Taiwan Food and Drug Administration

Assessment Report

Trade Name：速必一 乳膏 / Fespixon cream

Active Ingredient：

***Plectranthus amboinicus* extract-F4 (PA-F4) / *Centella asiatica* extract (S1)**

License Number：MOHW-PM 060827

Applicant：合一生技股份有限公司

Approval Date：2021/03/26

Indication：

糖尿病足部傷口潰瘍。
說明：臨床試驗結果主要來自於 Wagner Grade 1 及 Grade 2 之受試者。

Fespixon cream is indicated for use in the topical treatment of diabetic foot ulcers.
Note: The clinical evidence of Fespixon cream was demonstrated in patients with Wagner grade 1 or 2 diabetic foot ulcers.

1. Background Information

Trade Name	速必一 乳膏 / Fespixon cream
Active Ingredient(s)	*Plectranthus amboinicus* extract-F4 (PA-F4) / *Centella asiatica* extract (S1)
Applicant	合一生技股份有限公司
Dosage Form & Strengths	Cream 2.5mg/g / 10mg/g
Indication	糖尿病足部傷口潰瘍。 說明：臨床試驗結果主要來自於 Wagner Grade 1 及 Grade 2 之受試者。 Fespixon cream is indicated for use in the topical treatment of diabetic foot ulcers. Note: The clinical evidence of Fespixon cream was demonstrated in patients with Wagner grade 1 or 2 diabetic foot ulcers.
Posology	於患部每日塗抹兩次，須完全覆蓋傷口。詳見仿單。 Fespixon cream should be applied to the affected area twice daily, and cover the wound completely. Details refer to the PRESCRIBING INFORMATION.
Pharmacological Category **ATC Code**	N/A

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

***Plectranthus amboinicus* extract-F4 (PA-F4)**

Botanical drug substance, PA-F4, is extracted from *Plectranthus amboinicus*. PA-F4 is a green to dark green extract. Specification for the botanical drug substance includes suitable tests to confirm the quality. Analytical methods are described well and validated.

***Centella asiatica* extract (S1)**

Botanical drug substance, S1, is extracted from *Centella asiatica*. S1 is a light yellow to light brown yellow powder. Specification for the botanical drug substance includes suitable tests to confirm the quality. Analytical methods are described well and validated.

2.1.2 Drug Product

Botanical drug product is a cream for topical use containing 1.25% (w/w) of the two botanical drug substances (0.25% of PA-F4 and 1% of S1). All compendial excipients used in the botanical drug product formulation comply with compendial monographs.

Specification for the botanical drug product includes suitable tests to confirm the quality. Analytical methods are described well and validated.

Stability studies of the botanical drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The pharmacodynamic profiles of the individual plant extracts have been characterized in the literature. The literature showed that *Centella asiatica* extracts may accelerate wound healing by stimulating epithelialization *via* enhancement of collagen synthesis, stimulation of angiogenesis, and its own antioxidant activities. *Plectranthus amboinicus* extracts may give additional wound healing effects by reducing blood sugar levels and its own anti-inflammatory, antioxidant, anti-microbial, and antiviral activities.

In addition to the literature, the applicant has performed a number of pharmacodynamics studies. In STZ-induced diabetic rats and db/db mice, the wounds treated with Fespixon cream (ON101) healed more rapidly than untreated wounds, and the data revealed a beneficial synergistic potential of combining the two plant extracts. The two plant extracts' active fractions and specific ratios were determined for further clinical development based on these data. By measuring the exposure of asiaticoside and salvigenin, the low systemic exposure of topical ON101 was demonstrated in rabbits. A minimal systemic exposure was also observed in a pharmacokinetic clinical study.

2.2.2 Toxicological Studies

Several GLP toxicology studies have been conducted on the oral or topical administration of ON101. In rats, a single dose and repeated oral administration of ON101 DS for 28 days up to the highest dose tested (5000 mg/kg and 3000 mg/kg/day, respectively) did not produce any adverse toxic effects. Thirteen-week repeated topical application of ON101 at the highest dose tested, 21.68 times the clinical dose, did not produce significant toxic effects in rabbits. ON101 DS is not mutagenic in the in vitro (AMES, chromosomal aberration) studies and in vivo

(mouse micronucleus) study. ON101 is not an irritant to the skin and eye of the rabbit and is not considered a sensitizer in the guinea pig.

Orally administered ON101 DS revealed no maternal toxicity and embryo-fetal development toxicity at the highest dose tested (375 mg/kg/day) in rats. The evaluation of ON101 on the male and female reproductive organs has been performed in the repeated-dose toxicity studies, and no treatment-related toxicity was observed up to 3000 mg/kg/day in a 4-week oral toxicity study in rats or up to 10X clinical concentration in a 13-week wound application toxicity study in rabbits. Since a minimal systemic exposure and no evident accumulation of ON101 were demonstrated clinically, studies for fertility and early embryonic development, pre- and postnatal development, carcinogenicity, and safety pharmacology were unwarranted.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Fespixon cream contains two drug substances, first extract from *Centella asiatica* and second extract from *Plectranthus amboinicus* in a specific proprietary ratio of 4:1 respectively. The recommended dose regimen is applied to cover whole wound two times daily for the wound healing of diabetic patients with lower extremity ulcers.

The limited exposure of salvigenin and asiaticoside was detected in human after multiple dosing via topical administration. The data indicated that there was no drug accumulation in the systemic circulation.

2.3.2 Interaction Studies

Due to low systemic exposure of salvigenin and asiaticoside, the potential of drug-drug interaction is low and there were no formal drug-drug interaction studies of Fespixon cream.

Hence, there was no specific recommendation for drug-drug interaction.

2.3.3 Special Populations

Due to low systemic exposure of salvigenin and asiaticoside, there was no formal studies for special population of Fespixon cream.

There was no specific recommendation for special population.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Sponsor provided one Phase III study (ON101CLCT02) to support the efficacy of ON101

for the treatment of chronic diabetic foot ulcers. The key efficacy findings for this study are summarized below.

Study [ON101CLCT02] was a phase III, randomized, open-label, evaluator blinded, active-controlled, multi-center study to evaluate the efficacy of ON101 compared with Aquacel Hydrofiber dressing in the treatment of Wagner grade 1 or 2 diabetic foot ulcers. All randomized subjects received the assigned topic treatment for a maximum period of 16 weeks, until the ulcer closure for two consecutive visits at least 2 weeks apart, or until the study subject exited the study as lack of efficacy (defined as a worsening of Wagner grade to level of 3). After the treatment period, all subjects were followed for additional 12 weeks. During the follow-up period, Aquacel Hydrofiber was applied for subjects who had unhealed or recurrent wounds. The ulcer size at baseline was 4.5/2.6 cm^2 (mean/median) at the ON101group, comparable to 4.6/3.1 cm^2 (mean/median) at the Aquacel group. The majority (75.5%) of subjects had Wagner grade 2 ulcers with mean duration about 7 months.

The primary efficacy endpoint was the proportion of subjects whose target ulcer was complete healing. The definition of complete healing for the target ulcer was complete epithelialization and with no drainage for at least 2 weeks confirmed by a blinded assessor.

The primary analysis population was the full analysis set (FAS), defined as all subjects who were randomized. The subject was considered as “non-healing” if no available data for post-baseline wound/ulcer healing assessment. Otherwise, the method of last observation carried forward (LOCF) was used to account for incomplete observation.

The primary efficacy analysis was the logistic regression model including treatment as a fixed factor, baseline wound size and blinded evaluated Wagner grade as covariates. Of note, the baseline Wagner grade was evaluated by the blinded independent evaluator in the first interim analysis; however, it was amended to be evaluated by site investigators in the second interim analysis and in the final analysis.

In the original protocol, one interim analysis was pre-planned when 118 subjects (about 50% information) had completed the comparison period or early withdrawal of study intervention. In Protocol v6.0 (20190729), two interim analyses were planned when 118, and 212 subjects (about 50% and 90% information) completed the comparison period or early withdrawl from study intervention on a sequential basis. The Lan and DeMets version of the O’Brien-Fleming alpha-spending function was used to calculate the type I error rate.

- ***First interim analysis:***

The first interim analysis was conducted when 124 subjects completed the comparison period or early withdrawal. The results showed that a numerically greater proportion of subjects achieving complete ulcer healing was observed in the ON101 group (60.3% vs. 34.4%), however, the difference was not statistically significant (p = 0.00425 > critical value 0.003974). The analytical results based on the pre-planned interim time (N=118) were similar.

- ***Second interim analysis:***

At the time of the 2nd interim analysis (N = 212), a greater proportion of complete ulcer healing was observed in the ON101 group (62.2% vs. 34.7%) and the difference met the statistical significance (OR: 3.11, 95% CI: 1.76 to 5.48; p-value=0.00008 < significance level 0.03476). To evaluate the robustness of the 2nd interim results, several sensitivity analyses had been performed by the reviewers, including analyses based on blinded independent evaluators, and analyses for assessing the impacts of major protocol deviations and missing primary endpoint. All results supported the primary efficacy result at the 2nd interim analysis.

2.4.2 Safety Results

In Study ON101CLCT02, a total of 111 patients received ON101 and 101 patients received SOC of wound covered with Aquacel Hydrofiber. The median duration of treatment in both treatment groups were 15.9 weeks. Overall, 60.4% of subjects in the ON101 group experienced TEAEs compared with 69.3% in the Aquacel group.

The most common TEAEs were skin ulcer (ON101: 11.7% vs. Aquacel: 11.9%), cellulitis (ON101: 7.2% vs. Aquacel: 5.0%), and upper respiratory tract infections (ON101: 5.4% vs. Aquacel: 6.9%) in both treatment groups. Among the TEAEs, a total of 11 events occurred in 8 patients(4 ON101 and 4 Aquacel) were considered related to treatment. Each of the followings had a single event in the ON101 group: peripheral swelling, staphylococcal-infection, dermatitis contact, wound complication, erythema, rash and eczema.

The incidences of serious TEAE were slightly higher in the ON101 group, but all of these events were judged as not related to study treatment. Among the SAEs in both treatment groups, only one event of osteomyelitis in subject treated with Aquacel was considered to be related to study treatment.

There were no clinically significant changes or differences between the two treatment groups

for hematology and biochemistry values, vital signs, and ECG findings.

Based on the submitted data, the safety of ON101 for the treatment of Wagner Grade 1 or 2 DM foot was acceptable.

2.5 Bridging Study Evaluation

Considering the extremely low systemic exposure and most clinical studies were conducted in Taiwanese population, there is no bridging issue for ON101.

2.6 Conclusion

This multidisciplinary review recommends approval for Fespixon cream. Fespixon cream is indicated for use in the topical treatment of diabetic foot ulcers. The clinical evidence of Fespixon cream was demonstrated in patients with Wagner grade 1 or 2 diabetic foot ulcers.

3. Post-Marketing Requirements

For the new drug with new active pharmaceutical ingredients, the sponsor must conduct a Phase IV study to provide effectiveness for the approved indication. The final report of this PMR trial should be submitted to the central competent health authority for review and evaluation before license extension permit.