1. NAME OF THE MEDICINAL PRODUCT
CYCLO 3 FORT hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dry ruscus extract titrated in sterolic heterosides 150.0 mg
Hesperidin methyl chalcone 150.0 mg
Ascorbic acid ................. 100.0 mg

For one hard capsule
Excipient with known effect: Sunset yellow FCF (E110)
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Hard capsule with opaque yellow body and opaque orange cap.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Indicated in adults:
- Treatment of symptoms related to veno-lymphatic insufficiency (heavy legs, pain, restless legs syndromes)
- Used in the treatment of functional signs linked to haemorrhoid attacks.

4.2 Posology and Method of Administration
Posology:
- In veno-lymphatic insufficiency: usual dose is 2 to 3 capsules per day;
- In proctology: 4 to 5 capsules per day.
Method of administration:
Oral use
Capsules should be taken with a glass of water.

4.3 Contra-indications
- hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Iron storage disorders (thalassemia, hemochromatosis, sideroblastic anemia) due to the presence of ascorbic acid in the composition of the medicinal product.

4.4 Special warnings and special precautions for use
Special warnings
If diarrhea develops, discontinue treatment.
Hemorrhoidal attacks: treatment must be of short duration. The administration of the product is no substitute for specific treatment of other proctological diseases. If the symptoms do not resolve rapidly, proctological examination must be conducted and treatment must be reviewed.

Interference with laboratory tests:
Ascorbic acid as a reducing agent can influence the results of laboratory tests, such as determination of blood glucose, bilirubin, transaminase activity, lactate and others.

This medicinal product contains an azo colouring agent [sunset yellow FCF (E110)] and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
No studies on interactions with other medicinal products or with food have been performed.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are limited amount of data from the use of CYCLO 3 FORT in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (See section 5.3). As a precautionary measure, it is preferable to avoid the use of CYCLO 3 FORT during pregnancy.

Breast-feeding
It is unknown whether CYCLO 3 FORT metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. As a precautionary measure CYCLO 3 FORT should not be used during breast-feeding.

Fertility
There are no fertility data available.
4.7 Effects on ability to drive and use machines
No specific studies have been performed.

4.8 Undesirable effects

Adverse reactions observed from clinical trials:
The following undesirable effects have been observed during clinical trials.
Adverse reactions are presented according to the MedDRA system organ classification and listed below as 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).
The most commonly reported are diarrhea and abdominal pain.

Psychiatric disorders
Uncommon: Insomnia
Rare: Nervousness

Ear and labyrinth disorders
Rare: Vertigo

Vascular disorders
Rare: Peripheral coldness, Vein pain

Gastrointestinal disorders:
Common:
• diarrhea sometimes severe (associated with a risk of weight loss and fluids/electrolytes disorders if treatment is pursued), rapidly reversible on discontinuation of treatment (see section 4.4).
• abdominal pain
Uncommon: Dyspepsia, Nausea
Rare: Gastrointestinal disorder, Aphthous stomatitis

Hepatobiliary disorders
Rare: Alanine aminotransferase increased

Skin and subcutaneous tissue disorders
Uncommon: Erythema, Pruritus

Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasms, Pain in extremity

Adverse reactions reported from spontaneous reporting (frequency: not known):
Gastrointestinal disorders
• Reversible, essentially lymphocytic, microscopic colitis has been identified in certain cases (or in certain patients);

• Gastric pain.

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
No cases of overdose have been reported. However, excessive doses of ascorbic acid may lead to haemolytic anaemia in G6PD deficient subjects.
Management: in case of overdose, a symptomatic treatment should be administered

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
CAPILLARY STABILIZING AGENTS
C - CARDIOVASCULAR SYSTEM
ATC code: C05C

Venotonic action:
The following have been demonstrated:
- in vitro, in isolated perfused vein, Ruscus extract rapidly induces (within 5 to 8 minutes) a marked, progressive and lasting contraction;
- in vivo, in animals, Ruscus extract administration induces an increase in venous perfusion pressure. The intensity of the effects is comparable in healthy and rendered pathological veins.

Mechanism:
The venotonic effect of Ruscus extract is exerted by an adrenergic type mechanism at 2 levels:
- direct effect as an agonist of post-junctional alpha-adrenergic receptors in the smooth muscle cells of the vessel wall;
- indirect effect by noradrenaline release from pre-junctional neuronal storage sites.
The intensity of Ruscus extract action is proportional to temperature.
In humans, this action has been confirmed by Aellig’s method (stereomicroscopic measurement of venous compliance, assessed on a dorsal vein of the hand).
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule content: talc, magnesium stearate, hydrophobic colloidal silica, macrogol 6000.
Capsule shell: quinoline yellow (E104), sunset yellow FCF (E110), titanium dioxide (E171), gelatine

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
bottle (glass)

9. MARKETING AUTHORISATION HOLDER
PIERRE FABRE MEDICAMENT
45 Place Abel Gance
92100 Boulogne - FRANCE

10. DATE OF AUTHORISATION / REVISION
June 2014

The dose-effect relationship for a single dose, and the respective role of each constituent of the medicinal product on venous tone have also been demonstrated.

**Action on lymphatic circulation:**
- A significant and lasting increase in lymph flow rate measured in the thoracic canal of the dog.

**Vasculo-protective actions:**
- A reduction in capillary permeability was demonstrated in humans by the Landis test;
- In healthy humans, an increase in capillary resistance was demonstrated using Kramar’s method (use of suction to create a negative pressure inducing petechiae): significant increase in capillary resistance as of the first hour following dosing. Most of this activity is due to ascorbic acid.

5.2 Pharmacokinetic properties
Animal pharmacokinetic studies on tritium -labelled Ruscus heterosides and ¹⁴C- labelled hesperidin methyl chalcone have demonstrated the absorption of both ingredients, with a peak plasma concentration occurring, for both, at around the 2nd hour. Elimination is subsequently urinary and faecal, the latter excretion being linked to the entero-hepatic recycling.

This type of pharmacokinetic study cannot be conducted in humans but pharmacodynamic tests enable indirect appreciation of the product action kinetics.

The modification in venous compliance in healthy subjects after the equivalent of a capsule of the proprietary medicinal product measured by the Aellig’s test, demonstrates a maximum activity reached after 2 hours, with a return to the initial state after approximately 6 hours.

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

No study was performed to study the carcinogenicity potential. However, in mice, Hesperidin Methyl Chalcone alone did not show any carcinogenic effect after 96 weeks of oral administration (5% diet, i.e. 20 g/kg of body weight).