Taiwan Food and Drug Administration

Assessment Report

Trade Name：“松林”滅疥乳膏 /
PERMETHRIN CREAM 5% W/W

Active Ingredient：Permethrin

License Number：MOHW-PI 028575

Applicant：松林藥品有限公司

Approval Date：112/10/26

Indication：治療疥蟎感染（疥瘡）。

Indicated for the treatment of infestation with Sarcoptes scabiei (scabies).

Background Information

Trade Name	“松林”滅疥乳膏 / PERMETHRIN CREAM 5% W/W
Active Ingredient(s)	Permethrin
Applicant	松林藥品有限公司
Dosage Form & Strengths	乳膏劑 30g / tube、60g / tube
Indication	治療疥蟎感染（疥瘡）。 Indicated for the treatment of infestation with Sarcoptes scabiei (scabies).
Posology	成人和兒童 – 將本品塗抹全身。應在 8 至 14 小時後再洗去乳膏（淋浴或沐浴）。原則上單次治療即可。病人在治療後可能會出現持續性瘙癢。這很少是治療失敗的跡象，也不是再治療的表徵。14 天後觀察到疥蟲表示需要重新治療。 疥瘡很少感染成人的頭皮，但嬰兒和老年病人的髮際、頸部、太陽穴和前額可能會感染。一般成年人約使用 30 克劑量。嬰兒應在頭皮、太陽穴和前額上進行治療。
Pharmacological Category **ATC Code**	P03AC04

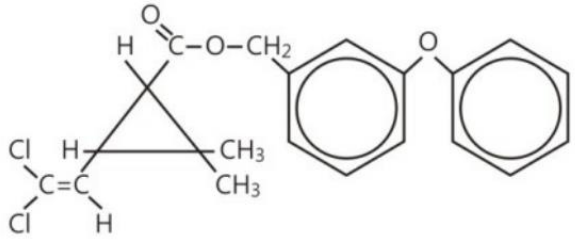
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Permethrin (1:3):

The drug substance, Permethrin (1:3), is chemically designated as mixture of the cis and trans isomers of the 3-(2,2-dichloroethenyl)-2, 2-dimethylcyclopropanecarboxylic acid, (3-phenoxyphenyl) methyl ester and has the following structure:



It is a colorless or slightly brownish viscous liquid, semi-solid or crystalline solid. The molecular formula and the molecular weight are $C_{21}H_{20}Cl_2O_3$ and 391.29 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of Permethrin (1:3) has been confirmed by elemental analysis, infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry.

Adequate specification has been presented for the drug substance and the test items include description, solubility, identification, water content, acidity, sulphated ash, assay, limit of isomers, residual solvents, related substances. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

PERMETHRIN CREAM 5% W/W:

The drug product is marketed in color-striped tubes, available in either 30g or 60g sizes, containing a cream with a strength of 5% w/w Permethrin (1:3).

The cream was white to off white, smooth, homogeneous for topical use. The specifications for excipients used in the PERMETHRIN CREAM 5% W/W formulation are adequate.

Sufficient specification has been presented for the PERMETHRIN CREAM 5% W/W and the test items include description, identification for permethrin & formaldehyde, minimum fill, pH, viscosity, specific gravity, globule size, uniformity in containers, related substances, assay of permethrin & formaldehyde, limit of isomers, microbial examination of non-sterile products, residual solvents. Batch analysis data from representative batches of the PERMETHRIN CREAM 5% W/W are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of the PERMETHRIN CREAM 5% W/W under long term conditions (25°C ± 2°C and 60% ± 5% RH) and accelerated condition (40ºC ± 2°C/%75% ± 5% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of PERMETHRIN CREAM 5% W/W can be granted for 36 months under the storage condition below 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Since permethrin's clinical and nonclinical safety pharmacology is well characterized, and permethrin has been applied in agriculture and veterinary medicine for several years, no additional nonclinical pharmacology studies were conducted.

2.2.2 Toxicological Studies

The evaluation of permethrin's toxicity was based on the US FDA Elimite™ Cream 5% assessment report. Dermal application of permethrin showed a low acute toxicity. In 10-day oral toxicity studies of mice and rats, increases in GOT, GPT, and LOH accompanied by dose-related increases in absolute and relative liver weights were noted; however, histopathological examination of the liver was not carried out. In the 3- and 6-month repeated-dose toxicity studies, permethrin was well tolerated in rats and dogs, respectively. Besides, permethrin was relatively well tolerated when applied topically on the skin. No tumorigenicity was seen in the rat studies. Permethrin showed no evidence of mutagenic potential in a battery of genetic toxicity studies. Reproduction studies in mice, rats, and rabbits have revealed no evidence of impaired fertility or fetal harm due to permethrin. In local tolerance, permethrin was minimally or mildly irritating to the eyes and skin of rabbits. Permethrin was shown to be a dermal sensitizer in guinea pigs.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

PERMETHRIN CREAM 5% is a topical use agent for the treatment of infestation with *Sarcoptes scabiei* (scabies). The posology for adult and children is to thoroughly massage permethrin cream 5% into the skin from the head to the soles of the feet. The cream should be removed by washing (shower or bath) after 8 to 14 hours. Usually, one single application of 30 grams is sufficient for an average adult. If living mites was observed after 14 days, indicating that retreatment is necessary.

Although PERMETHRIN CREAM 5% belongs to NCE in Taiwan, in fact, it is a generic drug (ANDA211303) of US FDA approved drug product, Elimite™ Cream (permethrin) 5% (NDA019855). PERMETHRIN CREAM 5% had conducted a BE study with clinical endpoint (Study No.: 71675502), and proved that PERMETHRIN CREAM 5% is bioequivalent to its RLD, Elimite™ Cream (permethrin) 5%. Besides, an IVRT comparison study also showed that the permethrin release rate of PERMETHRIN CREAM 5% is equivalent to Elimite™ Cream (permethrin) 5%. Thus, the absorption performance of PERMETHRIN CREAM 5% can be considered identical to Elimite™ Cream (permethrin) 5%.

Based on US FDA Elimite™ Cream 5% assessment report, the tolerance and systemic absorption studies (protocol 02-01 and 06-06A) showed that the systemic exposure of permethrin was low. The labeling of Elimite™ Cream 5% stated that permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine. One article also mentioned that permethrin is metabolized through ester cleavage and almost entirely excreted in the urine in free or glucuronide-conjugated forms following topical administration.

2.3.2 Interaction Studies

No formal DDI study was conducted.

2.3.3 Special Populations

No dedicated hepatic or renal impairment study was conducted. According to the mechanism of action and metabolism pathway, it can presume that no dose adjustment is required in hepatic impairment patients. Also, there does not appear to be an increased risk of toxic reactions in patients with impaired renal function when used as labeled. Besides, no dose adjustment is required based on age and gender.

Overall, the pharmacokinetic studies conducted were satisfactory and met the minimum requirements from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The clinical program of PERMETHRIN CREAM 5% includes an equivalence study (Study 71675502) and a copy of FDA's assessment report of the reference drug "Elimite™ Cream 5% (Prestium Pharma, Inc.)". Study 71675502, a double-blind, 1:1 randomized, controlled study, was designed to evaluate the therapeutic equivalence of permethrin cream, 5% (Encube Ethicals) compared to Elimite™ Cream 5% in the treatment of scabies. Adults and children aged 2 years of age and older with the diagnosis of active scabies (parasitological confirmation) were enrolled. Eligible patients were instructed to self-administer a single dose of study product. A second application may have been required if presence of scabies infestation was microscopically demonstrated around Day 14. The primary efficacy endpoint was the proportion of patients in each treatment group with Therapeutic Cure (parasitological cure plus clinical cure) of scabies at the test-of-cure visit conducted at Day 28 ± 4. A total of 254 patients were randomized and 236 patients were included in the per-protocol analysis set (117 in the testing group and 119 in the reference group).

The difference of the proportion of patients considered a Therapeutic Cure between the Permethrin Cream, 5% (Encube Ethicals Pvt. Ltd.) and the Elimite™ Cream (permethrin) 5% (Prestium Pharma, Inc.) groups was 3.8% (90% confidence interval [CI]: -5.9%, 13.4%). The 90% CI was contained within the equivalence interval of [-20%, 20%]. Therapeutic equivalence was demonstrated for the primary endpoint.

The FDA's medical assessment of Elimite™ Cream 5% (NDA019855) includes four clinical effectiveness studies. The clinical cure rate (with or without microscopic confirmed) of Elimite™ Cream 5% at Day 28 was around 89% to 100%.

2.4.2 Safety Results

The safety database of permethrin cream 5% is composed of the following parts: Study 71675502, FDA's assessment report of the reference cream, and domestic post-marketing experiences from the National ADR Reporting System (see Bridging Study Evaluation).

In Study 71675502, a total of 254 patients were enrolled to the safety analysis set. Fourteen patients reported at least one adverse event (AE) during the study (8 [6.4%] patients in the Test group, and 6 [4.7%] patients in the Reference group). Adverse events were reported one in each preferred term in the testing group except headache (2), and those preferred terms included enterocolitis, cellulitis, viral upper respiratory tract infection, bone pain, and erythema. The preferred term cellulitis was also recorded as a serous AE that observed in a 78 years old female with left toe cellulitis and resulted in hospitalization. All AEs were judged as not related to the study drug. No deaths were reported during the study. The safety database in FDA's medical assessment report includes 234 subjects in the testing group and 233 subjects in the control group. Dermal reactions recorded as a higher frequency than the control group were burning sensation and erythema.

2.5 Bridging Study Evaluation

Based on available data, it can conclude that the systemic exposure of Elimite™ Cream 5% was low, and its generic drug, PERMETHRIN CREAM 5%, also have low systemic exposure. Taken together, the PK characteristic of permethrin 5% cream, mechanism of action and metabolism pathway, the ethnic difference of PERMETHRIN CREAM 5% can be negligible, and bridging study can be waived from PK perspective.

The clinical program of permethrin cream 5% includes an equivalence study (Study 71675502) and a copy of FDA's assessment report of the reference cream. A total of 254 patients were randomized in Study 71665502 and 2% were Asian. Besides, domestic using of PERMETHRIN CREAM 5% had been authorized in accordance with Article 48-2 of Pharmaceutical Affairs Act under clinical needs. During the importing period (2022/03/07-2023/05/31), no case was reported to the National ADR Reporting System for any reaction related to permethrin. Taking the drug mechanism of action, characteristics of systemic exposure and clinical experiences into consideration, potential impact of ethnic difference could be minimal.

2.6 Conclusion

The data supported a favorable benefit-risk profile of PERMETHRIN CREAM 5% for the treatment of scabies in adults and children.

3. Post-Marketing Requirements

N/A