Version 3.0, 04/2013

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] 500 mg film-coated tablets

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.

Pink (salmon) coloured, oblong, biconvex coated tablets with the inscription D500 on one side. The dimensions of diosmin tablets are 19.1 mm x 7.4 mm x 5.8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] is indicated in adults as a short-term treatment of symptoms of established chronic venous insufficiency (CVI) adjuvant to conventional treatment of CVI.

4.2 Posology and method of administration

Posology

Adults (≥ 18 years)
The recommended daily dose is two tablets: one tablet at noon and one tablet in the evening, with food.

The maximum duration of treatment is 2 to 3 months.

Paediatric population
No data are available.

Method of administration
For oral use.
The tablets should be taken with food.

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

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 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.

Fertility
Reproductive toxicity studies in rats show no effect on fertility. No clinical data are available about the use of diosmin and fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, based on the overall safety profile, 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.

The following headings are used to rank the ADRs by frequency: 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). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

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

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.

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 aglycone derivative, diosmetin. Oral bioavailability is approximately 57.9%.

Distribution
Diosmetin has a volume of distribution of 62.1 L 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 acid which is mainly eliminated in its conjugated form. Metabolites found in small quantities include phenolic acids corresponding to 3-hydroxy-4 methoxybenzoic acid, 3-metoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxybenzoic acid.

Elimination
The elimination half-life of diosmetin showed a mean value of 31.5 hours, ranging between 26 and 43 hours. 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.

5.3 Preclinical safety data

Oral administration in mice, rats and monkeys of doses 180 times higher than the therapeutic dose in humans reveals no toxic or lethal effect.

There was no evidence of embryotoxicity or teratogenic effects in studies in rats. Reproductive toxicity studies in rats show no effect on fertility. No impairment of the reproductive function was found in rats after administration of an oral dose representing 37 times the daily therapeutic dose or concerning fertility of animals, embryotoxicity, and perinatal and postnatal development of the generation born to treated parents.

In-vitro and *in-vivo* tests reveal no mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline (E460)
Gelatin
Sodium starch glycolate type A
Talc
Magnesium stearate

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

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC-PVDC/aluminium blister packs.

Pack sizes:
30 or 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{MM/YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] 500 mg film-coated tablets

Diosmin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg diosmin.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[PRODUCT NAME] 500 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] 500 mg film-coated tablets

Diosmin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the patient

[PRODUCT NAME] 500 mg film-coated tablets

Diosmin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [PRODUCT NAME] is and what it is used for

Diosmin is a venotonic medicine. It increases the tone of veins and the resistance of the capillaries (small blood vessels).

Diosmin is used together with conventional treatment in adults for short-term (2-3 months) relief of symptoms associated with chronic venous insufficiency (poor flow of venous blood).

2. What you need to know before you take [PRODUCT NAME]

Do not take [PRODUCT NAME]
- If you are allergic to diosmin, other flavonoids or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking [PRODUCT NAME]
- if you suffer from liver problems
- if you suffer from kidney problems

Children and adolescents:
The use of [PRODUCT NAME] is not recommended in children and adolescents under the age of 18 years owing to the lack of data.

Other medicines and [PRODUCT NAME]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

No interactions with food or with other medicines are known, but in any case you should never take other medicines without consulting your doctor.

[PRODUCT NAME] with food and drink

Take [PRODUCT NAME] with food during meals.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You should not use [PRODUCT NAME] if you are pregnant, unless advised by your doctor.

Breast-feeding
It is not known whether this medicine passes into breast milk. [PRODUCT NAME] is not recommended during breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been described with diosmin.
[PRODUCT NAME] might cause dizziness and drowsiness. Do not drive or operate machines if you experience such side effects.

[PRODUCT NAME] contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take [PRODUCT NAME]

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended daily dose is two tablets: one tablet at noon and one tablet in the evening, with food.

If you take more [PRODUCT NAME] than you should
If you take more [PRODUCT NAME] than recommended or if a child accidentally takes this medicine, talk to your doctor or pharmacist.

No cases of overdose with diosmin have been reported.

If you forget to take [PRODUCT NAME]
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking [PRODUCT NAME] and contact your doctor immediately if you get any of the following symptoms that might indicate a serious side effect:
- swelling of the face or mouth (angioedema) causing difficulty in breathing. The frequency of the symptoms is not known (cannot be estimated from the available data).

Other side effects are:

Common (may affect up to 1 in 10 people)
- Nausea (feeling sick), vomiting (being sick), diarrhoea, heartburn (indigestion).

- Difficulty sleeping, dizziness, tiredness, anxiety, drowsiness.
- Muscle spasms, a forceful heartbeat that may be rapid or irregular palpitations, low blood pressure.

Uncommon (may affect up to 1 in 100 people)
- Diarrhoea, mucus and bleeding from the rectum caused by bowel inflammation.

Rare (may affect up to 1 in 1,000 people)
- Headache, malaise (feeling unwell), a spinning sensation (vertigo).
- Itchy rash (urticarial), rash, itching.

Not known (frequency cannot be estimated from the available data)
- swelling of the face, lips and eyelids (oedema).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [PRODUCT NAME]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after "EXP:". The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [PRODUCT NAME] contains

- The active substance is diosmin.
  Each film-coated tablet contains 500 mg diosmin.
- The other ingredients are:
  Tablet core: Cellulose, microcrystalline (E460), gelatin, sodium starch glycolate type A, talc, magnesium stearate
  Film-coating: Lactose monohydrate, hypromellose (E464), macrogol 4000, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172)

What [PRODUCT NAME] looks like and contents of the pack

[PRODUCT NAME] film-coated tablets are pink (salmon) coloured, oblong, biconvex coated tablets with the inscription D500 on one side. The dimensions of diosmin tablets are 19.1 mm x 7.4 mm x 5.8 mm.

[PRODUCT NAME] film-coated tablets are supplied in blister packs (PVC-PVDC/aluminium) of 30 or 60 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization holder
Alvogen IPCo S.àr.l.
5, Rue Heienhaff, L-1736,
Senningerberg,
Luxembourg

Manufacturer
Laboratories Cinfa, S.A.
Address 1: Ctra. Olaz-Chipi, 10, Pol. Ind. Areta, Huarte, 31620 Navarra
Address 2: Avda. de Roncesvalles, s/n°, Olloki, 31699 Navarra
Spain

This medicinal product is authorised in the Member States of the EEA under the following names:

Bulgaria (BG)	Флевенол 500 mg филмирани таблетки
Hungary (HU)	Flevenol 500 mg film-coated tablets
Iceland (IS)	Flevenol 500 mg filmuhúðuð tafla
Romania (RO)	Flevenol 500 mg comprimate filmate

This leaflet was last revised in {MM/YYYY}.