

FESPIXON[®] cream

Treatment of Diabetic Foot Ulcers

MOHW Manufacturing No. 060827
Prescription Only

1. Product Description

FESPIXON cream contains 125% extracts of *Plectranthus amboinicus* (PA-F4, 0.25%) and *Centella asiatica* (S1, 1%) with appearance in yellow-green to light green color and is for topical use.

2. Indication

Diabetic foot ulcer

Note: The clinical trial results are based on the subjects with Wagner Grade 1 and Grade 2 ulcers.

3. Dosage and Administration

The Cream is prescription-only.
The Cream shall be applied to the lesion twice daily by fully covering the ulcer.
Once the Cream is applied, gauze should be used to cover the ulcer area. The lesion shall avoid being overwrapped until healing of ulcer has occurred.

4. Contraindications

The Cream is contraindicated in the patients who are hypersensitive to the ingredients of the Cream, including *Plectranthus amboinicus*, *Centella asiatica* or excipients.

5. Warnings and Precautions

The Cream is for external use only and should not be taken orally or used in or around eyes or in mucosa.

6. Drug Interactions

The Cream hasn't been studied in drug-drug interaction with other medications. It is not known if the Cream interacts with other medications.

7. Use by Specific Populations

The Cream is for topical administration with very limited systemic exposure which raises no concerns in systemic effect. Clinical trials were conducted on adult patients with diabetic foot ulcers. There are currently no studies specifically carried out on the populations with liver and renal impairment, children, the elderly, pregnant women or breastfeeding women.

8. Pregnancy

Oral teratogenicity test in rats shows that the Cream is not teratogenic. However, there has been no clinical trials specifically conducted with the Cream on pregnant or breastfeeding women so it is also not known whether the Cream would cause fetal harm when it is administered to a pregnant woman or can affect reproductive capacity. The Cream should be given to pregnant women only if clearly needed.

9. Breastfeeding Women

It is not known whether PA-F4 and S1 are excreted in human milk. Because many drugs are secreted in human milk, extra caution should be exercised when the Cream is administered to breastfeeding women.

10. Clinical Pharmacology

10.1 Mechanism of Action

Plectranthus amboinicus and *Centella asiatica* extracts have been respectively used in human for a long period of time. According to literatures, *Plectranthus amboinicus* has antibacterial and anti-inflammatory effects and *Centella asiatica* can promote collagen production, angiogenesis, anti-oxidation to assist epithelialization and accelerate wound healing effect. The Cream contains 125% of PA-F4, *Plectranthus amboinicus* extract and S1, *Centella asiatica* extract. *In-vitro* and *in-vivo* studies have shown

that the Cream can alter the polarization of macrophages in chronic wounds by inhibiting inflammation and promoting specific-chemokines-induced transition of the microenvironment dominated by M1-macrophages into that dominated by M2-macrophages. M2-macrophages can exert the functions of (1) promoting angiogenesis and increase blood flow by regulating VEGF; (2) releasing TGF to recruit the stem cells to the lesion for tissue regeneration and promote fibroblast proliferation; (3) synthesizing collagen via hydroxyproline and trigger extracellular matrix collagen deposition as to achieve complete healing of wounds. In summary, the mechanism of the Cream is to restore the balance of M1- and M2-macrophages in the wound microenvironment by inhibiting M1-macrophages and activating M2-macrophages in order to forward the wounds from inflammation stage into the proliferative stage and achieve ulcer healing.

10.2 Non-clinical Toxicology

In genotoxicity studies, the Cream was found with no mutagenic potential in Ames test and no chromosome aberration potential in Chinese hamster ovary cells. Also, the Cream was found negative *in vivo* in the micronucleus assay with mouse peripheral blood.
The Cream was also evaluated in the single-dose toxicity study in rats, in subacute oral toxicity study for 28-day in rats and in repeat-dose dermal toxicity study on rabbits. No-Observed-Adverse-Effect-Level (NOAEL) of the Cream is 5000 mg/kg, 3000 mg/kg and 125% respectively.
In 28-day repeat-dose toxicity study in rats and 13-week repeat-dose toxicity study in rabbits, toxic effects on male and female reproductive organs were monitored and no treatment-related toxicity was observed. The Cream was found without teratogenic effect in the oral teratogenicity study in rats.
The Cream causes no dermal or ocular irritation and no sensitization on skin.
Carcinogenicity study has not been conducted for the product.

10.3 Pharmacokinetic

12 patients with chronic diabetic foot ulcers were included in a 2-week clinical trial for evaluation on the pharmacokinetic characteristics of salvigenin in PA-F4, *Plectranthus amboinicus* and asiaticoside in S1, *Centella asiatica*. The analysis results on single topical administration of the Cream showed that 10 of the 12 subjects were detected less than 2 pg/mL (the low limit of quantitation, LLOQ) of salvigenin in plasma concentration while only 2 out of 12 were with detectable plasma concentrations of no more than 12403 pg/mL; 7 of the 12 subjects were detected less than 1 ng/mL (LLOQ) of asiaticoside in plasma concentration, while only 5 out 12 subjects were with detectable plasma concentrations of no more than 9276 ng/mL. The analysis results on repeat topical administration by twice daily application of the Cream for 14 days, 8 out of 12 subjects were detected less than 2 pg/mL of (LLOQ) of salvigenin in plasma concentration, while 4 out of 12 were with detectable salvigenin in plasma concentration of no more than 16.972 pg/mL; 7 out of 12 subjects were detected less than 1 ng/mL (LLOQ) of asiaticoside and 5 out of 12 were with detectable asiaticoside in plasma concentration of no more than 6.154 ng/mL. The trial results concluded that the systemic exposure of the Cream is very limited without accumulation.

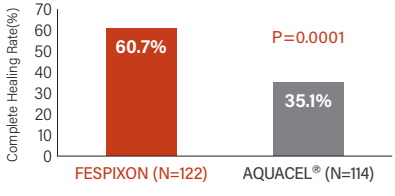
10.4 Clinical Trial

A randomized, controlled, multinational, multicenter phase 3 clinical study was conducted to evaluate the efficacy and safety of FESPIXON cream in treating patients with chronic diabetic foot ulcers. A total of 236 patients with Wagner grade 1 or grade 2 diabetic foot ulcers were randomized 1:1 to receive either FESPIXON cream (N=122) or AQUACEL[®] Hydrofiber[®] dressings (N=114) for treatment for up to 16 weeks in order to evaluate the complete healing rate and

time to complete ulcer healing.

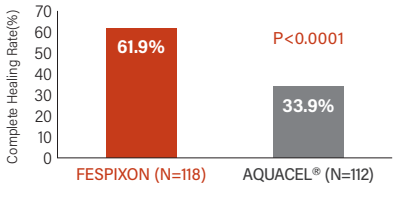
Figure 1 has shown the results in the full analysis set (FAS), 60.7% of patients in FESPIXON cream group achieved complete healing whereas 35.1% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing. The complete healing rate of patients treated with FESPIXON cream is higher. The p-value is 0.0001.
* Note: AQUACEL[®] Hydrofiber[®] dressing is used externally in the standard of care for chronic wound management.

Figure 1. Complete Healing Rate in the Full Analysis Set (FAS)



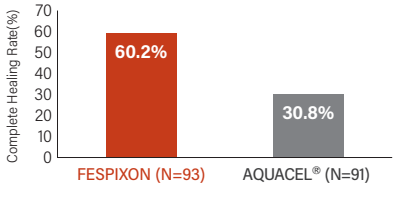
In the modified intention to treat (mITT) analysis set (Figure 2), 61.9% of patients in FESPIXON cream group achieved complete healing whereas 33.9% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing. The complete healing rate of patients treated with FESPIXON cream is higher. The p-value in the mITT analysis set is less than 0.0001.

Figure 2. Complete Healing Rate in the Modified Intention to Treat (mITT) Analysis Set



● **Evaluation on the incidence of complete healing in patients with grade 2 ulcers according to Wagner classification system when treatment was completed**
In the full analysis set (FAS) on patients with ulcers under grade 2 (Wagner=2), 60.2% patients of FESPIXON cream group achieved complete healing whereas 30.8% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing.

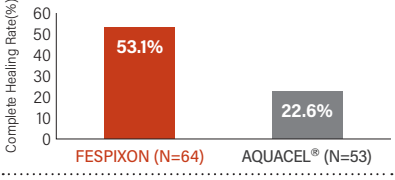
Figure 3. Complete Healing Rate of Patients with Wagner Grade 2 Ulcers – Full Analysis Set (FAS)



● **Evaluation on the incidence of complete healing in patients with plantar ulcer when treatment was completed**

The results in patients with plantar ulcers in the full analysis set (FAS) showed (Figure 4) that 53.1% of patients in FESPIXON cream group achieved complete healing whereas 22.6% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing.

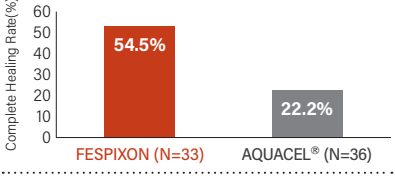
Figure 4. Complete Healing Rate of Patients with Plantar Ulcers – Full Analysis Set (FAS)



● **Evaluation on the incidence of complete healing in patients with bigger ulcer (>5 cm²) when treatment was completed**

The results in patients with bigger ulcers (>5 cm²) in the full analysis set (FAS) showed (Figure 5) that was 54.5% of patients in FESPIXON cream group achieved complete healing whereas 22.2% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing.

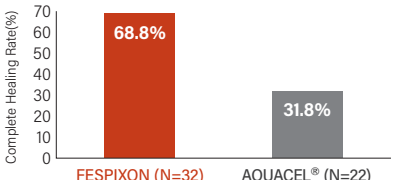
Figure 5. Complete Healing Rate of Patients with Bigger Ulcer (>5cm²) – Full Analysis Set (FAS)



● **Evaluation on the incidence of complete healing in patients with smoking habits when treatment completed**

The results in patients with smoking habits in the full analysis set (FAS) showed (Figure 6) that 68.8% of patients in FESPIXON cream group achieved complete healing whereas 31.8% of patients in AQUACEL[®] Hydrofiber[®] dressing group achieved complete healing.

Figure 6. Complete Healing Rate of Patients with Smoking Habits – Full Analysis Set (FAS)



● **Evaluation on time to complete ulcer healing**

The results (Figures 7 and 8) showed that in both full analysis set (FAS) and modified intention to treat (mITT) analysis set, FESPIXON cream group achieved complete healing earlier than the comparator, AQUACEL[®] Hydrofiber[®] group.

Figure 7. Kaplan-Meier Plots for Complete Healing-Full Analysis Set (FAS)

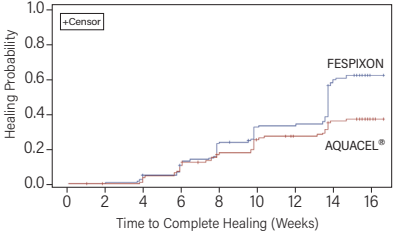
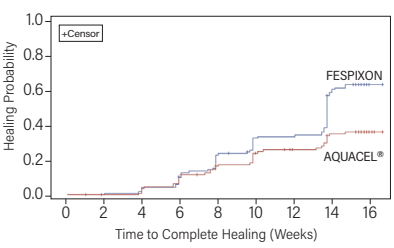
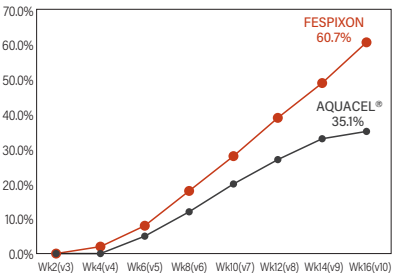


Figure 8. Kaplan-Meier Plots for Complete Healing-Modified Intention-to-treat Analysis Set (mITT)



The cumulative rate of complete wound healing in the FESPIXON cream group is higher than that in the AQUACEL[®] Hydrofiber[®] group at each observation time point. The cumulative rate of complete healing at each observation time point is shown in Figure 9:

Figure 9. Cumulative Rate of Complete Healing at Each Observation Time Point



10.5 Adverse Event

According to the clinical trial results, the adverse events occurred in FESPIXON cream treatment group were mild to moderate. In a multinational, multicenter phase 3 clinical trial with 236 subjects enrolled for 16-week treatment comparison with AQUACEL[®] Hydrofiber[®], the treatment-emergent adverse events with incidence ≥5% in FESPIXON cream group and AQUACEL[®] Hydrofiber[®] group are shown in Table 1. The related treatment-emergent adverse events in FESPIXON cream and AQUACEL[®] Hydrofiber[®] group are shown in Table 2:

Table 1. Summary of treatment emergent adverse events with incidence ≥5%

TEAs (%)	FESPIXON N=122	AQUACEL [®] Hydrofiber [®] N=114
No. of patients	76 (62.3%)	77 (67.5%)
Infection		
Cellulitis	8 (6.6%)	5 (4.4%)
Upper respiratory tract infection	6 (4.9%)	7 (6.1%)
Skin and subcutaneous tissue disorders		
Skin ulcer	14 (11.5%)	12 (10.5%)
Vascular disorders		
Hypertension	3 (2.5%)	6 (5.3%)

Table 2. Summary of related treatment-emergent adverse events:

Related TEAs (%)	FESPIXON N=122	AQUACEL [®] Hydrofiber [®] N=114
No. of patients	7 (5.7%)	5 (4.4%)
General disorders and administration site conditions		
Peripheral swelling	1 (0.8%)	0 (0.0%)
Pyrexia	0 (0.0%)	1 (0.9%)
Infections and infestations		
Cellulitis	0 (0.0%)	1 (0.9%)
Osteomyelitis	0 (0.0%)	1 (0.9%)
Staphylococcal infection	1 (0.8%)	0 (0.0%)
Injury, poisoning and procedural complications		
Wound complication	1 (0.8%)	0 (0.0%)
Investigations		
Weight increased	1 (0.8%)	0 (0.0%)
Metabolism and nutrition disorders		
Hyperuricaemia	2 (1.6%)	0 (0.0%)
Neoplasms benign, malignant and unspecified		
Skin papilloma	0 (0.0%)	1 (0.9%)
Skin and subcutaneous tissue disorders		
Dermatitis contact	1 (0.8%)	0 (0.0%)
Diabetic foot infection	0 (0.0%)	1 (0.9%)
Eczema	2 (1.6%)	0 (0.0%)
Erythema	1 (0.8%)	0 (0.0%)
Rash	1 (0.8%)	0 (0.0%)

In addition to the above-mentioned phase 3 clinical trial, the previous clinical trials added up to a total of 164 patients applied with FESPIXON cream. Only 7 patients had related treatment-emergent adverse events. None of the serious adverse events has been observed to be related to FESPIXON cream.

11. Excipients

Purified Water, Liquid Petrolatum, White Petrolatum, Propylene Glycol, Cetyl Stearyl Alcohol, Tween 60, Span 60, Methyl Paraben and Propyl Paraben

12. Package

No more than 1000 gram in an aluminum tube.

13. Shipping and Storage

Three-year shelf-life. Store at room temperature of 25°C. Keep out of the reach of children.

ONENESS
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Marketing Authorization Holder

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