1.3 Product Information

1.3.1 Summary of Product Characteristics (SPC)

Summary of Product Characteristics (SPC) is enclosed in this section.

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Reparil®-Gel N
Active substances: 1 % escin and 5 % diethylamine salicylate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:
100 g gel contains:

Escin	1 g
Diethylamine salicylate	5 g

Other ingredients:
For the complete listing of other ingredients see section 6.1.

3. PHARMACEUTICAL FORM

Gel
Reparil®-Gel N is a transparent, colourless to slightly yellowish gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Injuries with contusions, sprains, bruises, haematoma formation, tendinitis (inflammation of tendon sheaths).

Vertebral pain syndromes (intervertebral disk, nuchal pain, lumbago, sciatica).

Superficial phlebitis, varicose veins. For vein care following injections or infusions.

4.2 Posology and method of administration

Reparil®-Gel N should be applied once to several times daily.

Method of administration:
Reparil®-Gel N should be applied to the affected area and spread over the skin. It need not be rubbed in, but it may be done if desired.

4.3 Contraindications

Reparil®-Gel N should not be applied to broken skin (wounds), mucous membranes or skin areas which have been exposed to radiotherapy.

4.4 Special warnings and precautions for use

None known.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Prolonged treatment covering large areas should be avoided during pregnancy, and the gel should not be applied to the breast area during lactation.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Side effects' rating was based on the following frequency data:

Very common	≥ 1/10
Common	≥ 1/100 - < 1/10
Uncommon	≥ 1/1.000 - < 1/100
Rare	≥ 1/10,000 - < 1/1,000
Very rare	< 1/10,000
Not known	cannot be estimated from the available data

Allergic cutaneous manifestations may arise in very rare cases.

4.9 Overdose

No manifestations of overdosage or intoxication have been reported to date.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Analgesic; antiexudative/antiphlogistic agent for percutaneous application

ATC code: M02AC55

The target site of escin is the vascular wall. In the case of inflammatory raised permeability, escin inhibits exudation by reducing extravasation of fluid into the tissue spaces, and it accelerates reabsorption of the existing oedema. The mechanism of action is based on a change in the permeability of the capillary openings involved. Furthermore,

escin promotes capillary resistance, inhibits inflammatory processes and improves microcirculation.

Diethylamine salicylate (DEAS) has a pronounced analgesic effect. It penetrates freely through the skin and exerts its analgesic action in the depths of the affected area. The additional antiphlogistic action of DEAS enhances the anti-inflammatory effect of escin and thus combats the causal factors of the course of disease.

In three randomised, placebo-controlled double-blind studies on human pharmacology using the model of an experimenally induced haematoma (injection-induced haematoma), it was possible to demonstrate the effect of Reparil®-Gel N by means of the development of tenderness on pressure and haematoma absorption.

During the first 24 hours of treatment and also over a period of 19 days, a significant lessening of the tenderness on pressure was observed compared with the placebo and the individual components escin and DEAS. On the other hand, each of the two individual components had a significantly superior effect to placebo. In comparison to the reference preparation diclofenac and the placebo, a clear superiority of both active study medications *vs* the placebo was recorded in the same model. The comparison between Reparil®-Gel N and diclofenac revealed a trend in favour of the test preparation.

5.2 Pharmacokinetic properties

In order to investigate its percutaneous absorption, ^{3}H escin was applied to the dorsal or ventral skin of mice, rats, guinea pigs and pigs. An occlusive bandage was used to cover the site of apllication.

The concentration of total activity, non-volatile activity and acitivity of escin (after thin-layer chromatography) was determined in various tissues and organs at different times after the application. Biliary and urinary excretion were measured throughout the trial.

The absorption rate (estimated via the excretion in 1 – 2 days) was low in all species; it accounted for < 2 % of the applied dose. Relatively high escin concentrations, however, were found beneath the site of application and even in the deeper lying muscle tissues.

Twenty-four hours after percutaneous application, the concentration of non-volatile activity measured in pigs in the subcutis and muscle tissues beneath the area if apllication was approximately 50 times higher than that in the blood. Peak activity levels in cutis and subcutis were reached 6 hours after application.

In the course of the investigation, the activity in cutis and subcutis declined due to increasing diffusion. In the muscle tissues, however, it increased. Thin-layer chromatography revealed that approximately 50 % of this activity was identical escin. The results demonstrate that escin is absorbed by and also penetrates through the skin.

Very high escin concentrations, which are desirable are thus locally achieved in the muscle tissues at the site of application without considerable systemic involvement.

On the grounds of this pharmacokinetic behaviour, it is safe to assume that escin is very suitable for percutaneous treatment.

To determine the percutaneous absorption of the analgesic compound in Reparil®-Gel N, ^{14}C diethylamine salicylate was applied to the dorsal skin of Wistar rats. The determination of the absorption rate was carried out by ascertaining biliary and urinary elimination of the ^{14}C activities.

Additional measurements included the concentrations in the plasma, in various organs and tissues. The metabolism of ^{14}C diethylamine salicylate was also investigated. The absorption rate estimated by determination of excretion in 48 hours was on average 14 %. High concentrations of activity were recorded in the treated skin area, whereas the ^{14}C activities measured in the organs and tissues at different times after the application were low.

A clinico-pharmacological investigation was carried out to determine the absorption of escin after topical application. The trial was carried out as an open study. The sample consisted of 20 patients with proctoligal conditions requiring surgery. A 2 % escin cream was applied to the affected skin area for 7 days before the operation. The determination of the escin concentration in tissue samples removed from the area operated on revealed, in the cutis and subcutis, escin concentrations which significantly differed from 0 ($p < 0.001$). Furthermore, a significant difference was noted in the concentrations of the individual tissue samples between cutis and subcutis and the fatty tissue.

5.3 Preclinical safety data

Investigations into local and sytemic tolerability were carried out in rats, rabbits and pigs.

In rats and rabbits 200 or 500 mg Reparil® -Gel N was applied to the shaved dorsal skin over a period of 4 weeks. No macroscopically nor histologically specific local skin damage occurred. Changes in the sense of a low-grade acanthosis of the epidermis, as well as chronic inflammatory cellular infiltration into the sub-epidermal corium were also observed in the control after application of the gel base. Experience has shown that all findings are reversibel.

To investigate local mucosal tolerability 100 mg Reparil®-Gel N was instilled once into the conjunctival sac of the eye. Low to high-grade inflammatory changes occurred in the conjunctiva which however receded completely within 7 days. Rinsing of the eyes within 2 min following application clearly reduced the irritations.

In a long-term trial, 300, 1500 or 4000 mg/kg bodyweight was applied to the dorsal skin. Macroscopic examination revealed in the highest dosage group occasional erythemas. Histological examination revealed, apart from non-specific cutaneous reactions, e.g. suppurative pustular dermatitis, epidermal hyperplasia and hyperkeratosis, no specific reactions. Systemic substance-induced effects were not observed either.

6. PHARMACEUTICAL PARTICULARS

6.1 List of other excipients

Soium edetate, polyacrylic acid, macrogol-6-caprylic/caprinic acid glycerides, trometamol, isopropanol, odourants.

6.2 Incompatibilities

None known.

6.3 Shelf life

in aluminium tubes: 3 years

in laminate tubes 3 years

Shelf life after first opening of the container: 6 months

6.4 Special precautions for storage

Keep out of reach and sight of children.
Store below 30°C in a dry place.

6.5 Nature and contents of container

Packs of 40 g gel and 100 g gel filled in aluminium tubes or laminate tubes.

6.6 Special precautions for disposal and handling

None.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18.03.1995

10. DATE OF REVISION OF THE TEXT

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