ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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)
- 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. Contraindications

- 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

Warning

- If diarrhoea develops, discontinue treatment.
- Haemorrhoid 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 other parameters.

Precautions for use

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 effects 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:

Diarrhoea, 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, microscopic colitis, essentially lymphocytic, has been identified in certain patients (or in certain cases)

Gastric pain.

Skin and subcutaneous disorders:

Cases of maculo-papular erythema and urticarial have been reported.

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 case of overdose has 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

Pharmacotherapeutic group:

Capillary stabilizing agents

C – Cardiovascular system

ATC code: C05CX

Venotonic action:
The following has 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 induced 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).
The dose-effect relationship for a single dose administration, and the respective role of each constituent of the medicinal product on venous tone have also been demonstrated.

Action on lymphatic circulation:
- lymphatic flow measured on the thoracic duct in dogs shows a significant and lasting increase.

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 by 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. This core activity may be attributed to C Vitamin

5.2. Pharmacokinetic properties

Animal pharmacokinetic studies on tritium-labelled Ruscus heterosides and carbon 14-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 subsequently occurs via the urinary and faecal route, the latter being linked to enterohepatic cycling.

This type of pharmacokinetic study cannot be performed in humans; however, pharmacodynamic tests enable an indirect evaluation of the kinetics action of the product.

The modification of venous compliance in healthy subjects, after the equivalent of one hard capsule of the proprietary medicinal product, measured by means of the Aellig test, evidences peak activity reached after 2 hours, with a return to the previous state after approximately 6 hours.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional safety pharmacology, repeated-dose toxicity, genotoxicity and reproductive function studies.

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

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), gelatin.

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)

Pack-sizes of 30 hard capsules.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
45, PLACE ABEL GANCE
92100 BOULOGNE
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 330 384 7 2: 30 hard capsules in a vial (glass)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Item to be completed by the Marketing Authorisation Holder]

10. DATE OF REVISION OF THE TEXT

19 April 2017

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.