1. TRADE NAME OF THE PRODUCT

D I O S P E R®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 500mg of microionised purified flavonoid fraction corresponding to:

- 90% of diosmin, equivalent to 450mg per tablets
- 10% of flavoinoids expressed as hesperidine, equivalent to 50mg per tablet

3. PHARMACEUTICAL FORM

Film coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

- DIOSPER® may be used for the treatment of organic and functional chronic venous insufficiency of the lower limbs

- Symptomatic treatment of acute haemorrhoidal attacks.

4.2 Posology and method of administration

DIOSPER is used orally. Tablets should be swallowed with a small amount of water, during meals.

Chronic venous insufficiency

The usual dose is 2 tablets daily, one at midday and one in the evening during meals.

Haemorrhoidal attack

A 4-day course of 6 tablets daily, followed by 4 tablets daily over the next 3 days.

4.3 Contraindications

DIOSPER® is contra-indicated in patients, who have shown hypersensitivity to any of the substances present in the drug.

4.4 Special warnings and precautions for use

DIOSPER® contains glycerol, an excipient that may cause headaches, gastric disorders and diarrhoea.

The administration of this medicine for the symptomatic treatment of acute haemorrhoidal attack does not substitute the treatment of other rectal problems. The treatment should be short-term. If the symptoms persist, a rectal examination should be conducted and the treatment should be reviewed.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions have been reported upon co-administration of DIOSPER® with other medicines. Furthermore, no interaction was observed upon administration of DIOSPER® with anticoagulants of warfarin.

4.6. Pregnancy and Lactation

Pregnancy:

There were no teratogenic observations in human studies.

It is, however, recommended that DIOSPER® should not be administered during the first three months of pregnancy unless it is completely necessary.

Lactation

In the absence of data concerning the diffusion of the drug substance in the breast milk, breast feeding is not recommended during treatment.

4.7. Effects on ability to drive and usemachines

DIOSPER® does not interfere with the ability to drive or operate machines. In case of dizziness, the patient should not drive or use machines.

4.8 Undesirable effects

Gastrointestinal disorders

Common: diarrhoea, dyspepsia, nausea, vomiting.

Neurological disorders

Rare: dizziness, headache, feeling of discomfort.

Skin disorders

Rare: skin reaction.

4.9 Overdose

Overdose symptoms have not been reported with this drug and therefore there is no special treatment to be advised.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: C05CA53

DIOSPER® is a product that increases the venous tone and protects the vessels.

Pharmacological studies

Pharmacological studies have established that the product is acting on the venous system as follows:

- Regarding vessels, it decreases the venous dilatation and venous stasis.
- Regarding the micro-circulation, it brings to normal levels the capillary permeability and diminishes the capillary resistance.

Clinical pharmacology

Clinical pharmacology studies which allowed the validation and the quantitative determination of the drug action to the venous haemodynamics confirmed the pharmacological properties of the drug to human beings.

Dosage/result

In studies where the relation between dosage and result was examined, it was found that the relations of dosage/result are statistically important regarding the venous plethysmographic parameter: capacity, dilatation and discharge time. The best relation of dosage-result is achieved with the administration of two tablets per day.

Action on venous tone

Studies showing the drug action on the venous tone established that the drug increases the venous tone: the plethysmography of venous obliteration with Hg-pressure counter showed decrease of venous discharge time.

Action on micro-circulation

Regarding its action to the microcirculation, double-blind clinical trials showed a difference between this drug and the relative placebo which is statistically important. To patients showing capillary friability, the drug increases the capillary resistance, that can be measured by vasostereometry.

Clinical studies

Clinical studies proved the therapeutic action of the drug to phlebology for the therapy of lower limbs chronic venous insufficiency, of functional or organic origin.

5.2. Pharmacokinetic properties

After the oral administration in human beings of the drug contained ^{14}C- labelled diosmin, it was demonstrated that:

- The drug is excreted primarily in the faeces, and only 14% of the administered quantity is excreted in the urine.
- The plasma half life of the drug is 11 hours.

The drug is extensively metabolised in vivo, which is evident from the presence of various phenol acids in the urine.

5.3. Preclinical safety data

Acute oral administration to mice, rats and monkeys at a dose 180 times bigger than the recommended therapeutic dose for humans, did not have any toxic or lethal effect and did not cause any anatomic or histological disorder.

Repeated oral administration at a dose 35 times bigger that the recommended therapeutic dose for humans for 13 weeks to rats and for 26 weeks to monkeys did not have any toxic or lethal effect and did not cause any behavioural, biological, anatomic or histological disorder.

Studies on rats and rabbits did not show any fetotoxic or teratogen action. No reproduction disorders were observed.

In vitro and in vivo tests did not reveal any mutagenic action.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core: Sodium starch glycolate, Cellulose microcrystalline, Gelatin, Magnesium stearate, Talc.

Coating: White beeswax, OPADRY-OY-S-37207 Beige.

(OPADRY-OY-S-37207 Beige consists of: Glycerol, Hypromellose 2190, Macrogol 6000, Sodium lauryl sulphate, Iron oxide yellow E 172, Iron oxide red E 172, Titanium dioxide E 171, Magnesium Stearate).

6.2. Incompatibilities

None known.

6.3. Shelf life

48 months.

6.4. Special precautions for storage

DIOSPER® should be stored at room temperature ($\leq 25^{o}$C).

Keep out of the reach and sight of children.

6.5. –Nature and contents of container

Salmon-pink oblong tablets in PVC/aluminium blister printed with the product's characteristics. Each blister contains 10 tablets. A box contains 3 blisters, i.e. 30 tablets, along with a patient information leaflet.

6.6. Special precautions for disposal and other handling

There are no special instructions are required for use for this product.

7. MARKETING AUTHORISATION HOLDER

KLEVA SA. - Pharmaceutical Industry

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8. MARKETING AUTHORISATION NUMBER(S)

MA122/00501

9 . DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th November 2005

10. DATE OF REVISION OF THE TEXT

July 2013