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FESPIXON® cream

Treatment of Diabetic Foot Ulcers

Plectranthus amboinicus extract ..... 2.5 mg/g
Centella asiatica extract ..... 10 mg/g

Prescription only

1. Product Description
FESPIXON contains extracts of *Plectranthus amboinicus* (PA-F4, 2.5 mg/g) and *Centella asiatica* (S1, 10 mg/g) 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 non-ischaemic Wagner Grade 1 and Grade 2 chronic diabetic ulcers without active infection.

3. Dosage and Administration
FESPIXON is prescription-only.
FESPIXON shall be topically applied to the lesion twice daily by fully covering the ulcer.
Once FESPIXON 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
FESPIXON is contraindicated in the patients who are hypersensitive to the ingredients of FESPIXON, including *Plectranthus amboinicus, Centella asiatica* or excipients.

5. Warnings and Precautions
FESPIXON is for external use only and should not be taken orally or used in or around eyes or in mucosa.

6. Drug Interactions
FESPIXON hasn't been studied in drug-drug interaction with other medications. It is not known if FESPIXON interacts with other medications.

7. Use by Specific Populations
FESPIXON 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 FESPIXON is not teratogenic. However, there has been no clinical trials specifically conducted with FESPIXON on pregnant or breastfeeding women so it is also not known whether FESPIXON would cause fetal harm when it is administered to a pregnant woman or can affect reproductive capacity. FESPIXON 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 FESPIXON is administered to breastfeeding women.

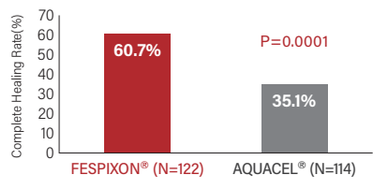
10. Clinical Pharmacology
• 10.1 Mechanism of Action
Plectranthus amboinicus and *Centella asiatica* extracts have been respectively used in human for a long period of time. According to literatures, *Plectranthus amboinicus* has antibacterial and anti-inflammatory effects and *Centella asiatica* can promote collagen production, angiogenesis, anti-oxidation to assist epithelialization and accelerate wound healing effect. FESPIXON contains *Plectranthus amboinicus* extract (PA-F4) and *Centella asiatica* extract (S1). *In-vitro* and *in-vivo* studies have shown that FESPIXON 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 FESPIXON 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, FESPIXON was found with no mutagenic potential in Ames test and no chromosome aberration potential in Chinese hamster ovary cells. Also, FESPIXON was found negative *in vivo* in the micronucleus assay with mouse peripheral blood.
FESPIXON 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 FESPIXON is 5000 mg/kg, 3000 mg/kg and 12.5% 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. FESPIXON was found without teratogenic effect in the oral teratogenicity study in rats.
FESPIXON 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 and asiaticoside in S1. The results of single topical administration of FESPIXON 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 12.403 pg/mL; 7 of the 12 subjects were detected less than 1 ng/mL (LLOQ) of asiaticoside in plasma concentration, while only 5 out of 12 subjects were with detectable plasma concentrations of no more than 9.276 ng/mL. The results of repeat topical administration by twice daily application of FESPIXON 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 FESPIXON is very limited without accumulation.

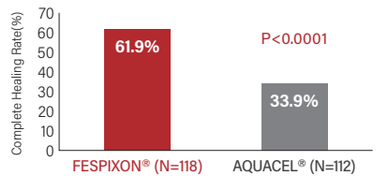
• 10.4 Clinical Trial
A randomized, controlled, multinational, multicenter phase 3 clinical study was conducted to evaluate the efficacy and safety of FESPIXON in treating patients with chronic diabetic foot ulcers. A total of 236 patients with Wagner grade 1 or grade 2 diabetic foot ulcers were randomized 1:1 to receive either FESPIXON (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. Subjects received FESPIXON or AQUACEL® Hydrofiber® dressing in a 1:1 ratio after debridement.
Figure 1 has shown the results in the full analysis set (FAS), 60.7% of patients in FESPIXON 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 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)



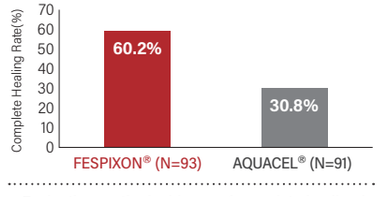
In the modified intention to treat (mITT) analysis set (Figure 2), 61.9% of patients in FESPIXON group achieved complete healing whereas 33.9% of patients in AQUACEL® Hydrofiber® dressing group achieved complete healing. The complete healing rate of patients treated with FESPIXON is higher. The p-value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

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



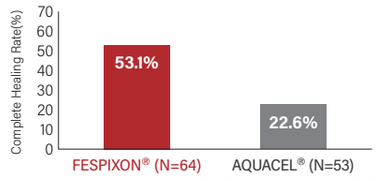
• Evaluation on the incidence of complete healing in patients with grade 2 ulcers according to Wagner classification system
In the full analysis set (FAS) on patients with ulcers under grade 2 (Wagner=2), 60.2% patients of FESPIXON group achieved complete healing whereas 30.8% of patients in AQUACEL®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

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



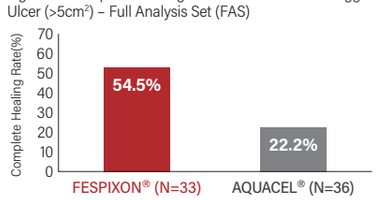
• Evaluation on the incidence of complete healing in patients with plantar ulcer
The results in patients with plantar ulcers in the full analysis set (FAS) showed (Figure 4) that 53.1% of patients in FESPIXON group achieved complete healing whereas 22.6% of patients in AQUACEL® Hydrofiber® dressing group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

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



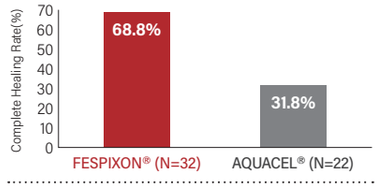
• Evaluation on the incidence of complete healing in patients with bigger ulcer (>5 cm²)
The results in patients with bigger ulcers (>5 cm²) in the full analysis set (FAS) showed (Figure 5) that was 54.5% of patients in FESPIXON group achieved complete healing whereas 22.2% of patients in AQUACEL® Hydrofiber® 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
The results in patients with smoking habits in the full analysis set (FAS) showed (Figure 6) that 68.8% of patients in FESPIXON 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 group achieved complete healing earlier than the comparator, AQUACEL® Hydrofiber® group.

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

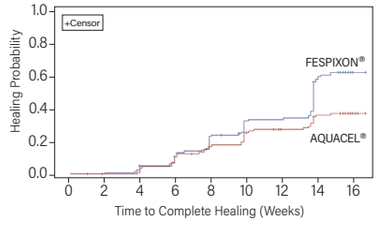
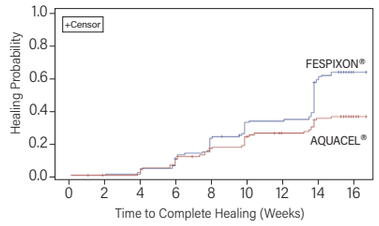
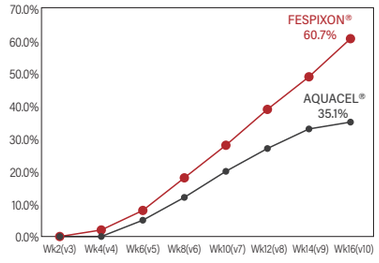


Figure 8. Kaplan-Meier Plots for Complete Healing-Modified Intention-to-treat Analysis Set (mITT)



The cumulative rate of complete wound healing in the FESPIXON 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 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 group and AQUACEL® Hydrofiber® group are shown in Table 1. The related treatment-emergent adverse events in FESPIXON and AQUACEL® Hydrofiber® group are shown in Table 2.

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

TEAEs (%)	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 TEAEs (%)	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. Only 7 patients had related treatment-emergent adverse events. None of the serious adverse events has been observed to be related to FESPIXON.

11. Excipients
Purified Water, Liquid Petrolatum, White Petrolatum, Propylene Glycol, Cetyl Stearyl Alcohol, Tween 60, Span 60, Methyl Paraben (1 mg/g, as preservative) and Propyl Paraben (0.1 mg/g, as preservative).

12. Package
Each box contains an aluminum tube of 15 gram cream.

13. Shipping and Storage
Do not store above 30°C. Keep out of reach of children.

14. In-use Shelf-life
60 days.

ONENESS
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