1. NAME OF THE MEDICINAL PRODUCT

DAFLON 500 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For a film-coated tablet:
Micronized purified flavonoid fraction ..... 500 mg
Corresponding to:
. Diosmin (90 %) ..... 450 mg
. Flavonoids expressed as hesperidin (10 %) ..... 50 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of symptoms related to venolymphatic insufficiency (heavy legs, pain, early morning restless legs).
- Treatment of functional symptoms related to acute hemorrhoidal attack.

4.2. Posology and method of administration

- Usual dosage: 2 tablets daily in two divided doses, midday and evening at meal times.
- Acute hemorrhoidal attack: 6 tablets per day for the first 4 days, then 4 tablets per day for 3 days.

4.3. Contraindications

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

4.4. Special warnings and special precautions for use

The administration of this product for the symtomatic treatment of acute hemorrhoids does not preclude treatment for other anal conditions. If symptoms do not subside promptly, a proctological examination should be performed and the treatment should be reviewed.

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

No interaction studies have been performed. No clinically relevant drug interaction has been reported to date from post marketing experience on the product.

4.6. Fertility, pregnancy and lactation

Pregnancy:

There are no or limited amount of data from the use of Micronised Purified Flavonoid Fraction in pregnant women.
Animal studies do not indicate reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Daflon during pregnancy.

Breast-feeding:

It is unknown whether the active substance/metabolites are excreted in human milk.
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from DAFLON therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility:

Reproductive toxicity studies showed no effect on fertility in male and female rats (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effects of flavonoid fraction on the ability to drive and use machines have been performed. However, on the basis of the overall safety profile of flavonoid fraction, DAFLON® 500 mg has no or negligible influence on these abilities.

4.8. Undesirable effects

Summary of the safety profile

Side effects reported with Daflon in clinical trials are of mild intensity. They consist mainly in gastro intestinal events (diarrhoea, dyspepsia, nausea, vomiting).

Tabulated list of adverse reactions
The following adverse effects or events have been reported and are ranked using the following 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 form the available data).

System Organ Class	Frequency	Preferred Term
Nervous system disorders	Rare	Dizziness
		Headache
		Malaise
Gastrointestinal disorders	Common	Diarrhoea
		Dyspepsia
		Nausea,
		Vomiting
	Uncommon	Colitis

	Not known*	Abdominal pain
Skin and subcutaneous tissue disorders	Rare	Pruritus
		Rash
		Urticaria
	Not known*	Isolated face, lip, eyelid oedema. Exceptionally Quincke's oedema

* Post-marketing experience

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9. Overdose

Symptoms
There is limited experience with DAFLON overdose. The most frequently reported adverse events in overdose cases were gastrointestinal events (such as diarrhoea, nausea, abdominal pain) and skin events (such as pruritus, rash).

Management
Management of overdose should consist in treatment of clinical symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Venotonic and vascular protector.
ATC code: C05CA53.

- **Pharmacology**

  It is active upon the return vascular system in the following way:
  - it reduces venous distensibility and stasis,
  - in the microcirculation, it normalises capillary permeability and increases capillary resistance.

- **Clinical pharmacology**

  Double blind controlled studies using methods by which the effects of the product on venous haemodynamics could be demonstrated and quantifed have confirmed the above pharmacological properties in man.

  - Dose-effect relationship: a statistically significant dose-effect relationship was established with respect to venous plethysmographic parameters: capacitance, distensibility and rate of emptying. The optimum dose-effect ratio was obtained with 2 tablets.
  - Venous tonic activity: DAFLON® 500 mg increases venous tone: venous occlusion plethysmography with a mercury stress gauge demonstrated a decrease in the rate of emptying.

- Microcirculatory activity: double-blind controlled studies showed a statistically significant difference between placebo and the drug. In patients presenting with signs of capillary fragility, DAFLON® 500 mg increases capillary resistance, as measured by angiosterometry.

➢ **Clinical trials**

Double-blind placebo-controlled trials have demonstrated the activity of the drug in phlebology, in the treatment of chronic venous insufficiency of the lower limbs (both functional and organic).

5.2. Pharmacokinetic properties

In man, following oral administration of the substance containing ^{14}C Diosmin:

- Excretion is mainly faecal, a mean of 14% of the dose administered is excreted in the urine.
- The elimination half-life is 11 hours.
- The drug is extensively metabolised as evidenced by the presence of various phenol acids in the urine.

5.3. Preclinical safety data

In animals, experimental studies did not show any teratogenic effect.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core: gelatin, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, talc.
Film-coating: glycerol, macrogol 6000, magnesium stearate, methylhydroxypropylcellulose, red iron oxide (E172), sodium lauryl sulfate, titanium dioxide, yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

30, 36, 60, 120 and 180 tablets in heat-sealed blister packs (PVC/aluminium).

6.6. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER

MA 066/00501

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

October 26th 2005/4th February 2013

10. DATE OF REVISION OF THE TEXT

November 22