第一支衛生署所核可新複方新藥
全方位針對慢性靜脈功能不全(CVI)的藥品

Esarin® Gel
凝沙®凝膠

藥 商：田上股份有限公司
製造廠：中國化學製藥股份有限公司
藥品許可證字號：衛署藥製字第051522號

Diethylamine Salicylate
預防靜脈曲張及腿部腫脹引起之疼痛及壓迫感

Heparinoid
恢復結締組織基質的粘性、滲透性和保水能力

Escin
改善靜脈功能不全所引起色素沉著及腿部潰瘍
成分：
Each gm contain:
Escin (Horse Chestnut Seed Extract ≥ 98%)  10 mg
Heparinoid (Activity ≥ 800 IU)  10 mg
Diethylamine Salicylate  50 mg
Other: Lavender oil (薰衣草精油)、Neroli oil (橙花精油)、Alcohol.

適應症：
Treatment of functional symptoms of chronic venous insufficiency.
(Varicose, Edema, Pigmentation, Leg Ulcers.)
Local treatment of benign trauma support and inflammatory complications.
(Like Bruises, Sprains, Contusion, Tenosynovitis, rheumatic pain, back pain, muscle cramps & stiffness.)

慢性靜脈功能不全(靜脈曲張、水腫、色素沉著、皮膚潰瘍)之輔助改善及創傷後(如：跌打損傷、扭傷、挫傷、腱鞘炎、風濕痛、腰背痛、肌肉痙攣及僵硬)之疼痛緩解。
### Chronic venous insufficiency (CVI)

慢性靜脈功能不全(CVI)，臨床上分為7個等級(Class 0~6)

<table>
<thead>
<tr>
<th>第一期</th>
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<tr>
<td>皮膚病變 (色素沈著、發炎、脂肪皮膚硬化症)</td>
<td>皮膚病變，伴有癒合性潰瘍</td>
<td>皮膚病變，伴有開放性潰瘍</td>
</tr>
</tbody>
</table>
Mechanism Action of Escin

- **Reduces Permeability of Capillaries**
  - Inhibit lysosomal activity and stabilize lysosomal membrane
  - Hinder the metabolism of protease
  - Reduce permeability of capillaries

- **Capillary Protector**
  - Inhibit proteases in blood from damaging the blood vessels
  - Protect Glycoproteins and Collagen fiber in vein wall

- **Improves Microcirculation**
  - Stimulate vein contraction to increase the flow of venous blood
  - Lower obviously blood viscosity

- **Anti-inflammatory**
  - Reduce the adhesiveness of neutrophils and associated release of inflammatory mediators
Mechanism of Action of Escin

- Reduces permeability capillaries
- Improves microcirculation
- Capillary protector
- Promotes tissue regeneration

Escin = Antiedematous
Recommend a clinically proven treatment for edema, hematoma and pain

Topical formulation 2-3 times per day on bruises, sprains or muscle tears, bursitis and tendinitis.

Escin had an evident therapeutic effect on both subjective symptoms (pain, spontaneous and provoked) either on some objective parameters, such as the extension of the hematoma and edema. In all cases, the improvement was obvious at the end of 11 days of therapy.

Mechanism Action of Heparinoid

● **Anticoagulant activity**
  - Heparinoid have an excellent local and systemic tolerability, no influence on blood coagulation has been observed.

● **Promote Absorption of Edema and Haematoma**
  - Inhibit hyaluronidase and Increase local blood flow
  - Accelerate absorption of corpuscular components and fibrin deposits of extravasates

● **Antithrombotic Action**
  - Improve blood flow in the thrombophlebitic skin areas
  - Accelerate the dissolution of thrombosis and improves the supply of the tissue with oxygen and nutrients
Mechanism Action of Heparinoid

● **Anti-inflammatory effect**
  - Inhibit the activity of hyaluronidase and prevent spreading of inflammation
  - Inhibit the synthesis of prostaglandin E2, activation of complement and release of leukotriene B4
  - Increase the release of tissue factor pathway inhibitor (TFPI) which is capable of binding to the TF thereby inhibiting its effects.

● **Improvement of Tissue Regeneration**
  - Inhibit various aggressive lysosomal enzymes that degrade important constituents of connective tissue, such as elastase, collagenase and hyaluronidase.
  - Stimulate the synthesis of hyaluronate that normalize the viscosity, permeability and binding capacity of the intercellular substance and regulate diffusion conditions and ion exchange at the same time.
Recommend a clinically proven treatment for superficial thrombophlebitis.

Heparinoid relieves systems of superficial thrombophlebitis 46% faster than placebo.
Recommend a clinically proven treatment for bruises.

Heparinoid dissolves bruises up to 50% faster than placebo.

Heparinoid for healing

Heparinoid accelerates healing. Heparinoid improves blood flow, promotes tissue regeneration by increasing collagen and elastin fibres in connective tissue and stimulates synthesis of hyaluronic acid which increases water-binding capacity. Studies have shown the Heparinoid penetrates the skin in effective concentrations.

Heparinoid is clinically proven.
Novel Topical Quick Penetrating Solution Of Heparin In Management Of Superficial Thrombophlebitis: Results Of Randomized Active Controlled Trial

Abstract:
To compare safety and efficacy of topical quick penetrating solution (QPS) of heparin 1000 IU/ml vs heparin gel 200 IU/g in the management of post infusion superficial thrombophlebitis.

Methods:
Total 202 patients of early, medium and advance stage of superficial thrombophlebitis were randomized to receive either treatment. Treatments were applied 3 times daily until healing or for a maximum of 7 days.

Primary efficacy endpoints were change in length of the venous lesion, proportion of patients with complete healing; while secondary efficacy endpoints included local symptoms, change in the grade of the lesion, global assessment by patients and investigator. Safety of treatment in all patients was evaluated.

IJPSR (2013), Vol. 4, Issue 11
Novel Topical Quick Penetrating Solution Of Heparin In Management Of Superficial Thrombophlebitis: Results Of Randomized Active Controlled Trial

Results:

Mean change in length of the venous lesion from baseline was significantly higher in heparin QPS group as compared to heparin gel on day 3 ($P=0.0144$). 90.0% patients in heparin QPS group were healed at day 7 which was significantly higher as compared to 65.7% patients in heparin gel group ($P=0.00001$). Heparin QPS was also found better in secondary efficacy endpoints. No adverse events were reported in either group.

Conclusions:

Heparin QPS was found more effective in treatment of post infusion superficial thrombophlebitis with similar safety profile to heparin gel.

IJPSR (2013), Vol. 4, Issue 11
臨床證實高劑量活性的 Heparinoid 能有效緩解靜脈阻塞症狀

使用14天後，高達84%的患者症狀消失，97%的患者評價高劑量活性的 Heparinoid 耐受性為好或非常好。
6. Heparinoid - 抗皮膚潰瘍作用

Heparinoid之抗凝血作用在一定高濃度活性下能改善微循環，透過降低血脂、抗血栓等生物學活性，對下肢皮膚潰瘍的患者，可改善局部微循環，增加血流量及血流速度，從而改善中間代謝，促進皮膚營養的供給及廢物的排泄，而達到治療潰瘍的效果。建議塗一薄層在受影響的皮膚的周圍，避免凝血功能障礙患者的變化因素。

市售一般含Heparinoid外用軟膏(如：喜療妥凝膠、喜美凝膠)：其每gm之活性含量均只有250 IU，只針對在腫脹及靜脈炎之局部治療，對慢性靜脈功能不全(CVI)依American Venous Forum在1994提出之CEAP分類法之第四、五、六期之臨床症狀(色素沉著、皮膚炎、皮膚潰瘍)無法作有效預防及治療。
Diethylamine Salicylate (DEAS) - 藥理特性

Anti-inflammatory (suppresses inflammation)
抗發炎（抑制炎症）

Analgesic (reduces pain)
止痛（降低疼痛）
Mechanism of action Diethylamine salicylate

Leukotriene (白三烯) → Arachidonic Acid (花生四烯酸) → Cycloendoperoxides

DEAS 抑制 → Prostacyclin (前列腺素環) → Prostaglandins (前列腺素) → Thromboxane A2 (TXA2)

Increased capillary permeability 毛細血管通透性增加
Stimulation of pain receptors 刺激疼痛受體
Isolation of lysosomal enzymes 溶酶體酶的分離
Mechanism of action: Diethylamine salicylate

Diethylamine Salicylate

- Interferes with the formation of inflammatory mediators, prostaglandin (PG) group
- Blocking of PG formation
- Reducing the inflammatory symptoms
- Inflammatory

Trauma

- Mechanical forces
- Tissue damage
  - Rupture blood vessels
- Release of inflammatory mediators
- Stimulation of pain receptors

DEAS

Inhibitor

Analgesic

Pain
Significant superiority vs. Diclofenac

Pressure until the first sensation of pain

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study design</th>
<th>Method</th>
<th>Measuring parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escin+Diethylamine Salicylate</td>
<td>double-blind</td>
<td>Injections hematoma</td>
<td>pressure pain sensitivity</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Number of patients: 119</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graph showing pressure over time for Escin+Diethylamine Salicylate and Diclofenac.
### Freedom from symptoms after 8 days treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Escin+Diethylamine Salicylate (Deas)</th>
<th>Placebo</th>
<th>Difference between the treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>61.1%</td>
<td>32.5%</td>
<td>P&lt;0.05 Rothhaar und Thiel 1982</td>
</tr>
<tr>
<td>Movement pain</td>
<td>51.3%</td>
<td>4.5%</td>
<td>P&lt;0.05 Study design: double blind / placebo controlled</td>
</tr>
<tr>
<td>Spontaneous pain</td>
<td>73.0%</td>
<td>10.3%</td>
<td>P&lt;0.05 Method: Measurement of symptoms after 8 days treatment</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>61.5%</td>
<td>11.9%</td>
<td>P&lt;0.05 Number of patients: 81 (39 Escin+DEAS combination gel, 42 placebo)</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>43.6%</td>
<td>4.8%</td>
<td>P&lt;0.05 Measuring parameters: see table</td>
</tr>
<tr>
<td>Felling of tension</td>
<td>76.9%</td>
<td>25.6%</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>91.7%</td>
<td>34.6%</td>
<td></td>
</tr>
<tr>
<td>Bruise</td>
<td>53.3%</td>
<td>21.4%</td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of action (Escin + Heparinoid + DEAS)

Mechanical forces
- Local ischemia
- Rupture of blood vessels
- Tissue damage
- Release of inflammatory mediators
- Bleeding

Escin
- Increase vascular permeability
- Inhibitor

Heparinoid
- Inhibitor
- Stimulation of pain receptors

Edema
- Increase the tissue pressure

Pain

Bruise

Diethylamine
Salicylate

Heparinoid

Escin
比較 Escin、Heparinoid、Diethylamine Salicylate 在單獨與合併使用時，其功能性恢復(疼痛、發炎及腫脹)的差異性評估

Topical Formulation - Antiedema

- Escin+Diethylamine Salicylate+Heparinoid
- Diethylamine Salicylate
- Heparinoid
- Escin

93.3% 73% 33% 6.7%

Functional Recovery After Topical Treatment

- Escin+Diethylamine Salicylate+Heparinoid
- Diethylamine Salicylate
- Heparinoid
- Escin

93.3% 41.7% 20% 1%

### Chronic venous insufficiency (CVI)

慢性靜脈功能不全(CVI)，臨床上分為7個等級(Class 0~6)

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<td>下肢水腫症狀</td>
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<tr>
<td>使用凝血凝膠 2週後：Heparinoid 和馬栗種子萃取物的協同作用下可達到滋養、促進血管彈性、張力及增加靜脈血液回流量，確實有效預防及治療靜脈曲張。</td>
<td>使用凝血凝膠 2~4週後：Heparinoid 及馬栗種子萃取物的協同作用下可達到滋養、促進血管彈性、張力及增加靜脈血液回流量及消除一般組織水腫，確實有效預防及治療靜脈曲張。</td>
<td>下肢水腫症狀使用凝血凝膠 4~8週後：抑制血液中蛋白酶的作用，可有效降低毛細血管的通透性，防止靜脈性水腫，在 DEA Salicylate作用下，更能有效減輕腿部腫痛、沉重感及改善腿部血液循環。</td>
</tr>
</tbody>
</table>

[Image of images]
慢性靜脈功能不全 (CVI)，臨床上分為 7 個等級 (Class 0~6)

| 期別   | 預防靜脈曲張等症狀
|---|---|
| 第四期 | 皮膚病變 (色素沈著、發炎、脂肪皮膚硬化症)  
 使用凝沙凝膠 2~8 週後：  
 高活性濃度的 Heparinoid 能改善  
 療癒的微循環及缺氧狀態，促進  
 皮膚組織新陳代謝，有效縮短炎症  
 症狀色素沈著的消退作用時間。 |
| 第五期 | 皮膚病變，併有癒合性潰瘍  
 使用凝沙凝膠 2~8 週後：  
 高活性濃度的 Heparinoid 能改善  
 潰瘍的微循環，防止微血栓形成  
 增加血液流量及速度，進而改  
 善組織新陳代謝及缺氧狀態，可  
 確實達到治療潰瘍的效果。 |
| 第六期 | 皮膚病變，併有開放性潰瘍  
 使用凝沙凝膠 2~8 週後：  
 高活性濃度 Heparinoid 和Escin的  
 協同作用可提高微循環作用，防  
 止微血栓形成而改善組織代謝，  
 並藉由刺激蛋白多醣生成而促進  
 結締組織再生，加速傷口癒合。 |

Abstract:

The involvement of the microcirculation in diabetic microangiopathy (DM) causes of severe incapacitation and ulceration. DM is characterized by a diffuse increase in flux, reduction in venoarteriolar response, associated with increased permeability resulting in edema and altered function of microlymphatics.

In DM, skin PO2 is decreased and PCO2 increased. In this condition capillary exchanges are altered and nutritional alterations eventually lead to skin lesions and ulcers.

The aim of this randomized, placebo-controlled study was to evaluate the effect of local (foot) treatment with Essaven gel (EG) in 35 subjects with DM and neuropathy and localized, small (< 0.5 cm in maximum diameter) ulcers treated for 2 weeks.

Methods:

Measurements of laser Doppler (LDF) flux, PO2, and PCO2 in standardized conditions showed positive microcirculatory changes (a significant decrease of the abnormally increased flux and PCO2 while PO2 increased) in the active EG group. Changes in the control group were not significant. In the placebo group variations were limited (mainly associated with skin manipulation and gel application).

<table>
<thead>
<tr>
<th>Time</th>
<th>LDF FLUX</th>
<th>LDF PO2</th>
<th>LDF PCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Placebo</td>
<td>EG</td>
</tr>
<tr>
<td>Inclusion</td>
<td>3.3</td>
<td>3.2</td>
<td>3.4</td>
</tr>
<tr>
<td>2Weeks</td>
<td>3.4</td>
<td>2.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Results:

In conclusion, local treatment for 2 weeks with standardized application of EG acutely improves the microcirculation in subjects with DM and small ulceration.

Angiology; Dec 2001 Supplement, Vol. 52, pS43
Escin/diethylammonium salicylate/heparin combination gel preparations are effective and safe for the treatment of blunt impact injuries.

Objectives:
To investigate the clinical efficacy and safety of escin-containing gels in the topical treatment of blunt impact injuries.

Methods:
Competitors in soccer, handball, or karate competitions were enrolled within two hours of sustaining a strain, sprain, or contusion and treated three times with the trial gel within a period of eight hours.

Patients were randomised to three parallel groups consisting of two active treatment gels, containing escin (1% or 2%), 5% diethylammonium salicylate, and 5000 IU heparin, or placebo gel.

Tenderness produced by pressure was measured at 0 (baseline), 1, 2, 3, 4, 6, and 24 hours after enrolment (within two hours of the injury). Tenderness was defined as the amount of pressure (measured by a calibrated caliper at the centre of the injury) that first produced a pain reaction as reported by the patient.

Escin/diethylammonium salicylate/heparin combination gel preparations are effective and safe for the treatment of blunt impact injuries.

Figure 1 Tenderness reaction (kp/cm²). Values are means (SEM). Intention to treat analysis.

Figure 2 Pain reaction (visual analogue scale). Values are means (SEM). Intention to treat analysis.

Escin/diethylammonium salicylate/heparin combination gel preparations are effective and safe for the treatment of blunt impact injuries.

Results:

A total of 158 patients were enrolled; 156 were evaluated in the intention to treat analysis. The primary efficacy variable was the area under the curve for tenderness over a six hour period. The gel preparations containing 1% and 2% escin were significantly more effective than placebo. The treatment effects were 5.7 kp h/cm² and 5.9 kilopond (kp) h/cm² between 1% escin and placebo and between 2% escin and placebo respectively.

These results were supported by secondary efficacy variables. The time to reach the baseline contralateral tenderness value (resolution of pain) at the injured site was shorter in the treatment groups than in the placebo group. Both active gel preparations produced more rapid pain relief than the placebo gel. No relevant differences were detected between the two active gels. The safety and tolerability of the escin-containing gels were excellent.

使用礙沙凝膠的優點

1. 可同時治療多種症狀，如局部性腫脹、靜脈炎、瘀青，並且療效優於傳統單方製劑(如喜療妥、益欣)。

2. 對於各種關節炎、腰背痛、腱鞘炎、風濕痛、挫傷、拉傷…等病症，透過 Esarin Gel 三種成分發揮協同抗炎作用，能迅速達到抑制發炎、緩解疼痛的目的。(可取代 Teria、Rheumon Gel)

3. 在需要修復組織的情況下，礙沙凝膠有高單位高活性的類肝素，能促進血液循環，加快傷口癒合。

4. 擔沙凝膠健保價=102，健保沒有設限，可依適應症(創傷後之疼痛緩解和慢性靜脈功能不全輔助改善)及病灶區大小調整處方依據，用量(請打Esa查詢ESRIN或是刷院內碼PWP030E)。
礙沙凝膠的使用方法

1. 一天塗抹2-3次，均勻塗抹在患部，薄薄的一層即可發揮效果。
2. 遇傷口部位，塗抹在傷口周圍，就能發揮消腫、消炎、散瘀、促進傷口癒合之作用，高活性高劑量 Heparinoid 不會引起傷口持續出血而無法癒合，使用於消除瘀血時，亦不會有內部出血不止的狀況產生。
3. 遇過敏現象，停止使用即可。
4. 懷孕用藥安全等級屬於 B 級，孕婦懷孕三個月後可使用礙沙凝膠。
5. 新生兒六個月以上即可使用礙沙凝膠。