DIOSMIN

ALVOLON

500 MG FILM-COATED TABLET

Vasoprotective

1. NAME OF THE MEDICINAL PRODUCT

Diosmin (Alvolon) 500 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg diosmin.

Excipients with known effect:
Each tablet contains 4.626 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Salmon-coloured, oblong, biconvex coated tablets.

4. CLINICAL pARTICULARS

4.1 Therapeutic indications

Diosmin (Alvolon) is indicated in adults as a short-term treatment of symptoms of established chronic venous insufficiency (CVI).

4.2 Posology and method of administration

Posology
The recommended adult daily dose is two tablets, taken twice a day: one tablet at noon and one tablet in the evening, with food.

The maximum duration of treatment is 2 to 3 months.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substance, other flavonoids or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

See section 4.6.

Warnings about the excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The efficacy and safety of the preparation have not been studied in the following groups/conditions, which has to be taken into account when the preparation is used:
- children and adolescents (under 18 years).
- hepatic and/or renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic and pharmacodynamic interaction studies have been performed with diosmin and other medicinal products or with diosmin and food.
In the extensive post-marketing experience, no interactions of diosmin and other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic or foetal development (see section 5.3).

The available clinical experience in pregnant women is too limited to exclude a risk, and administration of diosmin is therefore not recommended during pregnancy.

Breastfeeding
It is not known whether diosmin is excreted into human milk. Therefore, in the absence of further information, this medicinal product should not be administered during breastfeeding.

4.7 Effects on ability to drive and use machines

Diosmin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Gastrointestinal adverse reactions were the most common reported adverse drug reactions. They include nausea, dyspepsia, vomiting and diarrhoea.

The most serious ADR associated with the use of diosmin was angioedema.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

The following headings are used to rank the ADRs by frequency: common (≥ 1/100 to < 1/10), rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

MedDRA SOC	***Frequency***	***Undesirable effect***
Nervous system disorders	Rare	Headache, malaise, vertigo
	Common	Insomnia, dizziness, tiredness, anxiety, cramps, drowsiness
Cardiac disorders	Common	Palpitations, hypotension
Gastrointestinal	Common	Nausea, vomiting, diarrhea, dyspepsia
	Uncommon	Colitis
Skin and tissue disorders	Rare	Rash, pruritus, urticaria subcutaneous
	Not known	Angioedema, edema of the face, lips and eyelids

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasoprotectives, bioflavonoids, ATC code: C05CA03

Mechanism of action

Activity on veins
This medicinal product reduces the predisposition of veins to vasodilate and reduces venous stasis.

Activity on microcirculation
This product reduces capillary permeability and increases capillary resistance.

Pharmacodynamic effects
Pharmacological activity of this medicinal product in humans has been substantiated by controlled, double-blind clinical studies and also by objective and quantitative methods in investigating the influence of the active substance on venous haemodynamics.

Effects on venous tone
This medicinal product enhances venous tone and therefore, reduces the capacitance, distensibility and stasis of blood: venous occlusal mercurial plethysmography indicates reduction of emptying time of veins.
The final effect is a reduction in venous hypertension in patients with venous insufficiency.

Effects on lymphatic system
Diosmin stimulates the lymphatic activity, improving drainage of the interstitial space and increasing lymphatic flow. The administration of 1 g a day for 28 days is capable of reducing lymphatic capillary diameter and intralymphatic pressure, improving the number of functioning lymphatic capillaries, in patients with severe chronic venous insufficiency, without ulcers.

Anti-inflammatory effects
Diosmin reduces various inflammation indexes in peripheral microvascularisation. *In vitro* and in animal studies, diosmin reduces the release of different inflammation prostaglandin mediators E2 and F2α (PGE2 and PGF2α) and thromboxane A2 (TxA2). Consequently, it inhibits the adhesion of leukocytes to the vascular wall and reduces capillary permeability and resistance, thus favouring venous return.

Effects on microcirculation
Controlled, double-blind clinical studies demonstrate statistically significant difference between diosmin and placebo. In patients with capillary fragility, diosmin treatment increases capillary resistance and reduced the clinical manifestations.

A decrease in capillary permeability was also observed after administration of 1 g of daily diosmin for 6 weeks, with respect to placebo, using technetium-labelled albumin, or plethysmography.

Clinical efficacy and safety
Controlled, double-blind clinical studies demonstrate therapeutic activity of the product in adults as a short-term treatment of symptoms of established chronic venous insufficiency (CVI) adjuvant to conventional treatment of CVI.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, diosmin is rapidly hydrolyzed in the intestine by intestinal flora and absorbed as its aglicone derivative, diosmetin. Oral bioavailability is approximately 57.9%.

Distribution
Diosmetin has a volume of distribution of 62.1 1 indicating a broad distribution into tissues.

Biotransformation
Diosmetin is extensively metabolized to phenolic acids or to its glucuronide derivatives of aglycone that are eliminated in urine.

The major metabolite found in urine is m-hydroxyphenylpropionic which is mainly eliminated in its conjugated form. Metabolites found in small quantities include phenolic acids corresponding to 1-hydroxy-4 methoxybenzoic acid, 3-metoxi-4-hidroxiphenil benzoicacetic acid and 3,4-dihydroxybenzoic acid.

Elimination
Elimination in humans is relatively fast. In studies with ^{14}C radiolabelled diosmin, 34% of the dose is found in urine and faeces after 24 hours and approximately 86% of the dose were found in urine and faeces after 48 hours.

Linearity/non-linearity
Diosmin pharmacokinetics is linear.

5.3 Preclinical safety data

There was no evidence of teratogenic effects in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460)
Gelatin
Sodium starch glycolate
Talc
Magnesium stearate
Purified water

Film-coating
Lactose monohydrate
Hypromellose (E464)
Macrogol 4000
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please see outer packaging for the shelf-life data.

6.4 Special precautions for storage

Store at temperatures not exceeding 30 °C. This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVDC/aluminium blister packs of 30 film-coated tablet.

6.6 Special precautions for disposal

No special requirements.

Manufactured by: **Laboratorios Cinfa, S.A.** – Olaz-Chipi, 10 Poligono Industrial Areta 31620 Huarte-Pamplona (Navarra), Spain
for: **Alvogen Asia Pacific Holdings Limited** – 2F, Jonsim Place, No.228 Queen's Road East, Wanchai, Hongkong

Imported and Distributed by:
Metro Drug, Inc. – Mañalac Avenue, Bagumbayan, Taguig City, Philippines

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