速必一 乳膏

FESPIXON cream

衛部藥製字第 060827 號
本藥品須由醫師處方使用

1. 產品描述
速必一乳膏含有 1.25% 到手香萃取物 (PA-F4, 0.25%) 與積雪草萃取物 (S1,1%)。由植物萃取而成，乳膏外觀為黃綠色至淡綠色，供局部使用。

2. 適應症
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。

3. 用法用量
本品須由醫師處方使用。
本品於患部每日塗抹兩次，須完全覆蓋傷口。
塗抹藥膏後以紗布覆蓋傷口潰瘍區域，並儘量保持患部通風，直至潰瘍完全癒合。

4. 禁忌
本品禁用於以下病人：對本品成分有過敏反應者，包括對到手香、積雪草或賦形劑過敏。

5. 警語及注意事項
本品限於皮膚外用，不得內服，亦不得使用於眼睛內、眼睛四周或黏膜。

6. 藥物交互作用
本品未與其它藥品做過藥物交互作用研究，尚不確定本品是否會與其他藥物相互作用。

7. 特殊族群之使用
本品為局部外用製劑，全身暴露量極低，尚無引起全身性作用之疑慮。目前臨床上僅針對患有糖尿病足部傷口潰瘍成人病人進行研究，尚未針對肝腎功能不全、兒童、老年人、懷孕或授乳婦女等特殊族群進行研究。

8. 懷孕
大鼠口服致畸胎性試驗顯示本品不具有致畸胎性。然而，目前尚未針對懷孕或授乳婦女等特殊族群進行研究，仍不清楚在孕婦使用時是否會造成胎兒傷害，或者會影響生育能力。只有在明確需要時才可供給孕婦使用。

9. 授乳之母親
尚不確定 PA-F4 和 S1 是否會被分泌至人類乳汁。由於許多藥物會被分泌至乳汁中，在給授乳的母親使用本品時應格外小心。

10. 臨床藥理學
10.1 作用機轉
到手香與積雪草分別已有長久人體使用經驗，根據文獻研究，到手香具有抗菌、抗發炎作用；積雪草具有促進膠原蛋白生成、血管新生、抗氧化等幫助表皮細胞上皮化，加速傷口癒合作用。本品含有 1.25% 到手香萃取物 PA-F4 與積雪草萃取物 S1。於細胞及動物試驗顯示，本品經由抑制發炎反應及活化特定趨化因子，改變慢性傷口的巨噬細胞極化作用，將傷口潰瘍由 M1 型巨噬細胞為主之傷口微環境，轉化為 M2 型巨噬細胞為主之傷口微環境。M2 型巨噬細胞可以透過 (1) 調控 VEGF 促進血管新生，增加血液流量；(2) 影響 TGF 誘導產生組織再生之幹細胞到達患部，促使纖維母細胞增生；(3) 透過羥脯氨酸合成膠原蛋白，產生胞外基質沉積，使傷口達到完全癒合。綜上，本品之作用機轉為抑制 M1 型巨噬細胞，並活化 M2 型巨噬細胞，重塑傷口微環境 M1、M2 型巨噬細胞平衡，調控傷口之發炎期進入增生期，達到傷口潰瘍癒合的目的。

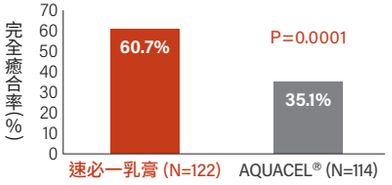
10.2 非臨床毒理學
在基因毒性研究上，本品於細菌逆突變試驗 (Ames test) 當中，無產生致基因突變性；於中國倉鼠卵巢細胞的染色體變異試驗，未造成結構染色體斷裂，於小鼠微核試驗，周邊血液細胞亦無微核現象發生。
在大鼠口服單一劑量毒性試驗、大鼠口服 28 天重覆劑量毒性試驗及兔子局部塗抹 13 週重覆劑量毒性試驗上，本品無不良反應劑量 (No-Observed-Adverse-Effect-Level，NOAEL) 分別為 5000 mg/kg、3000 mg/kg 及 12.5%。於大鼠口服 28 天毒性試驗及兔子局部塗抹 13 週重覆劑量毒性試驗，監測對雄性和雌性生殖器官的毒性作用，未觀察到與治療相關的毒性。大鼠口服致畸胎性試驗亦顯示本品不具有致畸胎性。本品不具有皮膚刺激性及過敏性，亦不會對眼睛造成刺激。目前尚未有本品致癌性之研究。

10.3 藥物動力學
於 12 位慢性糖尿病足部傷口潰瘍病人進行一項為期 2 週的臨床試驗，評估到手香萃取物 PA-F4 以及積雪草萃取物 S1 指標成分 salvigenin 與 asiaticoside 的藥物動力學特性。依據分析結果，於單次塗抹本品後，12 人中有 10 人 salvigenin 血中濃度小於最低偵測濃度 2 pg/mL，僅 2 人可測得之血中濃度最高不超過 12.403 pg/mL；12 人中有 7 人 asiaticoside 血中濃度小於最低偵測濃度 1 ng/mL，僅 5 人可測得血中濃度最高不超過 9.276 ng/mL。每天兩次連續投與本品 14 天後，12 人中有 8 人 salvigenin 血中濃度小於最低偵測濃度 2 pg/mL，僅 4 人可測得之血中濃度最高不超過 16.972 pg/mL；12 人中有 7 人 asiaticoside 血中濃度小於最低偵測濃度 1 ng/mL，僅 5 人可測得血中濃度最高不超過 6.154 ng/mL。試驗結果顯示本品全身性吸收量極低且不具蓄積性。

10.4 臨床試驗
在一項隨機、對照、多國、多中心的第三期臨床試驗中，評估速必一乳膏在治療慢性糖尿病足部傷口潰瘍病人中的療效和安全性。總共 236 位患有 Wagner 一級或二級的糖尿病足部傷口潰瘍的病人，按 1:1 比例隨機分派至速必一乳膏 (N=122) 或 AQUACEL® Hydrofiber® 敷料組 (N=114)，隨機分配到任一組的病人進行 16 週治療，評估其傷口完全癒合率及達到傷口完全癒合所需之時間。
圖一顯示全分析數據集 (FAS) 之結果，速必一乳膏組 60.7% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 35.1% 病人傷口完全癒合，接受速必一乳膏治療的病人傷口完全癒合率較高，P 值為 0.0001。

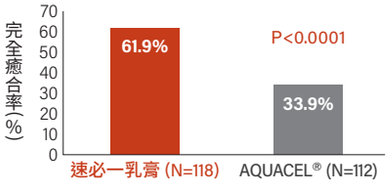
* 註：AQUACEL® Hydrofiber® 敷料為一個在標準治療 (Standard of Care) 中使用之傷口外用敷料，用於慢性傷口照護。

圖一、全分析數據集 (FAS) 之傷口完全癒合率



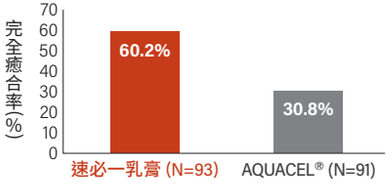
另於修正型意圖治療分析數據集 (mITT) 之結果顯示 (圖二)，速必一乳膏組 61.9% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 33.9% 病人傷口完全癒合，接受速必一乳膏治療的病人傷口完全癒合率較高，在修正型意圖治療分析數據集的 P 值小於 0.0001。

圖二、修正型意圖治療分析數據集 (mITT) 之傷口完全癒合率



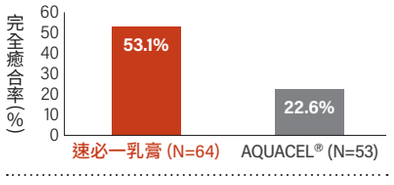
• 評估依據 Wagner 分級系統，傷口達到第二級嚴重程度 (Wagner=2) 之病人，於治療結束時傷口完全癒合的百分比
傷口達到第二級嚴重程度 (Wagner=2) 病人之全分析數據集 (FAS) 結果顯示 (圖三)，速必一乳膏組 60.2% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 30.8% 病人傷口完全癒合。

圖三、第二級嚴重程度 (Wagner=2) 病人之傷口完全癒合率 - 全分析數據集 (FAS)



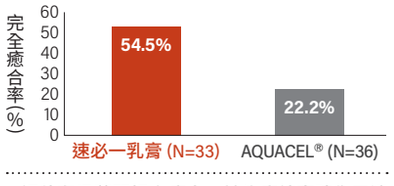
• 評估傷口位於足底部承受壓力區域 (Plantar Ulcers) 之病人，於治療結束時傷口達到完全癒合的百分比
傷口位於足底部承受壓力區域病人之全分析數據集 (FAS) 數據結果顯示 (圖四)，速必一乳膏組 53.1% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 22.6% 病人傷口完全癒合。

圖四、傷口位於足底部承受壓力區域病人之傷口完全癒合率 - 全分析數據集 (FAS)



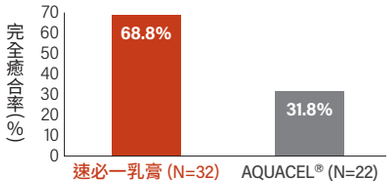
• 評估面積較大傷口 (>5 cm²) 病人，於治療結束時傷口達到完全癒合的百分比
面積較大傷口 (>5 cm²) 病人之全分析數據集 (FAS) 結果顯示 (圖五)，速必一乳膏組 54.5% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 22.2% 病人傷口完全癒合。

圖五、面積較大傷口 (>5 cm²) 病人之傷口完全癒合率 - 全分析數據集 (FAS)



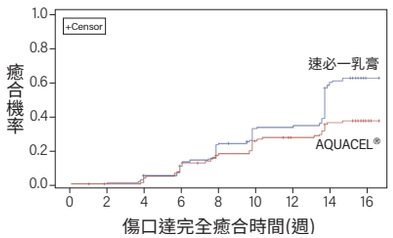
• 評估有吸菸習慣之病人，於治療結束時傷口達到完全癒合的百分比
有吸菸習慣病人之全分析數據集 (FAS) 結果顯示 (圖六)，速必一乳膏組 68.8% 病人傷口完全癒合；AQUACEL® Hydrofiber® 敷料對照組 31.8% 病人傷口完全癒合。

圖六、有吸菸習慣病人之傷口完全癒合率 - 全分析數據集 (FAS)

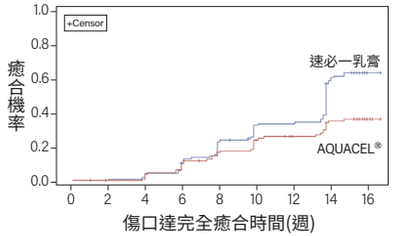


• 評估傷口達到完全癒合所需的時間 (Time to Complete Healing)
結果顯示 (圖七、圖八)，不論在全分析數據集 (FAS) 或修正型意圖治療分析數據集 (mITT)，速必一乳膏組達到傷口完全癒合的時間皆顯著早於 AQUACEL® Hydrofiber® 敷料對照組。

圖七、傷口完全癒合之卡普蘭 - 麥爾圖 (Kaplan-Meier plots) - 全分析數據集 (FAS)

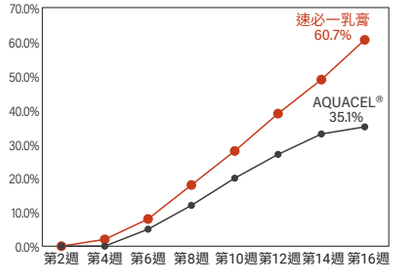


圖八、傷口完全癒合之卡普蘭 - 麥爾圖 (Kaplan-Meier plots) - 修正型意圖治療分析數據集 (mITT)



速必一乳膏組達到傷口完全癒合的累積比率，在各觀察的時間點，皆高於 AQUACEL® Hydrofiber® 敷料對照組，各觀察時間點達到完全癒合的累積比率如圖九所示：

圖九、在各觀察時間點的傷口完全癒合累積比率



10.5 不良事件
根據目前臨床試驗結果，速必一乳膏治療組發生的不良事件大多是輕度到中度。於一項多國、多中心執行收案 236 人，治療 16 週，以 AQUACEL® Hydrofiber® 對照之三期臨床研究中，速必一乳膏組 (N=122) 與 AQUACEL® Hydrofiber® 組 (N=114) 於治療期所發生 ≧ 5% 之不良事件如表一，於治療期所發生的藥品相關不良事件如表二。

表一、於治療期所發生≧ 5% 之不良事件

不良事件 (%)	速必一乳膏 N=122	AQUACEL® Hydrofiber® N=114
發生不良事件病人數	76 (62.3%)	77 (67.5%)
感染		
蜂窩性組織炎	8 (6.6%)	5 (4.4%)
上呼吸道感染	6 (4.9%)	7 (6.1%)
皮膚與皮下組織疾病		
皮膚潰瘍	14 (11.5%)	12 (10.5%)
血管疾病		
高血壓	3 (2.5%)	6 (5.3%)

表二、治療期所發生的藥品相關不良事件

治療期所發生的藥品相關不良事件 (%)	速必一乳膏 N=122	AQUACEL® Hydrofiber® N=114
發生不良反應病人數	7 (5.7%)	5 (4.4%)
一般性的異常與給藥部位狀況		
周圍腫脹	1 (0.8%)	0 (0.0%)
發熱	0 (0.0%)	1 (0.9%)
感染及侵染類疾病		
蜂窩性組織炎	0 (0.0%)	1 (0.9%)
骨髓炎	0 (0.0%)	1 (0.9%)
金黃色葡萄球菌感染	1 (0.8%)	0 (0.0%)
損傷、中毒和因醫療處置造成的併發症		
傷口併發症	1 (0.8%)	0 (0.0%)
各類檢查		
體重增加	1 (0.8%)	0 (0.0%)
代謝和營養失調		
高尿酸血症	2 (1.6%)	0 (0.0%)
良性、惡性及未明確腫瘤		
皮膚乳頭狀瘤	0 (0.0%)	1 (0.9%)
皮膚與皮下組織疾病		
接觸性皮膚炎	1 (0.8%)	0 (0.0%)
糖尿病足感染	0 (0.0%)	1 (0.9%)
濕疹	2 (1.6%)	0 (0.0%)
紅斑	1 (0.8%)	0 (0.0%)
皮疹	1 (0.8%)	0 (0.0%)

除上述三期臨床試驗外，整合其他已執行過之臨床試驗，共 164 位塗抹速必一乳膏受試者中，僅發生表二所列之 7 例與藥品相關之治療期所發生的不良事件，未觀察到與速必一乳膏相關之藥品嚴重不良反應發生。

11. 賦形劑
Purified Water、Liquid Petrolatum、White Petrolatum、Propylene Glycol、Cetyl Stearyl Alcohol、Tween 60、Span 60、Methyl Paraben、Propyl Paraben。

12. 包裝
1000 公克以下鋁軟管裝。

13. 運送與保存
25°C室溫可保存三年，應置於孩童無法觸及之處。

ONENESS
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製造廠：合一生技股份有限公司南州廠
廠　址：屏東縣南州鄉溪北村糖廠路 8 號

FESPIXON cream

Treatment of Diabetic Foot Ulcers

MOHW Manufacturing No. 060827
Prescription Only

1. Product Description
FESPIXON cream contains 1.25% 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.

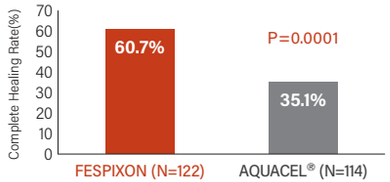
10. Clinical Pharmacology
10.1 Mechanism of Action
Plectranthus amboinicus and *Centella asiatica* extracts have been respectively used in human for a long period of time. According to literatures, *Plectranthus amboinicus* has antibacterial and anti-inflammatory effects and *Centella asiatica* can promote collagen production, angiogenesis, anti-oxidation to assist epithelialization and accelerate wound healing effect. The Cream contains 1.25% 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 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. 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 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 12 subjects were with detectable plasma concentrations of no more than 9.276 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.

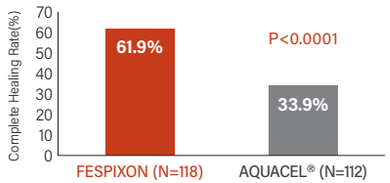
10.4 Clinical Trial
A randomized, controlled, multinational, multicenter phase 3 clinical study was conducted to evaluate the efficacy and safety of FESPIXON cream in treating patients with chronic diabetic foot ulcers. A total of 236 patients with Wagner grade 1 or grade 2 diabetic foot ulcers were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



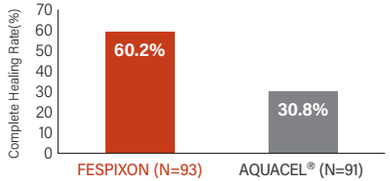
In the modified intention to treat (mITT) analysis set (Figure 2), 61.9% of patients in FESPIXON cream group achieved complete healing whereas 33.9% of patients in AQUACEL® Hydrofiber® dressing group achieved complete healing. The complete healing rate of patients treated with FESPIXON cream is higher.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



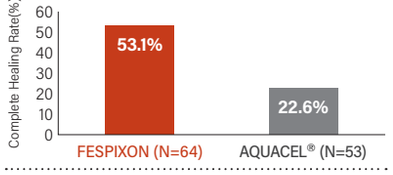
• Evaluation on the incidence of complete healing in patients with grade 2 ulcers according to Wagner classification system when treatment was completed
In the full analysis set (FAS) on patients with ulcers under grade 2 (Wagner=2), 60.2% patients of FESPIXON cream group achieved complete healing whereas 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)



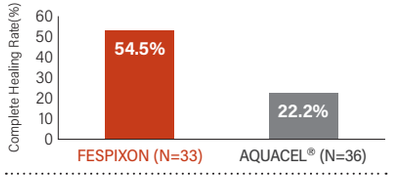
• Evaluation on the incidence of complete healing in patients with plantar ulcer when treatment was completed
The results in patients with plantar ulcers in the full analysis set (FAS) showed (Figure 4) that 53.1% of patients in FESPIXON cream group achieved complete healing whereas 22.6% of patients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

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



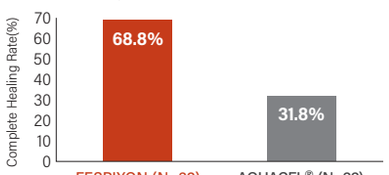
• Evaluation on the incidence of complete healing in patients with bigger ulcer (>5 cm²) when treatment was completed
The results in patients with bigger ulcers (>5 cm²) in the full analysis set (FAS) showed (Figure 5) that was 54.5% of patients in FESPIXON cream group achieved complete healing whereas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

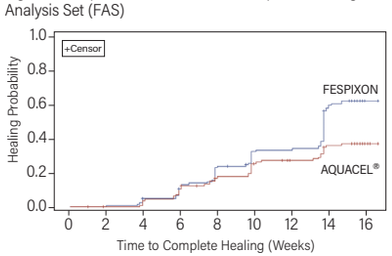
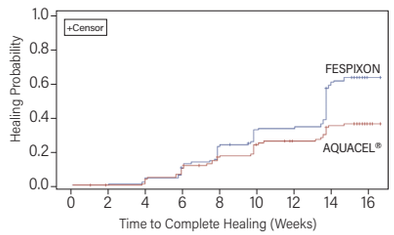
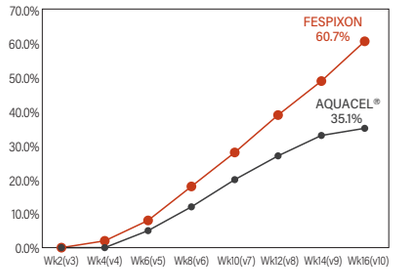


Figure 8. Kaplan-Meier Plots for Complete Healing-Modified Intention-to-treat Analysis Set (mITT)



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%

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 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.

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