Summary Report of Benefit-Risk Assessment

FESPIXON CREAM

NEW DRUG APPLICATION

Active Ingredient(s)	*Centella asiatica* extract, *Plectranthus amboinicus* extract
Product Registrant	Pharmeng Technology Pte Ltd
Product Registration Number	SIN16683P
Application Route	Abridged evaluation
Date of Approval	31 January 2023

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A INTRODUCTION

Fespixon cream is indicated for the treatment of diabetic foot ulcer.

The active substances, *Centella asiatica* and *Plectranthus amboinicus* extracts, promote specific-chemokines-induced transition of the microenvironment dominated by M1-macrophages into that dominated by M2-macrophages, to advance the wounds from inflammatory stage into the proliferative stage and achieve ulcer healing.

Fespixon is available as a cream containing 0.25% of *Plectranthus amboinicus* extract-F4 (PA-F4) and 1% of *Centella asiatica* extract (S1). Other ingredients in the cream are cetyl stearyl alcohol, liquid petrolatum, methyl paraben, propyl paraben, Span 60, Tween 60, propylene glycol, white petrolatum and purified water.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, PA-F4, is manufactured at [redacted]. The other drug substance, S1, is manufactured at [redacted]. The drug product, Fespixon cream, is manufactured at Oneness Biotech Co., Ltd., Nanchou Plant, Nanchou Township, Taiwan.

Drug substance: PA-F4

Adequate controls have been presented for the botanical raw materials and intermediates. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with the general principles described in ICH Q6A and are acceptable. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity and assay testing is presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C ± 2°C, 75% RH ± 5% RH with a re-test period of 24 months. The packaging is a high-density polyethylene (HDPE) bottle.

Drug substance: S1

Adequate controls have been presented for the botanical raw materials and intermediates. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with the general principles described in ICH Q6A and are acceptable. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity and assay testing is presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C ± 2°C, 75% RH ± 5% RH with a re-test period of 24 months. The packaging is a low-density polyethylene (LDPE) bag.

Drug product:

The cream is manufactured using a standard homogenising process. The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with the general principles described in ICH Q6A and are acceptable. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity and assay testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The in-use period after opening is 60 days and is supported with appropriate data. The container closure system is an aluminium tube with HDPE screw cap containing 15g of cream.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Fespixon cream in the treatment of diabetic foot ulcers (DFU) was based primarily on one pivotal Phase III Study ON101CLCT02. This was a randomised, multicentre, evaluator blinded, active-controlled study of Fespixon cream compared with Aquacel Hydrofiber dressing for treatment of Wagner grades 1 and 2 chronic DFUs in patients with Type 1 or 2 Diabetes mellitus (DM).

Patients in the study were randomised in a 1:1 ratio to receive 1.25% Fespixon cream applied twice daily or Aquacel Hydrofiber dressing that was changed daily or on alternate days or three times a week according to need (no longer than 7 days). The study treatment was applied to the selected ulcer for a maximum period of 16 weeks, until complete ulcer closure or until the patient exited the study as a treatment failure. All patients, regardless of wound healing at the end of treatment period, were followed for 12 weeks to investigate the durability of healing. During the follow-up period, Aquacel Hydrofiber was used by patients who had an unhealed wound or wound recurrence. Each target ulcer was monitored with wound photographs for blinded assessment at every scheduled visit. Post-debridement, moist wound dressings are considered as appropriate treatments for non-ischaemic Wagner grade 1 or 2 DFUs without

active infection and the use of Aquacel Hydrofiber dressing as an active comparator in the study was considered acceptable.

The main inclusion criteria were male or female subjects ≥20 and < 80 years of age with Type 1 or 2 DM with HbA1c < 12.0% and had Wagner grade 1 or 2 severity diabetic foot ulcers present for at least 4 weeks with a size ranging from 1-25 cm^2 after debridement. Subjects with ulcers above the ankle, active infection, poor nutritional status, presence of necrosis/purulence/sinus tract were excluded from the study. While the Wagner grading does not consider infection or ischaemia which are risk factors for ulcers and their healing, exclusion of subjects with active infection and ankle brachial index (ABI)>0.8 ensured recruitment of patients with adequate vascular perfusion and uninfected ulcers.

The primary efficacy endpoint was to demonstrate statistical superiority of the incidence of complete healing of the target ulcer with Fespixon cream compared to Aquacel Hydrofiber dressing at the end of treatment period of 16 weeks. Complete healing was defined as complete epithelialisation which is maintained with no drainage for at least 2 weeks and was confirmed by a blinded independent evaluator. There were two interim analyses planned at 50% and 90% of study completion and the O'Brien alpha spending function was used to control the overall type I error at 5%.

Analysis of primary endpoint and secondary endpoint were conducted in the full analysis set (FAS) which included all the randomised subjects as well as in the modified intent to treat population (mITT) which included patients in the FAS with eligible target ulcer at baseline. Key secondary efficacy endpoints were time to complete ulcer healing, percentage change in ulcer surface area from baseline, percentage of patients with a 50% reduction of ulcer surface area and incidence of infection of the target ulcer. The exploratory endpoint was recurrence of the target ulcer within follow-up period which was evaluated in patients who demonstrated complete wound healing at the end of treatment period.

A total of 236 patients were randomised in the study and were included in the FAS population: 122 patients in the Fespixon arm and 114 patients in Aquacel Hydrofiber arm. The study recruited patients with type 1 or 2 DM with a median age of 57 years (range: 22 to 79 years). The mean HbA1C was 8.1% and all subjects had HbA1C< 12%. All subjects had Wagner grade 1 or 2 severity diabetic foot ulcers that were ranging in size from 0.7-20 cm^2 after debridement. The majority of subjects in Fespixon arm had Wagner grade 2 ulcers (76%) compared to Wagner grade 1 ulcers (24%). The median duration of the ulcer was 2.3 months (range: 1.0 to 96.0 months) in Fespixon arm and 3.0 months (range: 1.0 to 120 months) in Aquacel Hydrofiber arm. There were some imbalances in the baseline characteristics which favoured the Fespixon arm, these included history of amputation (45.90% in Fespixon arm and 52.63% in Aquacel arm) and peripheral artery disease (36.89% in Fespixon arm and 42.98% in Aquacel arm).

While the baseline peripheral artery disease showed imbalances across the arms, ulcer aetiology due to peripheral vascular disease was balanced across the arms (24.59% in Fespixon arm and 26.32% in Aquacel arm). On the other hand, the proportion of subjects with plantar ulcers were higher in Fespixon arm (52.5% in Fespixon arm and 46.5% in Aquacel arm) and potentially favoured the comparator arm, as plantar ulcers are more difficult to heal due to direct contact during ambulation and the weight bearing pressure.

The study met the primary efficacy endpoint of demonstrating statistically superior complete ulcer healing with Fespixon cream (60.7% in FAS and 61.9% in mITT) compared to Aquacel Hydrofiber dressing (35.1% in FAS and 33.9% in mITT), with an odds ratio of 2.84 (95% CI:

1.66,4.84) in FAS population and 3.15 (95% CI: 1.82,5.43) in mITT population (the lower limit [LL] of 95% CI exceeded 1 in favour of Fespixon arm).

Results of the subgroup analyses also consistently favoured the Fespixon arm with respect to complete healing rate, including Wagner grade 2 ulcers (HR: 3.51; 95% CI: 1.89, 6.53), ulcer area >5cm^2 (HR:4.09; 95% CI: 1.42, 11.80), plantar ulcers (HR: 3.94; 95% CI:1.73, 8.98), baseline HbA1c >7% (HR:2.84; 95% CI:1.48, 5.45), current smoker (HR: 5.04 ; 95% CI:1.52, 16.67); plantar and wound area >5cm^2 (HR:4.95; 95% CI:0.69, 35.68), and ulcer duration ≥6 months (HR: 3.99; 95% CI:1.09, 14.63). While numerical benefit was observed for complete ulcer healing with Fespixon in Wagner grade 1 ulcers, the magnitude of benefit was lower (62.1% in Fespixon arm versus 52.2% in Aquacel Hydrofiber arm; Δ = 9.9%) compared to that observed in Wagner grade 2 ulcers (60.2% in Fespixon arm versus 30.8% in Aquacel Hydrofiber arm; Δ = 29.4%). While the incidence of ulcer healing remained consistent in the Fespixon arm for both Wagner grade 1 and 2 ulcers, the lower effect size observed in the Grade 1 ulcers could be attributed to the higher healing rate achieved with the standard of care due to the lesser complexity and depth of grade 1 ulcers.

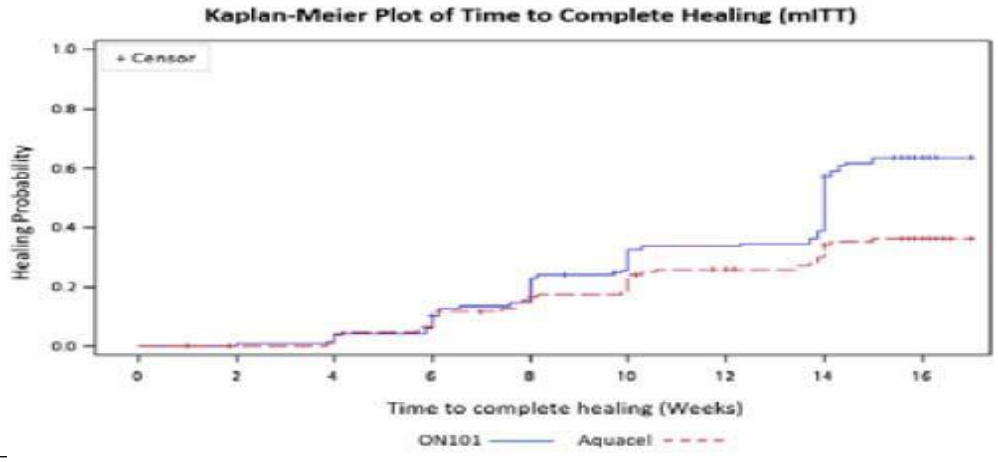
Subgroup analyses for complete healing rate based on amputation history (51.8% in Fespixon arm versus 36.7% in Aquacel arm) and peripheral vascular disease (66.7% in Fespixon arm versus 40.0% in Aquacel arm) showed a trend in favour of Fespixon arm, suggesting that the imbalance observed at baseline in favour of Fespixon arm may not have biased the outcome of the primary efficacy endpoint.

Summary of primary efficacy endpoint and subgroup analyses

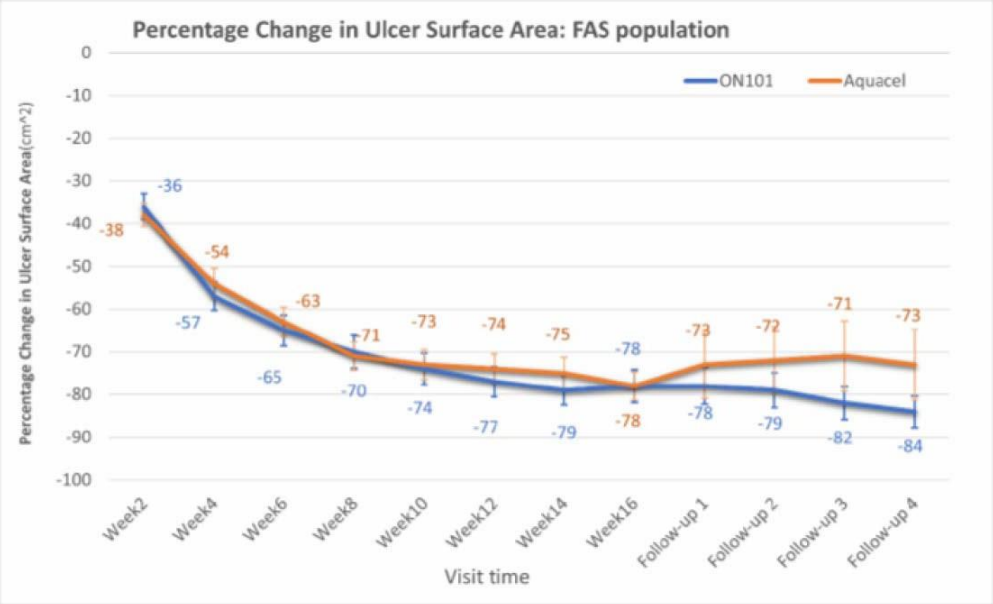
Complete ulcer healing	**Fespixon® Cream**	**Aquacel® Hydrofiber®**	**Odds ratio (95% CI) p-value**
Primary efficacy endpoint			
FAS	74/122 (60.7%)	40/114 (35.1%)	2.84 (1.66,4.84)
mITT	73/118 (61.9%)	38/112 (33.9%)	3.15 (1.82, 5.43)
Subgroup analyses based on complete healing rate			
Wagner Grade 2 (FAS)	56/93 (60.2%)	28/91 (30.8%)	3.51 (1.89, 6.53) 0.0001
Wagner Grade 2 (mITT)	55/90 (61.1%)	26/89 (29.2%)	3.88 (2.06, 7.31) <0.0001
Ulcer Areas of >5 cm^2 (FAS)	18/33 (54.5%)	8/36 (22.2%)	4.09 (1.42, 11.80) 0.0056
Ulcer Areas of >5 cm^2 (mITT)	18/32 (56.3%)	8/36 (22.2%)	4.35 (1.50, 12.64) 0.0040
Plantar ulcers (FAS)	34/64 (53.1%)	12/53 (22.6%)	3.94 (1.73, 8.98) 0.0008
Plantar ulcers (mITT)	34/62 (54.8%)	11/52 (21.2%)	4.50 (1.94, 10.47) 0.0002
HbA1c >7% (FAS)	51/91 (56.0%)	23/75 (30.7%)	2.84 (1.48, 5.45) 0.0011
HbA1c >7% (mITT)	50/87 (57.5%)	22/74 (29.7%)	3.16 (1.63, 6.13) 0.0004
HbA1c ≤7% (FAS)	23/31 (74.2%)	17/39 (43.6%)	3.70 (1.30, 10.51) 0.0102

HbA1c ≤7% (mITT)	23/31 (74.2%)	16/38 (42.1%)	3.91 (1.37, 11.18) 0.0075
HbA1c >7% and Plantar Ulcers (FAS)	25/50 (50.0%)	7/36 (19.4%)	4.44 (1.56, 12.61) 0.0038
HbA1c >7% and Plantar Ulcers (mITT)	25/48 (52.1%)	6/35 (17.1%)	5.43 (1.82, 16.16) 0.0012
HbA1c ≤7% and Wound Area> 5 cm^2 (FAS)	9/11 (81.8%)	5/15 (33.3%)	10.9 (1.26, 94.97) 0.0143
HbA1c ≤7% and Wound Area> 5 cm^2 (mITT)	9/11 (81.8%)	5/15 (33.3%)	10.9 (1.26, 94.97) 0.0143
Plantar and Wound Area> 5 cm^2 (FAS)	5/12 (41.7%)	2/14(14.3%)	4.95 (0.69, 35.68) 0.1166
Plantar and Wound Area> 5 cm^2 (mITT)	5/11 (45.5%)	2/14(14.3%)	7.14 (0.84, 60.98) 0.0849
Current smoker (FAS)	22/32 (68.8%)	7/22 (31.8%)	5.04 (1.52, 16.67) 0.0075
Current smoker (mITT)	22/32 (68.8%)	7/22 (31.8%)	5.04 (1.52, 16.67) 0.0075
Non-current smoker (FAS)	52/90 (57.8%)	33/92 (35.9%)	2.37 (1.30, 4.35) 0.0031
Non-current smoker (mITT)	51/86 (59.3%)	31/90 (34.4%)	2.69 (1.45, 4.99) 0.00101
Prior Ulcer Duration ≥6 months	12/36 (33.3%)	4/35 (11.4%)	3.99 (1.09, 14.63) 0.0272
With a history of amputation	29/56 (51.8%)	22/60 (36.7%)	1.82 (0.85, 3.88) 0.1011
Without a history of amputation	45/66 (68.2%)	18/54 (33.3%)	4.30 (1.99, 9.33) 0.0001
Peripheral vascular disease	20/30 (66.7%)	12/30 (40.0%)	

The secondary endpoint of time to complete healing was faster in Fespixon arm compared to Aquacel Hydrofiber arm (HR: 1.80; 95% CI: 1.23, 2.65) with the Kaplan-Meier (KM) curves starting to separate by 8 weeks and clearly separated by 14 weeks.



Incidences of infection were numerically lower in Fespixon arm (4.92% in FAS and 3.39% in mITT) compared to Aquacel arm (6.14% in FAS and 6.25% in mITT). There was no benefit observed with Fespixon cream compared to Aquacel Hydrofiber dressing for the percentage change in ulcer surface area (-78% in both arms) and percentage of patients with 50% reduction in ulcer size (82.79% versus 85.96%) at the end of treatment period. This might take longer time given the complex ulcer healing processes. Nevertheless, the difference in percentage change in ulcer surface area between treatment arms started to favour Fespixon arm towards the end of the follow-up period.



The exploratory endpoint showed a higher incidence of recurrence of the healed ulcers in the Fespixon arm compared to Aquacel Hydrofiber arm in the 12-week follow-up period (20.27% vs 17.5%). Further analysis revealed that this recurrence was contributed by plantar ulcers for which an imbalance was observed in favour of Aquacel Hydrofiber arm at baseline.

There were also other imbalances which were not in favour of Fespixon arm which included lesser use of off-loading devices (51.6% in Fespixon arm versus 64.2% in Aquacel Hydrofiber arm) and longer mean duration of plantar ulcers (5.69 months in Fespixon arm versus 2 months in Aquacel Hydrofiber arm). These imbalances might have contributed to the higher recurrence in the completely healed ulcers of the Fespixon arm. Furthermore, post-hoc analysis of primary endpoint of complete healing of ulcers with exclusion of recurred ulcers provided reassurance as this showed benefit with Fespixon cream compared to Aquacel Hydrofiber dressing for overall ulcers (48.4% vs 28.9%) and also for plantar ulcers (40.6% vs 18.9%), respectively.

Taken together, the pivotal Phase 3 study ON101CTC02 provided evidence for statistically significant superior complete healing of Wagner grade 1 and 2 non-ischaemic diabetic foot ulcers (without active infection) with Fespixon cream compared to Aquacel Hydrofiber dressing. All the subgroup analyses based on the Wagner grade, ulcer size, site of ulcers (including plantar ulcers), baseline HbA1c, smoking status, wound area, ulcer duration, amputation history, and peripheral artery disease favoured the Fespixon arm consistently.

The secondary endpoint of time to complete ulcer healing was faster with Fespixon cream (median of 14.0 weeks) compared to Aquacel Hydrofiber dressing (median not reached) supporting the primary efficacy endpoint. While some secondary endpoints such as

percentage reduction in ulcer size and proportion of subjects with 50% reduction in ulcer size did not demonstrate efficacy, the primary endpoint of complete healing was a robust and hard endpoint. Overall, the evidence presented was considered adequate to demonstrate efficacy of Fespixon.

A Phase 3, multicentre, randomised study (ON101CLCT04) of Fespixon cream in chronic DFUs is currently ongoing and the final results of this study will be required to confirm the efficacy and safety of Fespixon cream in the treatment of patients with chronic DFUs.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Fespixon cream was based primarily on safety data derived from the pivotal Phase III study ON101CLCT02 comprising a total of 236 patients who had received at least one dose of study treatment: 122 subjects in the Fespixon arm and 114 subjects in the Aquacel arm.

In addition, a total of 176 human subjects had received Fespixon cream based on one Phase I pharmacokinetic (PK) study ON101CLPK01, two Phase II studies (Study ON101CLAS01 and Study DCB-WH1-CP001) and one Phase III study ON101CLCT02. The median duration of exposure in the Phase III study was similar in the Fespixon arm (16.0 weeks) and the Aquacel arm (15.9 weeks).

Overview of treatment-emergent adverse events (TEAEs)

	Study ON101CLCT02		**Study DCB-WH1- CP001**		**Study ON101CLAS01**		**Study ON101CLPK01**
TEAEs	**Fespixon (N=122)**	**Aquacel (N=114)**	**Fespixon (N=30)**	**Placebo (N=11)**	**Fespixon (N=12)**	**Aquacel (N=12)**	**Fespixon (N=12)**
Any TEAE	76 (62.3%)	77 (67.5%)	22 (73.3%)	9 (81.8%)	5 (41.7%)	5 (41.7%)	3 (25.0%)
Serious TEAE	14 (11.5%)	9 (7.9%)	8 (26.7%)	2 (18.2%)	0	0	0
Discontinuations due to TEAE	2 (1.6%)	2 (1.7%)	1 (3.3%)	1 (9.1%)	0	0	0
Deaths due to TEAE	0	0	1 (3.3%)	0	0	0	0

In the Phase III study ON101CLCT02, the proportions of subjects who had experienced a TEAE were comparable between the two arms (62.3% in Fespixon arm versus 67.5% in Aquacel arm). The majority of TEAEs were mild in severity (> 83% in Fespixon arm and >84% in Aquacel Hydrofiber arm) with less than 5% being severe in nature. There were 16 events in 12 patients (11 events in Fespixon arm and 5 events in Aquacel Hydrofiber) considered by the investigator to be related to treatment. These included peripheral swelling, staphylococcal-infection, weight increased, 2 events of hyperuricaemia, dermatitis contact, wound complication, erythema, rash and 2 events of eczema in the Fespixon arm; and pyrexia, osteomyelitis, cellulitis, diabetic foot infection, and skin papilloma in Aquacel Hydrofiber arm (osteomyelitis was a serious adverse event). There were no severe AEs considered related by the investigator in the Fespixon arm.

There were 24 serious TEAEs reported in 14 patients in the Fespixon group and 14 serious TEAEs in 9 patients in the Aquacel Hydrofiber group during the comparative period of the study and these were mainly for infection. There were no serious TEAEs considered related to treatment by the investigator in the Fespixon arm. Only one case of serious TEAE in the Aquacel Hydrofiber arm was considered related to treatment (osteomyelitis) by the investigator.

Discontinuation due to TEAEs were observed in two subjects in Fespixon arm and two in Aquacel Hydrofiber arm. The TEAE leading to discontinuation which was considered related to Fespixon by the investigator was necrosis of the diabetic foot. There was one death during the follow-up period in the Fespixon arm and was considered unrelated to the study medication by the investigator (septic shock, acute kidney injury and acute respiratory failure). There were also no signals of systemic toxicity or hypersensitivity reactions.

Fespixon cream was generally well tolerated with few TEAEs considered related to treatment and most of the TEAEs were mild (~80%) and none of the severe or serious TEAEs were considered related by the investigator to the Fespixon arm. Taking together the non-clinical toxicology data, low systemic absorption based on clinical pharmacology data, and the lack of imbalances in systemic events in the pivotal study, systemic toxicity was not considered as a concern. Overall, the safety profile was comparable to the standard of care with no major concerns.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Foot ulcers are important complication of diabetes mellitus and usually precede lower-extremity amputation. The aim of treatment of DFUs is quick and complete healing as well as prevention of recurrence in healed ulcers. Sharp debridement of the necrotic tissue and the surrounding callus, treatment of underlying infection and ischaemia are critical in management of DFUs. In line with the current standard of care, a warm, moist environment (by dressings, etc,) that is protected from external contamination is most conducive to wound healing.

The use of Fespixon cream in Wagner Grade 1 and 2 diabetic foot ulcers was supported by one pivotal Phase III Study ON101CLCT02 which was a randomised (1:1), multicentre, evaluator blinded, active-controlled study comparing the efficacy and safety of Fespixon cream with Aquacel Hydrofiber dressing.

The study demonstrated that Fespixon cream resulted in statistically greater complete healing compared to Aquacel Hydrofiber dressing (60.7% versus 35.1% in FAS and 61.9% versus 33.9% in mITT respectively) with the LL of 95% CI of the odds ratio exceeding 1 in favour of Fespixon arm. While there were some imbalances in certain baseline characteristics, the subgroup analyses based on the Wagner grade, ulcer size, site of ulcers (including plantar ulcers), baseline HbA1c, smoking status, wound area, ulcer duration, amputation history, peripheral artery disease favoured the Fespixon arm consistently. Complete healing was also observed to occur earlier in Fespixon arm compared to Aquacel were the KM curves started to separate by about 8-10 weeks after start of treatment. There were also numerically lower incidences of infection observed with Fespixon arm compared to Aquacel Hydrofiber arm (4.92% vs 6.14%). The observed benefit was mainly driven by Wagner grade 2 ulcers, and numerical benefit was also observed in grade 1 ulcers.

There was a slightly higher incidence of ulcer recurrence observed in the healed ulcers in Fespixon arm compared to Aquacel Hydrofiber arm (20.27% vs 17.5%). Further analysis suggested that the baseline imbalances favouring Aquacel Hydrofiber arm in the proportion of subjects with plantar ulcers and other factors like ulcer size, duration, use of off-loading devices might have contributed to the observations. Additional analysis of proportion of subjects with complete healing after excluding the recurrent ulcers consistently demonstrated benefit of Fespixon arm over Aquacel Hydrofiber arm (48.4% vs 28.9%).

Fespixon cream was well tolerated with the overall safety profile similar to the comparator. No hypersensitivity reactions were observed. There were no serious or severe TEAEs considered related to the study drug by the investigator reported in the study. The discontinuation rates due to TEAEs were comparable between the two treatment arms. No signal of systemic toxicity due to systemic absorption was observed.

Overall, the benefit-risk profile of Fespixon cream for the treatment of Wagner grade 1 and 2 non-ischaemic chronic diabetic foot ulcers without active infection was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of Fespixon cream have been demonstrated to outweigh the risks of the treatment for Wagner grade 1 and 2 non-ischaemic chronic diabetic foot ulcers without active infection. Approval of the product registration was granted on 31 January 2023.

The approval of this application is subject to the submission of the final results of the ongoing Phase 3 study (ON101CLCT04) to confirm the efficacy and safety of Fespixon cream in the treatment of patients with Wagner grade 1 and 2 non-ischaemic chronic DFUs.

APPROVED PACKAGE INSERT AT REGISTRATION

File Name	ON101-Insert_Singapore
Size	w34X20cm
Draft Date	2023/01/20

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.

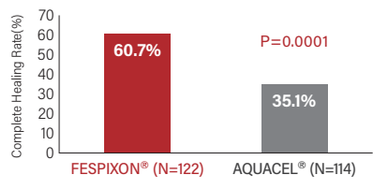
10. Clinical Pharmacology
• 10.1 Mechanism of Action
Plectranthus amboinicus and *Centella asiatica* extracts have been respectively used in human for a long period of time. According to literatures, *Plectranthus amboinicus* has antibacterial and anti-inflammatory effects and *Centella asiatica* can 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.

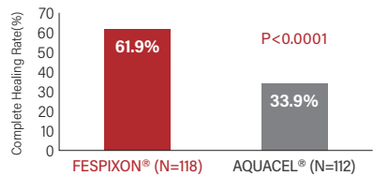
• 10.4 Clinical Trial
A randomized, controlled, multinational, multicenter phase 3 clinical study was conducted to evaluate the efficacy and safety of FESPIXON in treating patients with chronic diabetic foot ulcers. A total of 236 patients with Wagner grade 1 or grade 2 diabetic foot ulcers were randomized 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)



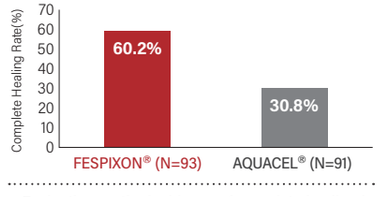
In the modified intention to treat (mITT) analysis set (Figure 2), 61.9% of patients in FESPIXON group achieved complete healing whereas 33.9% of patients in AQUACEL® Hydrofiber® dressing group achieved complete healing. The complete healing rate of patients treated with FESPIXON is higher. The p-value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

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



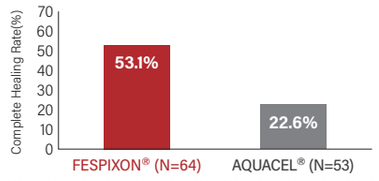
• Evaluation on the incidence of complete healing in patients with grade 2 ulcers according to Wagner classification system
In the full analysis set (FAS) on patients with ulcers under grade 2 (Wagner=2), 60.2% patients of FESPIXON group achieved complete healing whereas 30.8% of patients in AQUACEL®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

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



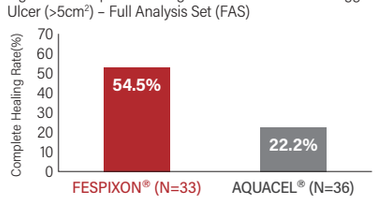
• Evaluation on the incidence of complete healing in patients with plantar ulcer
The results in patients with plantar ulcers in the full analysis set (FAS) showed (Figure 4) that 53.1% of patients in FESPIXON group achieved complete healing whereas 22.6% of patients in AQUACEL® Hydrofiber® dressing group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

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



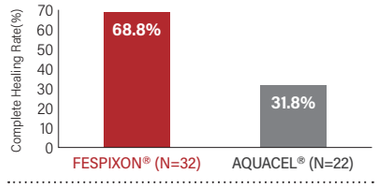
• Evaluation on the incidence of complete healing in patients with bigger ulcer (>5 cm²)
The results in patients with bigger ulcers (>5 cm²) in the full analysis set (FAS) showed (Figure 5) that was 54.5% of patients in FESPIXON group achieved complete healing whereas 22.2% of patients in AQUACEL® Hydrofiber®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

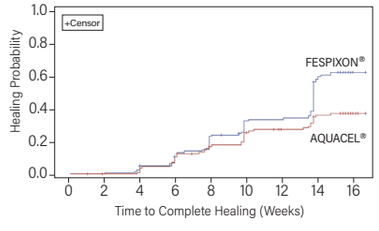
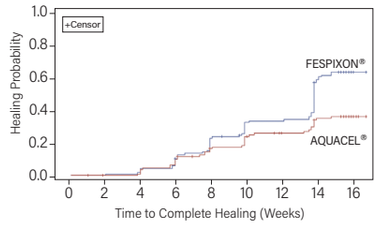
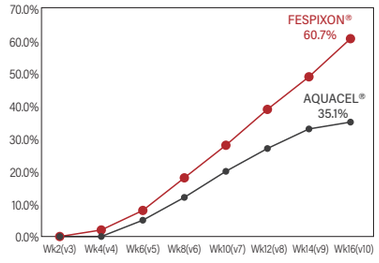


Figure 8. Kaplan-Meier Plots for Complete Healing-Modified Intention-to-treat Analysis Set (mITT)



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
Oneness Biotech Co., Ltd.

Manufacturer:
Oneness Biotech Co., Ltd., Nanchou plant
No. 8, Tangchang Rd., Nanchou Township, Pingtung County 926, Taiwan, R.O.C.