SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANGIOFLUX "600 LRU/2 ML INJECTABLE SOLUTION"
ANGIOFLUX "250 LRU SOFT CAPSULES"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ANGIOFLUX 600 LRU/2 ml injectable solution
One vial contains:
Active substance:
- Sulodexide LRU 600

Excipients with known effects: sodium chloride (18 mg each vial)

ANGIOFLUX 250 LRU soft capsules
One capsule contains:
Active substance:
- Sulodexide LRU 250

Excipients with known effects:
Ethyl parahydroxybenzoate sodium (0,224 mg each capsule)
Propyl parahydroxybenzoate sodium (0,112 mg each capsule)

For the complete list of excipients, see paragraph 6.1

3. PHARMACEUTICAL FORM

- Injectable solution
- Soft capsules

4. CLINICAL INFORMATION

4.1. Therapeutic indications

Chronic venous ulcers

4.2 Posology and method of administration

Soft capsules: 1 capsule 2 times per day, away from meals.
Vial: 1 vial per day i.m. or i.v.
We mainly recommend starting therapy with the vials and, after 15 – 20 days, continuing with the capsules for 30 – 40 days.
The complete therapeutic cycle should be continued at least twice a year. Depending on the doctor's opinion, the quantity and frequency of the dose may be varied.

Pediatric population
The safety and efficacy of Angioflux in children and adolescents under 18 years old have not been established yet.

4.3 Contraindications

Hypersensitivity to the active substance or to one of the excipients listed in paragraph 6.1.

As the molecular structure is similar to heparin, do not administer ANGIOFLUX to patients hypersensitive to heparin and heparinoids. Hemorrhagic diathesis.

4.4. Special warnings and special precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product must be clearly recorded.
Patients should consult their doctors for instructions as to the correct way of administering the drug.
In all cases, where treatment is in progress with anti-coagulants, we recommend periodically controlling the haemo-coagulation parameters.

Angioflux contains less than 1 mmol (23 mg) of sodium for each dose, therefore is essentially "sodium-free".

Angioflux soft capsules contains parabens (preservatives) such as Ethyl parahydroxybenzoate sodium and Propyl parahydroxybenzoate sodium which can cause allergic reactions (even delayed).

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

As sulodexide is a heparin-similar molecule, it may increase the anti-coagulation effects of heparin and of oral anti-coagulants if administered at the same time.

4.6. Fertility, Pregnancy and lactation

Pregnancy

As a precaution, it is preferable to avoid using Angioflux during pregnancy.
Fetal toxicity studies on animals have not revealed toxic effects on the embryo or fetus.

Lactation

It is not known whether Sulodexide, or its metabolites, are excreted in breast milk. Risks for the newborn cannot be excluded.
Angioflux must not be used during breastfeeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility.

4.7. Effects on ability to drive vehicles and use machines

ANGIOFLUX does not influence the ability to drive vehicles or to use machinery.

4.8. Undesirable effects

Side effects are listed by MedDRA system organ class (SOC) and preferred term level (PT).
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, <1/10), uncommon (≥1 /1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

Soft capsules:

Gastrointestinal pathologies

Not known: gastrointestinal disorders with nausea, vomiting and epigastralgia.

Injectable solution:
General disorders and administration site conditions
Not known: pain, burning and hematoma at the injection site.

Reporting of side effects
The reporting of suspected adverse reactions that occur after authorization of the medicine is important, as it allows continuous monitoring of the benefit/risk ratio of the medicine.
Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Hemorrhagic accident is the only effect obtainable from an overdose. In case of hemorrhage it is necessary to inject Protamine sulphate at 1% (3 ml i.v. = 30mg) as adopted for "heparinic hemorrhage".

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic category: Anti-thrombotic/Heparinic, ATC Code: B01AB11
Action mechanism:
The action mechanism depends on the complementary action of its constituents: the drug exerts an anti-thrombosis action mainly due to the inhibition of the activated coagulation factor (X). It also decreases haematic viscosity, has a fibrinolytic effect due to the release of the tissue plasminogen activator of the vessel wall (t-PA) and reduces the haematic levels of the plasminogen inhibitor activator (PAI).

5.2. Pharmacokinetic properties

The plasmatic kinetics of sulodexide has been studied in rat for years for the administration methods foreseen in therapy; in other words parenteral and oral administration. The parenteral administration of sulodexide proves to be characterised by a rapid distribution phase in organs and tissues and successive bi-phase elimination according to a double-compartmental criterion.
When administered orally, the absorption appeared less rapid and more gradual, with a maximum haematic concentration after 60' instead of after 5 – 15'. The kinetics for oral administration can be interpreted by a mono-compartmental model. On the basis of the respective AUC, the bio-availability of Sulodexide taken orally proves on average to be 50% of that for intramuscular administration. Sulodexide is mainly excreted in urine. The minimum recovery in the first 24 hours corresponds to around 50% and reaches 67% after 48 hours.

5.3. Preclinical safety data

The pre-clinical data proves an absence of risk in man on the basis of conventional pharmacological safety studies: toxicity from repeated administration, genotoxicity, cancerogenic potential, reproduction toxicity studies.

6. PHARMACEUTICAL INFORMATIONS

6.1. List of excipients

Injectable solution:
Sodium chloride, Water for injectable solutions.

Soft capsules:
Migliol 812, Sodium laurylsulphate, Precipitated silica, Gelatin, Glycerol, Ethyl parahydroxybenzoate sodium, Propyl parahydroxybenzoate sodium, Red Iron Oxide (E172).

6.2. Incompatibilities

As Sulodexide is an acid polysaccharide, if it is administered in extemporaneous associations, it may react by bonding with all the basic substances. Incompatible substances commonly used in extemporaneous associations for drips are: vitamin K, B complex vitamins, hydrocortisone, hyaluronidase, calcium gluconate, quaternary ammonia salts, cloramphenicol, tetracycline, streptomycin.

6.3. Validity period

Injectable solution: 5 years
Soft capsules: 4 years

6.4. Special precautions for storage

Storage:
250 LRU Soft capsules: store below 30°C.
600 LRU/2ml injectable solution: this medicine does not require any particular conservation conditions.

6.5. Nature and content of the container

Injectable solution
type I neutral white glass vial of 2 ml, containing an in injectable solution.
600 LRU/2ml injectable solution – 10 vials of 2 ml

Soft capsules
Aluminium and PVC blister containing 50 soft capsules.
250 LRU Soft capsules - 50 Capsules

6.6 Use instructions

Unused product and refuse derived from this medicine must be disposed of in conformity with local laws.

7. MARKETING AUTHORISATION HOLDER

Aesculapius Farmaceutici S.r.l.
Via Cefalonia, 70 - 25124 Brescia.

8. MARKETING AUTHORISATION NUMBERS

ANGIOFLUX 600 LRU/2 ml Injectable solution – 10 vials of 2 ml A.I.C. no. 027932019
ANGIOFLUX 250 LRU Soft capsules – 50 capsules A.I.C. no. 027932021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewal date: May 2008

10. DATE OF REVISION OF THE TEXT

July 2020