

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VENOSMIL 200 mg hard capsules
VENOSMIL 20 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENOSMIL 200 mg hard capsules
Each capsule contains 200 mg hidrosmin.

VENOSMIL 20 mg/g gel
Each gramme of gel contains 20 mg hidrosmin.

Excipients with known effect: Each gramme of gel contains 1 mg methyl parahydroxybenzoate (E-218) and 0.5 mg propyl parahydroxybenzoate (E-216).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

VENOSMIL capsules:
Hard, orange gelatine capsules containing a fine yellow powder.

VENOSMIL gel:
Transparent slightly yellowish gel.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VENOSMIL is a medicinal product indicated for:

- Short-term (2-3 months) relief from oedema and symptoms related to chronic venous insufficiency in adults.

4.2. Posology and method of administration

Posology

Adults

VENOSMIL capsules: One 200 mg capsule three times a day.

VENOSMIL gel: Three applications per day.

Method of administration

VENOSMIL capsules:

Oral route.

Once removed from the blister, the capsule must be taken immediately. It can be taken with water or another drink to aid swallowing.

VENOSMIL gel:

Cutaneous use.

For external use only on intact skin.

1. Unscrew the cap of the tube and perforate the metal opening of the tube sufficiently using the back of the cap.
2. Apply approximately 3-4 cm of product to the skin.
3. Spread over the affected region by gently rubbing to form a thin layer of gel.

4.3. Contraindications

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

Venosmil gel must not be applied to mucosa, irritated regions of skin or to wounds, and must not be used to treat dermatitis, eczema or urticaria.

4.4. Special warnings and precautions for use

VENOSMIL gel

- Use only on intact skin.
- Avoid contact with the eyes, ears and mouth.
- Do not apply simultaneously with other medicinal products for cutaneous use in the same region.

Patients must be advised that they must not use the medicinal product for long periods without medical supervision.

Warnings on excipients

VENOSMIL gel contains methyl parahydroxybenzoate (E-218) and propyl parahydroxybenzoate (E-216). It may cause allergic reactions (possible delayed) due to its content of methyl parahydroxybenzoate (E-218) and propyl parahydroxybenzoate (E-216).

VENOSMIL capsules

Patients must be advised that they must not use the medicinal product for long periods without medical supervision.

Paediatric population

- The risk/benefit balance of administering the medicinal product to children and adolescents must be evaluated.

4.5. Interactions with other medicinal products and other forms of interaction

No specific studies have been made of possible pharmacokinetic and/or pharmacodynamic interactions between hidrosmin and other medications or foods.

4.6. Fertility, pregnancy and lactation

Pregnancy

No clinical data are available for Venosmil capsules and gel as regards the use of hidrosmin in pregnant women.

Animal studies have shown no direct or indirect hazardous effects on pregnancy, foetal development, delivery or postnatal development.

However, as a precautionary measure, the use of Venosmil is not recommended during pregnancy unless, in the physician's opinion, the potential benefits of its administration outweigh the possible risks.

Lactation

No clinical data are available on hidrosmin use in breastfeeding women. It is not known whether hidrosmin is excreted in human breast milk, therefore its use during breastfeeding is not recommended.

Fertility

No data are available in humans.

4.7. Effects on ability to drive and use machines

The influence of VENOSMIL on the ability to drive and use machines is non-existent or negligible.

4.8. Undesirable effects

During the period of marketing of hidrosmin, the following undesirable effects have been reported, though their frequency has not been clearly established.

The most commonly observed undesirable effects are:

VENOSMIL capsules

Immune system disorders: hypersensitivity (allergic) reactions to the active substance or to one of the excipients.

Nervous system disorders: headache, dizziness.

Gastrointestinal disorders: epigastric pain, nausea.

Skin and subcutaneous tissue disorders: rash, pruritus.

VENOSMIL gel

Immune system disorders: hypersensitivity (allergic) reactions to the active substance or to one of the excipients (see Section 4.4 Special warnings and precautions for use: Warnings on excipients).

Skin and subcutaneous tissue disorders: rash, pruritus.

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.

4.9. Overdose

No cases of overdose have been described. The good tolerance of VENOSMIL means that, in practice, the possibility of intoxication is non-existent, even in cases of accidental overdose.

5. Pharmacological Properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Capillary stabilising agents. Bioflavonoids C05CA05.

Actions

The only active substance in VENOSMIL is a drug known as hidrosmin which, as a result of its chemical composition, belongs to the flavonoid group. This drug is a standard mixture mainly comprising 5'- and 3'-mono-*O*-(β -hydroxyethyl)-diosmin and 5,3'-di-*O*-(β -hydroxyethyl)-diosmin.

Although the mechanism of action of hidrosmin has not been fully elucidated, it could be related to inhibition of the degradation of catecholamines, specifically inhibition of catechol-*O*-methyltransferase. Although the exact mechanism of action is unknown, hidrosmin has four main pharmacological actions:

- a) It reduces the capillary permeability induced by various agents such as histamine, bradykinin, etc. and reduces the capillary fragility induced by a deficiency diet.
- b) It increases the deformability of red blood cells and the viscosity of the blood.
- c) It induces the contraction of smooth muscle in the vein wall in a gradual and sustained manner.
- d) It produces dilation of the lymphatic collectors and increases the rate of lymphatic conduction, thereby improving lymphatic flow.

The efficacy of VENOSMIL was evaluated in two clinical trials in a total of 70 patients with acute and chronic venous disease, who were treated with 200 mg hidrosmin orally three times per day and/or 2 g hidrosmin topically (gel) two or three times per day for one and two months. Hidrosmin was effective at reducing oedema, ulcers and varicose eczema. VENOSMIL therefore possesses intrinsic activity against the consequences of venous stasis secondary to varicose dilation of the veins in the lower limbs, producing an improvement in the clinical symptoms of peripheral venous insufficiency (pain, heaviness, oedema, etc.) that is significantly different to that produced by placebo.

5.2. Pharmacokinetic properties

After oral administration of single doses of hidrosmin in healthy volunteers, a biphasic curve of plasma concentrations of the product with respect to time was observed. An initial peak was observed at 15 minutes post-administration, subsequently decreasing slowly. A new increase in plasma levels was observed at 4 hours post-administration, with a stabilisation phase being achieved at between 5 and 8 hours post-administration. Plasma levels subsequently decreased, being practically undetectable at 24 hours post-administration.

Elimination of hidrosmin is relatively fast, with 90% of the dose being excreted in 48 hours. It is mainly excreted in faeces, with approximately 80% of the dose administered being eliminated via this pathway. Only 16-18% is excreted via the urine.

5.3. Preclinical safety data

After oral, intraperitoneal and intravenous administration in rat and mouse, the acute LD50 for hidrosmin is very high (>5000 mg/kg) with respect to the clinical dose (10 mg/kg/day).

In sub-acute toxicity studies (1 month), oral doses of 70, 700 and 7000 mg/kg/day in rat and oral doses of 50, 250 and 750 mg/kg/day in dog did not produce significant alterations in the various biological and anatomical/histological parameters studied that could be related to the drug.

Chronic toxicity studies with hidrosmin (6 months) did not show that the product produced any significant alteration in rat or dog administered oral doses of 50, 500, 2500 mg/kg/day and 25, 125 mg/kg/day, respectively.

No signs of teratogenicity or embryotoxicity were observed in teratogenicity studies in rabbit, rat and mouse at doses of 3-150, 6-600 and 50-200 times the clinically recommended therapeutic range, respectively.

6. Pharmaceutical Particulars

6.1. List of excipients

VENOSMIL capsules:

Magnesium stearate

The gelatine capsule comprises gelatine, erythrosine (E-127), quinoline yellow (E-104), titanium dioxide (E-171) and water.

VENOSMIL gel:

Carbomer

Triethanolamine

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Distilled water.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

5 years

6.4. Special precautions for storage

VENOSMIL capsules: No special storage conditions are required.

VENOSMIL gel: Store below 30 °C.

6.5. Nature and contents of container

Venosmil capsules

Aluminium/Aluminium blister packs containing 60 or 90 capsules.

Venosmil gel

Aluminium tube containing 60 g of 2% gel.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

FAES FARMA, S.A.
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8. MARKETING AUTHORISATION NUMBER(S)

VENOSMIL capsules: 56,707
VENOSMIL gel: 56,709

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 5 December 1985
Date of last renewal: 25 June 2010

10. DATE OF REVISION OF THE TEXT

October 2014.