1. NAME OF THE MEDICINAL PRODUCT

DAFLON® 500 mg,film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Micronised purified flavonoid fraction ..... 500 mg

Corresponding to:

Diosmin: 90 per cent ..... 450 mg

Flavonoids expressed as hesperidin: 10 per cent ..... 50 mg

For one film-coated tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Salmon coloured, oval shaped 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

Posology

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

Paediatric population
The safety and efficacy of DAFLON 500mg in children and adolescents under 18 years of age have not been established.

Method of administration

Oral route.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hemorrhoidal attack:

The administration of this product does not preclude treatment for other anal conditions. The treatment must be short-term. 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 the ability to drive and use machines

No specific 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 have 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 from 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 the national reporting system.

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 : VASOPROTECTIVES / CAPILLARY STABILIZING AGENTS / BIOFLAVONOIDS (C05CA53: Cardiovascular system)

Pharmacodynamic effects
- In pharmacology:
  DAFLON exerts an action on the vascular return system:
  - at the venous level, it reduces venous distensibility and reduces venous stasis;
  - at the microcirculatory level, it normalises capillary permeability and reinforces capillary resistance.
- In clinical pharmacology:
  Controlled, double-blind studies using methods that allow demonstrating and quantifying the activity on venous haemodynamics have confirmed the pharmacological properties of this medicinal product in humans.
  - dose/effect relationship:
    Statistically-significant dose-effect relationships have been demonstrated for the following venous plethysmography parameters: capacitance, distensibility and emptying time. The best

dose/effect ratio is obtained with 2 tablets.

- o venotonic activity:
  It increases venous tone: venous occlusion plethysmography with a mercury strain gauge revealed a reduction in venous emptying time.
- o microcirculatory activity:
  Controlled, double-blind studies have demonstrated a statistically-significant difference between this medicinal product and placebo. In patients with signs of capillary fragility, it increases capillary resistance as measured by angiosterrometry.

Efficacy and clinical safety

- In clinical practice:

Controlled double-blind clinical studies versus placebo demonstrated the therapeutic activity of the medicinal product in phlebology, in the treatment of chronic venous insufficiency (functional and organic) of the lower limbs.

5.2. Pharmacokinetic properties

In humans, following oral administration of the medicinal product with carbon 14-labelled diosmin:

- Excretion is essentially faecal and urinary excretion is on average 14% of the administered quantity,
- The elimination half-life is 11 hours,
- The product is highly metabolised, this metabolism is revealed by the presence of different phenol acids in the urine.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction. .

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium starch glycolate, microcrystalline cellulose, gelatine, magnesium stearate, talc.

Film-coating: titanium dioxide (E 171), glycerol, sodium lauryl sulphate, macrogol 6000, hypromellose, yellow iron oxide (E 172), red iron oxide (E 172), magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

30 film-coated tablets in blister packs (PVC-Aluminium).

6.6. Special precautions for disposal

No special requirements.

7. Manufacturer

Les Laboratoires Servier Industries
45520 Gidy
France

8. Product Registration Holder

Servier Malaysia Sdn Bhd
Unit No.25-02, Level 25, Imazium
No.8, Jalan SS21/37, Damansara Uptown
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