Physiological approach to

vascular disease[1,2]

SULODEXIDE

VESSEL - VESSEL DUE F - ATERINA

endothelial first aid[2,3]

THE ONLY ONE WITH EVIDENCE TESTED BY CLINICIANS
VESSEL • VESSEL DUE F • ATERINA • BECCEH • US IA WEI
2,4

ALFASIGMA

Submitted to AIFA on 28/05/2020 COD. CORP-2020-05
Drug subject to Medical Prescription. RR. Class C; 250 ULS soft Caps, 50 caps Price € 32,50; 10 vials. Price € 23,00

SULODEXIDE

VESSEL - VESSEL DUE F - ATERINA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
VESSEL 250 ULS soft capsules
VESSEL 600 ULS/2 ml injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Soft capsules: 250 ULS Sulodexide
Ampoules: 600 ULS Sulodexide
Excipients with known effects
Soft capsules:
sodium methyl para-hydroxybenzoate: 0.26 mg per capsule
sodium propyl para-hydroxybenzoate: 0.13 mg per capsule
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Soft capsules.
Injectable solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Chronic venous ulcers.
Vessel is indicated for adults.
4.2 Dosage and administration method
Dosage
Vessel 250 ULS soft capsules: 1 capsule twice a day away from meals.
Vessel 600 ULS/2 ml injectable solution: 1 ampoule a day for intramuscular or intravenous administration. It is recommended to start the treatment with the ampoules and after 15-20 days continue with the capsules for 30-40 days. The complete therapeutic cycle is to be repeated at least twice a year. The dosage may be changed in amount and frequency on the judgement of the physician.
Paediatric population
The safety and effectiveness of Sulodexide in children and adolescents under 18 years of age have not yet been established. No data are available.
4.3 Contraindications
Hypersensitivity to the active ingredient or any one of the excipients listed in section 6.1 and to heparin and heparinoids.
Diathesis and haemorrhagic diseases.
4.4 Special warnings and precautions for use
Traceability
In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded. Because of its pharmaco-toxicological properties, there are no particular precautions for the use of Vessel.
However, in cases where a treatment with anticoagulants is in progress, it is advisable to periodically check the blood coagulation parameters. Vessel soft capsules contains sodium ethyl para-hydroxybenzoate and sodium propyl para-hydroxybenzoate which can cause allergic reactions (possibly delayed). Vessel contains less than 1 mmol (23 mg) of sodium per dosage unit (soft capsule or ampoule), i.e. it is essentially "sodium-free".
4.5 Interaction with other medicines and other forms of interaction
Sulodexide is a heparin-like molecule and therefore may increase the anticoagulant effects of heparin and oral anticoagulants if administered simultaneously.
Also see section 6.2.
4.6 Fertility, pregnancy and breast-feeding
Pregnancy
The quantity of data on use of sulodexide in pregnant women is limited (less than 300 pregnancy results). Studies on animals do not indicate direct or indirect harmful effects on reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid using sulodexide during pregnancy.
Breast-feeding
It is not known whether Sulodexide or its metabolites are excreted in human or animal milk. A risk for new-born babies cannot be excluded.
Vessel must not be used during breast-feeding.
Fertility
Studies on animals do not indicate direct or indirect harmful effects on male and female fertility.
4.7 Effects on ability to drive and use machines
Vessel does not alter or negligibly alters the ability to drive or use machines.
4.8 Undesirable effects
Clinical studies
The incidences of adverse drug reaction (ADR) associated with the treatment with sulodexide come from three clinical trials conducted on 430 patients treated with standard dosage and treatment times.
The table below includes the adverse reactions from clinical trials listed according to the MedDRA System Organ Classes (SOC) and, in addition, according to the preferred terms in order of severity where possible.
The adverse reactions have been divided by frequency classes according to the following convention: 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).

MedDRA System Organ Class	Common	Uncommon
Nervous system diseases		Headache, loss of consciousness
Ear and labyrinth diseases	Vertigo	
Gastrointestinal diseases	Upper abdominal pain, diarrhoea	Gastric haemorrhage
Skin and subcutaneous tissue diseases	Skin eruption	Eczema, nettle-rash
Systemic diseases and administration site-related conditions		Bleeding during injection, peripheral oedema

Post-marketing experience
During marketing of Sulodexide other undesirable events were reported. It is not possible to determine the frequency of these undesirable events as the data derive from spontaneous reports. Consequently, the frequency of these adverse events is indicated with "unknown" (it cannot be defined based on the available data).
Soft capsules:

MedDRA System Organ Class	Frequency unknown
Haemolymphopoetic system diseases	Anaemia
Metabolism and nutrition disorders	Plasma protein metabolism disorders
Gastrointestinal diseases	Epigastralgia, nausea, vomiting, melaena, flatulence, dyspepsia
Skin and subcutaneous tissue diseases	Angioedema, ecchymosis, erythema
Reproductive system and breast diseases	Genital oedema, genital erythema, polymenorrhea

Solution for injection:

MedDRA System Organ Class	Frequency unknown
Psychiatric disorders	Derealizing
Nervous system diseases	Convulsions, tremor
Eye diseases	Sight disorder
Cardiac diseases	Palpitations
Vascular diseases	Hot flushes
Respiratory, thoracic and mediastinal diseases	Haemoptysis
Skin and subcutaneous tissue diseases	Itchiness, purpura, generalized erythema
Renal and urinary diseases	Vesical stenosis, dysuria
Systemic diseases and administration site-related conditions	Chest pain, pain, burning during injection

Reporting suspected adverse reactions
Reporting suspected adverse reactions that occur after authorisation of the medicine is important, as it allows continuously monitoring the benefit/risk ratio of the medicine. Health workers are requested to report any suspected adverse reaction through the national reporting system at the address https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.
4.9 Overdose
Haemorrhage is the only effect that may occur with an overdose. In the event of haemorrhage, inject protamine sulphate (1% solution) according to the use in "heparin haemorrhages".

5. PHARMACOLOGICAL PROPERTIES
Sulodexide has a marked antithrombotic action on both the arterial and the venous side.
5.1 Pharmacodynamic properties
Pharmacotherapeutic class: Sulodexide is classified among heparin antithrombotic drugs - ATC code: B01AB11.
Action mechanism
Sulodexide performs an antithrombotic action on both arterial and venous level through a series of action mechanisms, such as inhibition of some factors involved in the coagulation cascade, in particular activated factor X, fibrinolytic action and inhibition of platelet adhesion. Interference with thrombin is minimal and this limits the anticoagulant action. By promoting the reduction of fibrinogen levels, sulodexide is effective in normalizing the altered blood viscosity of patients with vascular diseases and thrombotic risk. In addition, through activation of the lipoprotein lipase, sulodexide is effective in normalizing the altered lipidic levels.
Pharmacodynamic effects
Specific studies have shown that administration of Sulodexide does not have an anticoagulant effect.
Clinical effectiveness and safety
The therapeutic activity of sulodexide was evaluated in patients affected by vascular diseases with thrombotic risk, both on the arterial and the venous side. The medicinal product proved to be particularly effective in elderly and diabetic patients.
5.2 Pharmacokinetic properties
Absorption
Absorption after oral administration in man, studied with the marked product, showed that a first blood level peak occurs after 2 hours and a second between 4 and 6 hours, after which the drug is no longer detectable in the plasma; it is again detected at about 12 hours and then remains constant until about 48 hours. The constant blood level found after 12 hours is probably due to the slow release of the drug by the absorption organs and in particular, the vessel endothelia.
Metabolism
The metabolism is mainly hepatic and the excretion mainly urinary.
Elimination
Urinary elimination
Using the marked product, 55.23% of the radioactivity administered is excreted with the urine during the first 96 hours. This elimination shows a peak after about 12 hours and a mean urinary value of 17.6% of the dose administered in the 0-24 hour interval; a second peak around the 36th hour with urinary elimination of 22% between 24 and 48 hours; a third peak around the 78th hour with a urinary elimination of 14.9% in a period of time of 48-96 hours. After 96 hours, the radioactivity is no longer detectable in the samples collected.
Faecal elimination
The total radioactivity recovered in the faeces is 23% in the first 48 hours, after which no marked substance can be detected.
Linearity/non-linearity
Pharmacological tests conducted in man with intramuscular and intravenous administration of the product show a linear dose/effect relation.
5.3 Preclinical safety data
The preclinical data based on conventional studies on pharmacological safety, toxicity at repeated doses, genotoxicity, reproductive and development toxicity do not show particular risks for man.

6. PHARMACEUTICAL INFORMATION
6.1 List of excipients
Vessel 250 ULS soft capsules
Sodium lauroyl sarcosinate, silicon dioxide, triacetin, gelatine, glycerol, ethyl para-hydroxybenzoate, sodium propyl para-hydroxybenzoate, titanium dioxide (E 171), red iron oxide (E 172).
Vessel 600 ULS/2 ml injectable solution
Sodium chloride, water for injectable preparations
6.2 Incompatibility
As Sulodexide is an acid polysaccharide, it may react by complexing with all basic substances if administered extemporaneously. Commonly used substances incompatible in extemporaneous associations for intravenous drip are: vitamin K, complex B vitamins, hydrocortisone, hyaluronidase, calcium gluconate, quaternary ammonium salts, chloramphenicol, tetracycline, streptomycin.
6.3 Shelf-life
Soft capsules and injectable solution: 5 years.
6.4 Special precautions for storage
Store at a temperature below 30°C.
6.5 Nature and content of the container
Vessel 250 ULS soft capsules: cardboard box containing 2 PVC/PVDC-ALU/PVDC blister packs of 25 capsules each.
Vessel 600 ULS/2 ml injectable solution: cardboard box containing a polystyrene tray of 10 dark glass ampoules of injectable solution.
6.6 Special precautions for disposal and other handling
No particular instruction. Unused medicine and the waste deriving from this medicine must be disposed of in compliance with the local regulations in force.

7. MARKETING AUTHORISATION HOLDER
Alfasigma S.p.A. – Via Ragazzi del '99, no 5 - 40133 Bologna (BO)

8. MARKETING AUTHORISATION NUMBER(S)
"250 ULS soft capsules": 50 capsules in 2 PVC/PVDC-ALU-PVDC blister packs: MA No 022629113
"600 ULS/2 ml injectable solution": 10 ampoules of 2 ml: MA No 022629101

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION
09/10/1972 - 01/06/2010

10. DATE OF TEXT REVISION
25/05/2021

References:
1) Summary of Product Characteristics
2) SCoccheri et al. Drug Design, Development and Therapy, 2014:8 49–65
3) BJCarroll et al. Journal of Thrombosis and Haemostasis, 2019:17 31–38
4) JLasierra-Cirujeda et al. Journal of Blood Medicine, 2010:1 105–115

ALFASIGMA