts of pyrethroid metabolites in urine samples from the general population; however, no evidence of adverse effects has been reported for such levels of exposure.

Symptomatic acute cases generally follow accidental overexposure or lack of care in handling the compounds at the workplace, whereas accidental ingestion of high doses is the main cause of poisonings for the general population. Acute poisoning very rarely poses a life-threatening risk to the exposed subjects, but severe poisonings and even potential for causing mortality may arise if concentrated formulations are swallowed. In occupational poisonings, the initial symptoms are skin burning, itching or dizziness. These sensations reported in exposed subjects might not be the result of skin reactions, but signs of peripheral nerve involvement. About half of the occupational patients develop abnormal facial sensitization (paraesthesia). In the case of swallowing, the main symptoms are epigastric pain, nausea and vomiting. The prognosis of acute occupational poisonings from pyrethroids is usually good, without any chronic or long-term consequence. In follow-up studies, the affected workers showed a complete recovery. Permethrin exposure does not seem to entail a risk of cancer in humans.

There are limited data on the use of permethrin containing medication in pregnancy; however, the amount of permethrin absorbed systemically following a whole body application is extremely low. According to the European guideline for the management of pediculosis pubis, permethrin appears to be safe in pregnancy. Because less than 2% is absorbed after topical application, rapid metabolism to inactive metabolites and safe application directly on infants' skin, topical permethrin products are acceptable in nursing mothers. Permethrin 5% cream therapy was well tolerated in seven infants, even when treated several times.

The 1% permethrin cream rinse for head lice is available over the counter. This product has been more thoroughly tested than any pediculicide ever introduced. More than 21,000 patients have been followed under controlled conditions, including 18,000 monitored during post-marketing surveillance. The overall reported adverse events were approximately 2.5 per 1,000 patients, which is extremely low for any topical

medication. These events include reports of pruritus. Overall, permethrin appears to be safe when used as directed.

2.5.6.3 Overall Conclusion

Numerous clinical trials and over thirty-year worldwide experience support the claim that permethrin can be used effectively and safely for the treatment of scabies and crab lice. The proposed pharmaceutical formulation of the drug products does not contain any novel excipients, or excipients being administered by a novel route, and therefore, there is no unexpected toxicological potential.

Although the nature of the cited scientific literature does not allow any comment on the Good Laboratory Practice (GLP) and the Good Clinical Practice (GCP) status, most of the cited experimental studies have been published in peer-reviewed journals; and monographs are published in reference textbooks of clinical pharmacology, and in formularies. These limitations are not considered as critical predominantly because of its over thirty-year history of clinical use and previously well-described toxicity profile.

In order to demonstrate therapeutic equivalence a randomized, double-blind, multicentric, parallel group, comparative clinical study was performed in full accordance, as applicable, with current standards of Good Manufacturing Practice (GMP), GCP, and GLP, complied with these standards, was in accordance with the Declaration of Helsinki, and was subject to independent Ethics Committee review.

The benefits of permethrin and its place as an anti ectoparasite medicine drug have been established in the last thirty-one years of clinical usage, within the EU, the US and in many other countries all over the world.

The SmPC (Summary of Product Characteristics) proposed by the Applicant takes the available pharmacodynamic, pharmacokinetic, toxicological, and clinical evidence into account, and is in accordance with the current knowledge in respect of the active moiety.

The pharmaceutical drug products meet the requirements for essential similarity, as defined by article 10.1(a)(iii) of E.U. Directive 2001 / 83 / EC, as modified.

Permethrin 5% Cream of [redacted] contains the same active substance, permethrin, in the same formulation and in the same pharmaceutical dosage when used as directed, with respect to the cited Reference Product, Permethrin 5% Cream of Medgenix Benelux NV (Belgium) and therapeutic equivalence has been demonstrated in full accordance with all applicable current guidance.

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In conclusion, the assessment of available evidence on permethrin and the widespread clinical use of such drug products favour the benefit from the availability of the

Applicant's new drug product, which is essentially similar to reference formulation marketed in the EU, US, and elsewhere in the world, for in excess of 10 years.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.7 Cited Literature References

Module	#	References
5	1.	[redacted]
[redacted]	[redacted]	[redacted]
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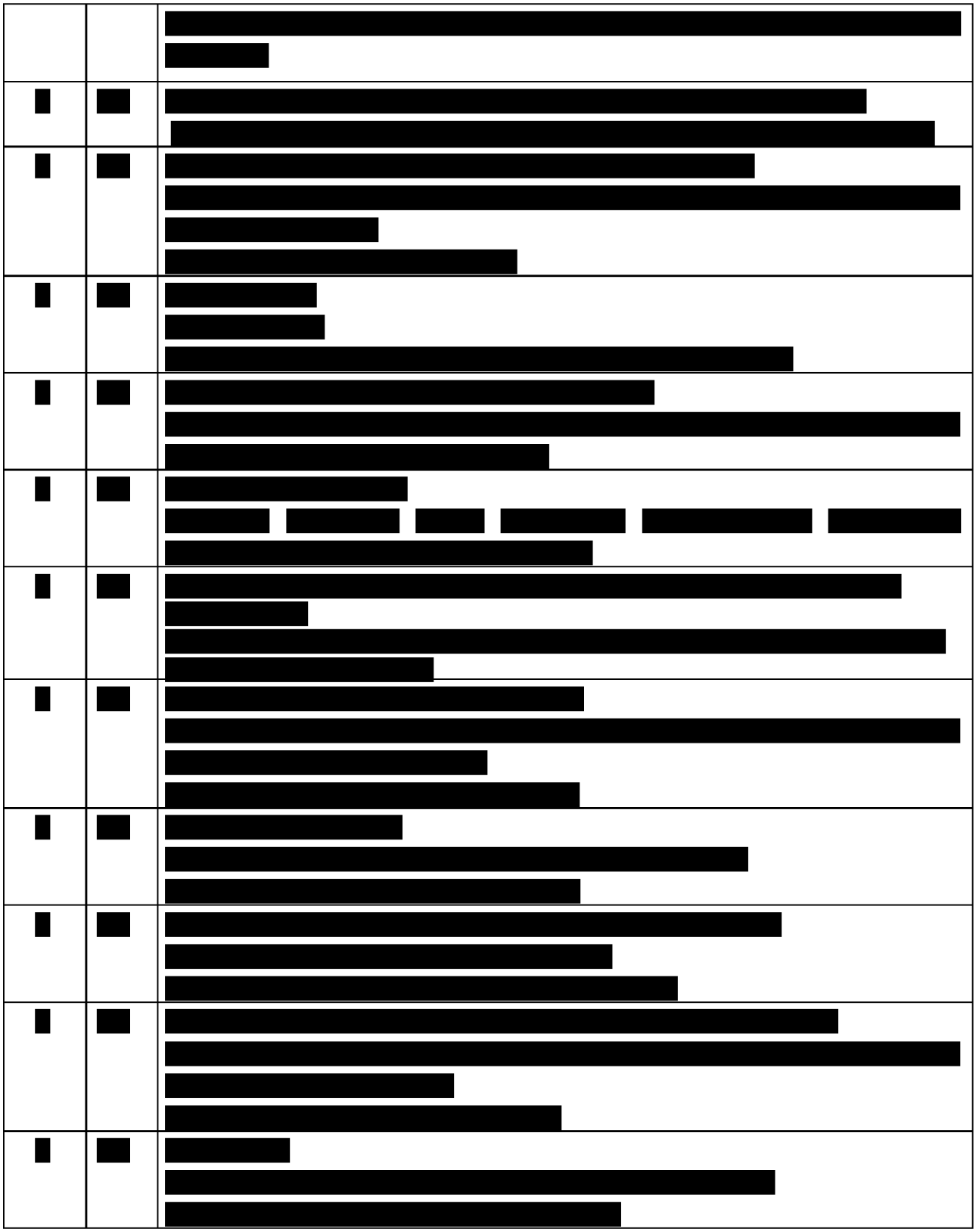

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