SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Venoruton capsules 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule contains 300 mg oxerutines.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the adjunctive treatment of varicose veins in all stages.

4.2 Posology and method of administration

Posology

2-3 capsules for a day.

Take the capsules unchewed with some liquid during or immediately after meals.

The duration of treatment depends on the symptoms. In general, there is no time limit on the duration of use. If symptoms persist, treatment can be continued for a prolonged period of time after consultation with a doctor.
Its success depends largely on consequent adherence to the prescribed dosage and duration of treatment.

Children and adolescents under 18 years of age
No data are available, therefore the use of oxerutines is not recommended in this age group.

Patients with cardiac, renal or hepatic impairment
Patients who have oedema of the lower limbs due to cardiac, kidney or liver disorders should not use oxerutines because the efficacy of oxerutines has not been shown in these indications.

4.3 Contraindications

Hypersensitivity to the active substance oxerutines or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The use of oxerutines in children is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

None known.
Oxerutines do not show any interaction with anticoagulant drugs of the coumarin type.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient experience with the use of Venoruton 300 in the first months of pregnancy. For the second and third trimesters of pregnancy, various studies with more than 1,400 pregnant women have shown no evidence of harm to the foetus. Use in pregnancy should proceed only when absolutely necessary and from the fourth month of pregnancy onwards.

Breast-feeding
For humans, no studies on the passage of the active substance into human milk have been performed. Breast-feeding women should seek medical advice before taking oxerutines. Animal studies showed only small amounts of active substance in the milk and no effects on nursing offspring even at very high maternal doses of the substance. Hence, the amount excreted in milk at therapeutic concentrations is probably harmless for the infant.

4.7 Effects on ability to drive and use machines

In very rare cases tiredness and dizziness have been reported.
If affected, patients are advised not to drive or operate machines.

4.8 Undesirable effects

The frequencies of adverse reactions are defined according to the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class Frequency	**Adverse reaction**
Immune system disorders Very rare	Hypersensitivity reactions including anaphylactoid reactions
Nervous system disorders Very rare	Dizziness, headache
Vascular disorders Very rare	Flushing
Gastrointestinal disorders Rare	Gastrointestinal disorders
Skin and subcutaneous tissue disorders Rare	Allergic skin reactions, pruritus, urticaria
General disorders and administration site conditions Very rare	Fatigue

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il.

4.9 Overdose

Venoruton has been in therapeutic use for more than 30 years. During this time, there have been no reported cases of intoxication due to overdose. Intoxication is unlikely to occur. Moreover, acute toxicity testing revealed no indications of any specific toxicity profile. Thus, concrete information for the treatment of intoxication due to overdose is currently not possible. Treatment should probably be aimed at symptomatic measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Partially synthetic rutoside
ATC code: C05CA54

The main pharmacological effect of oxerutines (HR) consists of a reduction in the capillary filtration rate for water and microvascular permeability for proteins. This has been shown both in various animal models and in clinical studies in chronic venous insufficiency (CVI), liver cirrhosis, idiopathic oedema and diabetic retinopathy. The effect on microvascular function may be explained by a reduction in interendothelial cell gaps, a modification of the interendothelial cell matrix and increased adhesion of endothelial cells to the microvascular wall.
Furthermore, the results of numerous experimental models *in vitro* can be attributed to the interactions of HR with integral membrane components, which trigger changes not only in the barrier function of biological membranes, their fluidity and osmotic stability, but also in the activity of membrane-bound enzymes and active transport systems.
Inhibition of red cell aggregation and improved red cell deformability, which may explain the observed improvement in microvascular flow and cutaneous oxygen levels, have also been shown in humans.
These pharmacological effects lead to oedema reduction and associated symptoms in chronic venous insufficiency (CVI) and other indications characterised by increased local microvascular permeability.
Furthermore, a significant protective effect has been demonstrated in membrane lesions caused by radioactive radiation. In addition, it has been shown that Venoruton does not reduce the radiation sensitivity of tumour tissue.

5.2 Pharmacokinetic properties

The pharmacokinetics of oxerutines has been studied in rats, mice, rabbits, dogs, rhesus monkeys and humans. Increasing substitution of the hydroxyl groups of the rutin base matrix by hydroxyethyl groups leads to increased water solubility, increased resistance of the molecule to bacterial degradation in the intestinal tract and a decrease in protein binding. The reversible protein binding of HR is about 30%. In rats, HR glycosides and glucuronides were found in the urine and bile (14-20% of the orally administered dose). Elimination is mainly via biliary (about 65%) and renal pathways and is complete after 24-48 hours. In addition, there is pronounced enterohepatic circulation. HR does not cross the blood/brain barrier. Following oral or intravenous administration, placental passage of HR is minimal; only traces were found in the foetus of rats and mice. Likewise, only traces were found in the milk of lactating rats.
In humans, after oral administration of ^{14}C-HR, peak plasma concentrations are reached after

1-9 hours. Measurable levels persist for about 120 hours. Its decline is biphasic: 3-6% of the administered radioactivity is excreted with the urine within 48 hours. The total elimination half-life ranges from 10-25 hours but is relatively constant intraindividually. Biliary elimination of HR and its glucuronidated metabolites has been confirmed in humans.

5.3 Preclinical safety data

Oxerutines can be described as practically non-toxic upon single oral and parenteral administration. It has not been possible to determine the $LD_{50.}$ Similarly, tests to determine subacute, subchronic, chronic toxicity in dogs after parenteral administration, as well as teratogenicity studies, produced no evidence of substance-specific toxic properties, even at the highest doses. No mutagenic potential was observed in corresponding trials.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: macrogol 6000
Tablet coat: gelatin; water; titanium dioxide; yellow iron oxide; sodium laurilsulfate; black ink (shellac glaze in ethanol, isopropyl alcohol, iron oxide black, N-butyl alcohol, propylene glycol, ammonium hydroxide 28%).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the printing materials.

6.4 Special precautions for storage

Store below 25 °C. Protect from moisture.

6.5 Nature and contents of container

Blister strips of PVC/ aluminium, PVC/PVDC-aluminium or PVC/PE/PVDC-aluminium.

Available pack size:
20 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Devries & CO. LTD
32 HaBarzel ST., 69710 Tel Aviv

8. MANUFACTURER

STADA ARZNEIMITTEL AG
Stadastraße 2–18
61118 Bad Vilbel

Germany

9. MARKETING AUTHORISATION NUMBER

115-96-22946-01

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