Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fibrovein 0.5% Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fibrovein 0.5 % Solution for Injection
Each ml solution for injection contains 5 mg sodium tetradecyl sulfate.
Each 2 ml ampoule contains 10 mg sodium tetradecyl sulfate.

Excipient(s) with known effect
Contains benzyl alcohol 20 mg/ml.
Contains sodium up to approximately 1.3 mg/ml.
Contains potassium 0.3 mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless, sterile solution free from visible particles.
pH 7.5 – 7.9.
Osmolality 247 – 273 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of uncomplicated primary varicose veins, recurrent or residual varicose veins following surgery, reticular veins, venules and spider veins of the lower extremities that show simple dilation.

Fibrovein is indicated in adults.

4.2 Posology and method of administration

Posology
Fibrovein is for intravenous use only. The strength of solution required depends on the size and degree of varicosity. Spider veins should only be treated with the 0.2%, reticular veins with 0.5%, the 1% solution will be found most useful for small to medium varicosities and the 3% solution for larger varicosities. The size of non-visible varicose veins should be measured under ultrasound.

The sclerosant should be administered intravenously in small aliquots at multiple sites along the vein to be treated either as a liquid or as a sclerosant/air mixture (foam), for the treatment of larger veins with the 1% and 3% solutions. The objective is to achieve optimal destruction of the vessel wall with the minimum concentration of sclerosant necessary for a clinical result. If the concentration is too high necrosis or other adverse sequelae may occur.

Adults

Concentration	***Normal volume injected intravenously at suitable sites per session***	***Maximum total volume to be injected per session***
	Liquid	*Liquid*
Fibrovein 0.5 %	*0.1 to 1.0 ml*	*10 ml*

Where special caution is indicated it is recommended that a test dose of 0.25 to 0.5 ml Fibrovein should be given followed by observation of the patient for several hours before administration of a second or larger dose.

As the volume to be injected is limited per session, repeated sessions are usually needed (2 to 4 on average). To prevent a possible allergic reaction, it is recommended that a small test dose of Fibrovein should be given at the beginning of each session.

Elderly population
No specific dose recommendations apply.

Paediatric population
The safety and efficacy of Fibrovein in children and adolescents have not been established. No data are available.

Method of administration

Strict aseptic technique must be maintained while handling Fibrovein.
Fibrovein is a single-use parenteral product. Once the container is opened, use immediately and discard any unused portion. Visually inspect for particulate matter before use. Solutions that contain particulate matter should not be used.

4.3 Contraindications

- Hypersensitivity to active substance or any of the excipients listed in section 6.1 and allergic conditions
- Unable to walk due to any cause, bedridden
- High risk of thrombosis e.g. a congenital predisposition to blood clots or multiple risk factors such as hormonal contraception or hormone replacement therapy, significant obesity, smoking or extended periods of immobility
- Recent acute superficial thrombophlebitis, deep vein thrombosis or pulmonary embolism
- Recent surgery
- Varicosities caused by pelvic or abdominal tumours unless the tumour has been removed
- Uncontrolled systemic disease such as diabetes mellitus, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases
- Evolutive cancer
- Significant valvular incompetence of the deep veins
- Occlusive arterial disease
- Huge superficial veins with wide open communications to deeper veins
- Phlebitis migrans
- Acute cellulitis
- Acute infections

In addition when the sclerosant has been converted to foam:

- Known symptomatic patent foramen ovale (PFO).

4.4 Special warnings and precautions for use

General precautions
Fibrovein should only be administered by a healthcare professional experienced in venous anatomy and the diagnosis and treatment of conditions affecting the venous system and familiar with proper injection technique.

Emergency resuscitation equipment should be immediately available. Allergic reactions, including anaphylaxis have been reported. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat it appropriately.

Before treatment, healthcare professional should investigate patient's risk factors and inform them about the risks of the technique.

As a reminder, sclerotherapy is contraindicated in patients with high risk of thromboembolic events, but should also be avoided in most situations at lower risk. Sclerotherapy is notably not recommended in patients with a history of thromboembolic events

Nevertheless, if sclerotherapy is judged necessary, preventive anticoagulation can be initiated.

Patent foramen ovale (PFO)
Due to the risk of circulation of product, bubbles or particulates in the right heart, the presence of a PFO may enhance the occurrence of serious arterial adverse events. In patients with history of migraine with aura, serious cerebrovascular events or pulmonary hypertension, it is recommended to search for PFO before sclerotherapy.

In patients with asymptomatic but known PFO, it is recommended to use smaller volumes and avoid Valsalva manoeuvre in the minutes after injection.

Patients with a PFO have been shown to be more likely to suffer from adverse events such as temporary neurological events, visual disturbances and migraine. A symptomatic PFO is a contraindication for use of Fibrovein as a foam (see section 4.3)

Migraine
Previous migraine sufferers should be treated with care. Patients with previous migraine have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Use smaller volumes in patients with history of migraine.

TIA
Patients with a past medical history of TIA should be treated with care.
Patients with previous TIA have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Truncular varicosities
For the treatment of truncular varicosities, there should be a minimal distance of 8 to 10 cm between the site of foam injection and the saphenofemoral junction.

Lymphoedema
If venous insufficiency is associated with lymphoedema, the sclerosant injection may worsen local pain and inflammation for days or several weeks. Patients should be informed of this expected phase, which does not compromise efficacy.

Extravasation
Severe adverse local effects, including tissue necrosis, may occur following extravasation; therefore, extreme care in intravenous needle placement and using the minimal effective volume at each injection site are important. Pigmentation may be more likely to result if blood is extravasated at the injection site (particularly when treating smaller surface veins) and compression is not used.

Intra-arterial injection
Sclerosants must never be injected into an artery as this can cause extended tissue necrosis and may result in loss of the extremity. Injection under duplex ultrasound is recommended in order to avoid extravasations and arterial injection.

Healthcare professional should monitor the patient during and after the administration of Fibrovein. Symptoms of hypersensitivity (redness, pruritus, cough) or neurological symptoms (scotoma, amaurosis, migraine with aura, paraesthesia, focal deficit) may happen.

Respiratory disease
Special care should be taken in patients with laboured breathing (bronchial asthma) or a strong predisposition to allergies (see section 4.2).

Pre-injection evaluation
Because of the danger of thrombosis extension into the deep venous system, thorough pre-injection evaluation for valvular competency should be carried out and slow injections with a small amount (not over 2 mL) of the preparation should be

injected into the varicosity. Deep venous patency must be determined by non-invasive testing such as duplex ultrasound. Venous sclerotherapy should not be undertaken if tests such as Trendelenberg and Perthes, and angiography show significant valvular or deep venous incompetence.

Follow-up
Healthcare professional should see the patient again after 1 month for a control of treatment efficacy and safety, by clinical and ultrasound evaluation.

The development of deep vein thrombosis and pulmonary embolism have been reported following sclerotherapy treatment of superficial varicosities. Patients should have post-treatment follow-up of sufficient duration to assess for the development of deep vein thrombosis. Embolism may occur as long as four weeks after injection of sodium tetradecyl sulfate. Adequate post-treatment compression may decrease the incidence of deep vein thrombosis.

Underlying arterial disease
Extreme caution in use is required in patients with underlying arterial disease such as severe peripheral atherosclerosis or thromboangiitis obliterans (Buerger's disease).

Foot and malleolar area
Special care is required when injecting the foot and malleolar area where the risk of inadvertent injection into an artery may be increased.

Excipients
This medicinal product contains:

- less than 1 mmol sodium (23 mg) per vial/ampoule, i.e. essentially 'sodium-free'.
- less than 1 mmol potassium (39 mg) per vial/ampoule, i.e. essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety for use in pregnancy has not been established. There are no or limited amount of data from the use of sodium tetradecyl sulfate in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Treatment should be postponed until after childbirth.

Fibrovein should be used only when clearly needed for symptomatic relief and when the potential benefits outweigh the potential hazards to the fetus.

Breast-feeding
It is not known whether sodium tetradecyl sulfate is excreted in human milk. Caution should be exercised when used in nursing mothers.

Fertility
It is not known whether sodium tetradecyl sulfate affects fertility.

4.7 Effects on ability to drive and use machines

Fibrovein has no or negligible direct influence on the ability to drive and use machines. However, a bandage and/or compression stockings may be added after treatment. This could affect the ability to drive.

4.8 Undesirable effects

The most commonly reported side effects are pain on injection urticaria, superficial thrombophlebitis and temporary skin pigmentation after treatment. Very rarely a permanent discoloration may remain along the path of the sclerosed vein segment.

Ulceration may occur following extravasation of the drug. It is important to use the lowest strength that will sclerose the vein as many of the common side effects are caused by using a concentration that is too high.

Intra-arterial injection although very rare has been reported resulting in significant tissue necrosis including loss of the extremity.

The most serious side effects are anaphylactic shock and pulmonary embolism and deaths have been reported in patients receiving sodium tetradecyl sulfate.

Adverse events are listed below by system organ class and estimated frequency from published clinical data. Frequencies are defined using the following convention:
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: (includes isolated reports) <1/10,000

Immune system disorders	**Using liquid**
Systemic allergic reactions e.g. anaphylactic shock, asthma, generalised hives.	Very rare

Nervous system disorders	**Using liquid**
Migraine	Very rare
Headache, local sensitivity disturbances, (paraesthesia). Vaso-vagal reactions e.g. fainting, confusion, dizziness, loss of consciousness.	Very rare
Nerve damage after extravasation of the drug	Very rare
Weakness (hemiparesis, hemiplegia), transient ischaemic attack (TIA), palpitations.	Very rare
Stroke	Very rare

Eye disorders	**Using liquid**
Scotoma, scintillating scotoma.	Very rare

Vascular disorders	**Using liquid**
Superficial thrombophlebitis, phlebitis.	Common
Matting (growth of very fine spider veins in treated area).	Uncommon
Deep vein thrombosis (mostly muscular and distal).	Very rare
Pulmonary embolism, vasculitis, circulatory collapse.	Very rare
Distal tissue necrosis following intra-arterial injection, may lead to gangrene. Most cases have involved the posterior tibial artery above the medial malleolus. Arterial spasm can occur despite intravenous injection.	Very rare

Respiratory thoracic and mediastinal disorders	**Using liquid**
Coughing, shortness of breath, sensation of pressure/tightness in the chest.	Very rare

Gastrointestinal disorders	**Using liquid**
Nausea, vomiting, diarrhoea, feeling of swollen/thick tongue, dry mouth.	Very rare

Skin and subcutaneous tissue disorders	**Using liquid**
Skin discolouration (hyperpigmentation, more rarely - haematoma & ecchymosis).	Uncommon
Local allergic and non-allergic skin reactions e.g. erythema, urticaria, dermatitis, swelling/induration.	Uncommon
Local sloughing and necrosis of skin & tissues.	Rare

General disordersand administration site conditions	**Using liquid**
Pain or burning (short term at the injection site).	Common
Fever, hot flushes.	Very rare

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 HPRA pharmacovigilance website: www.hpra.ie.

4.9 Overdose

No case of systemic overdose has been reported. Using a higher concentration than recommended in small veins may lead to pigmentation and/or local tissue necrosis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasoprotectives, Sclerosing agents for local injections, ATC code C05BB04.

Sodium tetradecyl sulfate is a sclerosing agent. Intravenous injection causes intima inflammation and thrombus formation. This usually occludes the injected vein. Subsequent formation of fibrous tissue results in partial or complete vein obliteration that may or may not be permanent.

Published clinical series have shown that Fibrovein converted to a foam is very effective at treating larger varicose veins e.g. great saphenous vein and tributaries. The foam is able to displace the blood and the sclerosant has more time to act on the endothelium compared to the liquid form. Some adverse events are more frequent following foam sclerotherapy than liquid sclerotherapy e.g. headache, migraine and visual disturbances. Adverse neurological events may also occur but these are rare

5.2 Pharmacokinetic properties

Absorption
Fibrovein containing sodium tetradecyl sulfate is administered directly into the lumen of the isolated segment of vein/venule.

Distribution
In humans, the majority (75 %) of an injected dose of radiolabelled 3 % sodium tetradecyl sulfate rapidly disappeared from the empty varicose vein injection site into communicating blood vessels with rapid passage into the deep calf veins.

In rats, at 72 hours after intravenous dosing of radiolabelled sodium tetradecyl sulfate, tissue levels of radiolabel found in the sampled tissues (liver, kidney, lipid and skeletal muscle) were extremely low. Although there was some evidence of radiolabel associated with the injection site, the levels were very low.

Biotransformation
The metabolism of sodium tetradecyl sulfate has not been confirmed.

Elimination
Of an intravenously administered radiolabelled dose, 70 % was recovered in the urine of rats within the first 24 hours post-dosing. At the end of the 72 hour post-dose period, 73.5 % of the radiolabel had been recovered from the urine and 18.2 % recovered from the faeces.

Hepatic/renal impairment
No pharmacokinetics studies have been performed in patients with hepatic or renal impairment.

5.3 Preclinical safety data

There are no additional data of relevance to the prescriber other than those already mentioned in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Disodium phosphate dodecahydrate
Potassium dihydrogen phosphate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product is not compatible with heparin.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After first opening, the medicinal product should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special temperature conditions.
Do not freeze.
Keep the vial/ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml ampoule (Type I glass).
5 ml vial (Type I glass) with a stopper (chlorobutyl) and aluminium seal with flip-off cap (polypropylene).

Fibrovein 0.5 % Solution for Injection
Pack size of 5 ampoules of 2 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal
No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

STD Pharmaceutical (Ireland) Limited
Block 1, Blanchardstown Corporate Park,
Ballycoolen Road,
Blanchardstown
D15 AKK1
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22778/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT