IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fibrovein 0.5% Solution for Injection
Sodium tetradecyl sulfate
PA22778/002/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number CZ/H/0944/001-004 with the CZ as RMS. The responsibility of RMS was transferred to Ireland on 17th September 2026 under procedure number IE/H/1502/001/004.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22778/002/001-004
Marketing Authorisation Holder: STD Pharmaceutical (Ireland) Limited

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

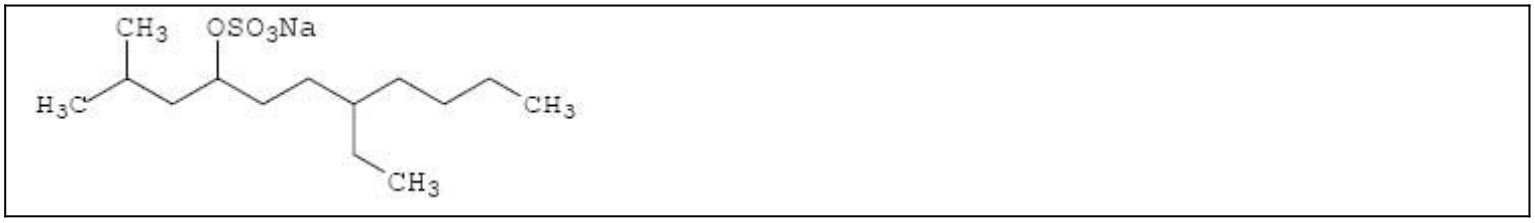
Name of the product	Fibrovein 0.5% Solution for Injection
Name(s) of the active substance(s) (INN)	Sodium tetradecyl sulfate
Pharmacotherapeutic classification (ATC Code)	C05BB04
Pharmaceutical form and strength(s)	0.5% Solution for Injection
Marketing Authorisation Number(s) in Ireland (PA)	PA22778/002/002
Marketing Authorisation Holder	STD Pharmaceutical (Ireland) Limited Block 1 Blanchardstown Corporate Park Ballycoolen Road Blanchardstown Dublin 15 D15 AKK1 Ireland
MRP/DCP No.	IE/H/1502/002
Reference Member State	IE
Concerned Member State(s)	AT, DE, FR, NL, PL, RO

On 9 August 2012, Czech Republic, France, Portugal, Spain and the UK agreed to grant Marketing Authorisations (MAs) to STD Pharmaceutical Products Limited for the medicinal products Fibrovein 0.2%, 0.5%, 1% & 3% Solution for Injection. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (UK/H/2775/001-4/DC) conditions of granting these licences were that the applicant was to commit to 5 follow-up measures after the completion of the procedure. These follow-up measures are detailed in full in the Clinical Aspects section of this report. After the national phase, MAs were granted in the UK on 9 October 2012 (PL 00398/0204-7). In the RMS, these products are on restricted prescription (hospital use only).
These are abridged, bibliographic applications for Fibrovein 0.2%, 0.5%, 1% and 3% Solution for Injection, submitted under Article 10a (well-established use) of Directive 2001/83/EC, as amended. The proposed products contain sodium tetradecyl sulphate (STS) as the active substance. Commercially available injectable formulations of STS were initially marketed in the UK by STD Pharmaceutical Products Limited since 1967 under the name STD Injection and then renamed Fibro-Vein in 1992. Fibro-Vein is a well-established medicinal product with acceptable efficacy and safety for the treatment of varicose veins by compression sclerotherapy.
Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is identical in formulation to Fibro-Vein and thus no direct biopharmaceutical investigations or clinical studies have been performed on Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection.
The proposed indication of Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection administered as a liquid or foam in the treatment of varicose veins, venules and spider veins by compression sclerotherapy.
No new non-clinical or clinical studies were conducted, which is acceptable given that these are bibliographic applications for an active of well-established use. The clinical data in the dossier is based on published literature and not direct randomised evaluation of the efficacy and safety of the sclerosant solution STS. The applicant has also included a number of observational studies in support of their applications. (see Clinical Aspects).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent

authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active substance is well established.
The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic medicinal product and there is no reason to conclude that the marketing of this product will change the overall use pattern of the existing market.

II. QUALITY ASPECTS

ACTIVE SUBSTANCE SODIUM TETRADECYL SULPHATE General Information
Nomenclature BP Name: Sodium Tetradecyl Sulphate **Chemical Name** Sodium 7-ethyl-2-methyl-4-undecyl sulphate
Structure



Molecular formula: C14H29NaO4S Molecular Mass: 316.4 **Description:** Sodium tetradecyl sulphate is a clear colourless gel
Solubility: Soluble in water, ethanol and isopropanol
The active substance, sodium tetradecyl sulphate, is the subject of a British Pharmacopoeia (BP) monograph.
Manufacture
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
MEDICINAL PRODUCT Description and Composition
The proposed product is a clear, colourless solution for injection. Each mL of the product is formulated to contain 2 mg, 5 mg, 10 mg and 30 mg of the active ingredient, sodium tetradecyl sulphate respectively.
Other ingredients consist of the pharmaceutical excipients, benzyl alcohol, disodium phosphate dodecahydrate, potassium dihyrogen phosphate, sodium hydroxide (for pH adjustment) and water for injections.
All excipients used comply with their respective European Pharmacopeial monograph. Satisfactory certificates of analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided. The applicant has provided a declaration to confirm that there are no materials of human or animal origin contained in the product, or used in the manufacturing process. Furthermore, no genetically modified organisms are used in the manufacture of the excipients. There are no novel excipients used.
Pharmaceutical Development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. Injections containing sodium tetradecyl sulphate have been marketed in the UK since 1967, the formulation for the proposed product Fibrovein is identical to that currently marketed in the UK by the same MAH Fibro-Vein 0.2%, 0.5%, 1% and 3% (PL 00398/0004, PL 00398/0002, PL 00398/0003 and PL 00398/5000 respectively).
Manufacture
A description and flow-chart of the manufacturing process has been provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.
Finished Product Specification

The finished product specifications are provided for both release and shelf-life and are acceptable. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, Test methods have been described and have been validated. The batch analysis results show that the finished product meets the specification proposed. Certificates of Analysis have been provided for all working standards used.

Container Closure System

The finished product is licensed for marketing in either Type I glass ampoules or Type I glass vials with a stopper (chlorobutyl) together with an aluminium seal with flip-off cap (polypropylene). The ampoules are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.

Fibrovein 0.2% Solution for Injection (5 mL vial)- pack sizes of 2, 5 or 10 vial per pack.
Fibrovein 0.5% Solution for Injection (2mL ampoule)- pack size of 5 ampoules per pack
Fibrovein 1% Solution for Injection (2mL ampoule)- pack size of 5 ampoules per pack
Fibrovein 3% Solution for Injection (2mL ampoule)- pack size of 5 ampoules and 5 mL vials- pack size of 2, 5 and 10 vials. Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended); the glass vials and ampoules comply with Ph Eur requirements and are suitable for contact with intravenous preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years (before first opening) and should be used immediately after first opening has been set. The storage conditions for the unopened product are, "Do not freeze", "Keep the vial/ampoule in the outer carton in order to protect from light" have been set. .

Quality Overall Summary

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vita* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPCs, PIL and labelling are acceptable from a pharmaceutical perspective. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the Competent Authority for approval before packs are marketed. The labelling texts fulfil the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that is contains. The text of the SmPC, PIL and label is satisfactory and consistent with that for the reference product.

Conclusion

From a pharmaceutical point of view, it is recommended that Marketing Authorisations are granted for these applications.

III. NON-CLINICAL ASPECTS

Pharmacology

Sodium tetradecyl sulphate is a long-chain fatty acid salt of an alkali metal and has been marketed in the UK for over three decades, for use as a sclerosing agent. Studies reported in the literature using intravenous administration of sodium tetradecyl sulphate in rats, rabbits and mice show it to be an effective sclerosant. The detergent action produces endothelial damage leading to thrombus formation and the formation of scar tissue in the vein, which produces a fibrous cord and results in vascular sclerosis. The absence of safety pharmacology studies is acceptable given the long clinical experience.

Pharmacokinetics

Limited information is available in the literature on pharmacokinetics.

An intravenous dose of sodium tetradecyl sulphate was rapidly excreted in the rat, with the majority of the dose eliminated in the urine. Levels in the tissues that were measured were very low.

Pharmacokinetic drug interactions

No pharmacokinetic interaction studies have been conducted. Compatibility studies have not been conducted either and therefore Fibrovein should not be mixed with other medicinal products.

Toxicology

Non-clinical data are relatively limited, but are generally superseded by clinical experience.

Sodium tetradecyl sulphate shows low acute toxicity in rodents, and repeated oral dosing showed only the kidney to be a potential target organ. There are no repeated-dose studies using the intravenous route; repeated intraperitoneal dosing in mice resulted in peritonitis, infections and in some cases, deaths, but was likely due to puncture of the peritoneum during dosing rather than a toxic effect of sodium tetradecyl sulphate, as the remaining animals showed no effects.

A mouse lymphoma L5178Y TK+/- study was negative, and given the nature of the active substance, sodium tetradecyl sulphate is not expected to have carcinogenic potential.

Relevant reproductive toxicity studies have not been conducted.

A range of studies have been reported in which the local tolerance of various sodium tetradecyl sulphate solutions were administered to rats, rabbits and dogs via subcutaneous, intradermal or intra-arterial routes. Findings included erythema, ulceration, necrosis and gangrene and suggest the importance of using the correct, intravenous, route of administration.
An environmental risk assessment (ERA) has been provided. Sodium tetradecyl sulphate is not considered to pose a risk to the environment.
The non-clinical sections of the SmPCs have been revised as requested and are acceptable.
The non-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vita of the expert has* been provided.
There are no objections to approval of Fibrovein 0.2%, 0.5%, 1% & 3% Solution for Injection from a non-clinical point of view.

IV. CLINICAL ASPECTS

Varicose veins and current treatments
Varicose veins arise when the valves of superficial veins fail and become incompetent, allowing retrograde flow of blood towards the feet in the superficial veins. The veins dilate in response to this with the largest dilations seen in the tributaries of the great saphenous vein (GSV) and small saphenous vein (SSV). In some patients, dilations of small veins less than 3 mm diameter are seen. These are referred to as reticular varices. In many patients telangiectases (dilated venules within the skin) are seen. Both reticular veins and telangiectases tend to proliferate in patients with varicose veins
There are currently three distinct treatment options available for varicose veins: conservative treatment [consisting of lifestyle advice and the use of compression hosiery (graduated elasticated stockings)], endovenous treatment (e.g. sclerotherapy and thermal ablation) and surgery. According to a Cochrane review conducted by the Peripheral Vascular Diseases Group (Rigby 2004), despite the prevalence of varicose veins and the vast numbers of people being treated, the criteria for each of the various treatments are not well defined (Rigby 2004). Furthermore, there is no general consensus over which intervention is the most effective (Rigby 2004).
Sclerotherapy; Sclerotherapy is one method, used to treat varicose veins and involves the injection of a sclerosant into the varicosities followed by a period of compression treatment using bandaging or compression hosiery. Injecting the unwanted veins with a sclerosing solution causes the target vein to immediately shrink, and then dissolve over a period of weeks as the body naturally absorbs the treated vein. Sclerotherapy is preferred over laser for eliminating large spider veins (telangiectasiae) and smaller varicose leg veins. Unlike a laser, the sclerosing solution additionally closes the "feeder veins" under the skin that are causing the spider veins to form, thereby making a recurrence of the spider veins in the treated area less likely. Multiple injections of dilute sclerosant are injected into the abnormal surface veins of the involved leg. The patient's leg is then compressed with either stockings or bandages that they wear usually for two weeks after treatment. It is common practice for the patient to require at least two treatment sessions separated by several weeks to significantly improve the appearance of their leg veins.
Sclerotherapy can also be performed using foamed sclerosants under ultrasound guidance to treat larger varicose veins, including the great and small saphenous veins. In ultrasound-guided sclerotherapy, ultrasound is used to visualize the underlying vein so the physician can deliver and monitor the injection. Sclerotherapy should be done under ultrasound guidance after venous abnormalities have been diagnosed with duplex ultrasound.
Endovenous thermal ablation involves heating the vein wall from within by using a laser or radio frequency catheter to generate heat in the centre of the vein. The thermal damage to the vein wall results in fibrosis and obliteration of the vein. Many surgical treatments are practiced; these may involve ligation of the affected stem vein (great or small saphenous veins), stripping of the affected stem veins, and avulsions (tearing away) of the varicosities. Some surgeons use a combination of surgery and injection sclerotherapy. Newer surgical treatments include subfascial ligation and Perforate Invaginate stripping (PIN) stripping.
Subfascial ligation is a procedure that involves cutting through the skin and deep fascia (a sheet of connective tissue) and ligating (tying off) the incompetent perforating veins that link the veins in the skin to the deep veins in the muscle.
PIN-stripping is a technique that involves stripping the vein into itself in a manner similar to turning a stocking inside out. This results in a smaller exit wound.
Pharmacokinetics
No new studies have been conducted in support of these applications. The actual metabolic profile in humans is currently unknown. The metabolism and elimination of STS has been studied to a limited extent.
STS injection is a synthetic, surface-active substance first described by Reiner in 1946. STS injection is composed of sodium 1 -isobutyl-4-ethyloctyl sulphate, benzyl alcohol 2% and phosphate buffered to a pH of 7.5. It is recommended that solutions be protected from light. It is a long-chain acid salt of an alkali metal with the properties of a soap. The solution is clear, non-viscous, has a low surface tension, and is readily miscible with blood, leading to a uniform distribution after injection. It primarily acts on the endothelium of the vein because, if diluted with blood, the molecules attach to the surface of red blood cells (RBCs), causing haemolysis. The recommended maximum dosage in a treatment session suggested by the manufacturer (STD Pharmaceutical Products Limited, Hereford) is 4 ml of a 3% solution. It is available as a 0.2%, 0.5%, 1% or 3% solution.
Biopharmaceutical investigations, including studies to investigate bioavailability and bioequivalence have not been performed on Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection. This is because it is an intravenous formulation containing Sodium Tetradecyl

Sulphate BP in the same concentration and aqueous solution as other existing approved intravenous formulations e.g., Fibro-Vein. This is in accordance with the EU Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1402/98, 2001) (*EMEA 2001*).
In humans, the majority (75%) of an injected dose of technetium pertechnetate radiolabelled 3% STS was lost from the injected varicosity within 2 to 13 seconds (T½ 7 seconds) followed by a slower phase of loss at 40 to 600 seconds (T½ 120 seconds). In deep calf veins the loss of radioactivity ranged from 5 to 12 seconds (T½ 7 seconds) (***Windle 1982***).
The route and time course of excretion of STS has been investigated in rats following injection of tritiated STS into the tail vein (Meehan 1996). Within 24 hours about 70% of the injected dose was excreted in the urine and a further 13% in the faeces. The level of radiolabel remaining in the tissues at the end of the 72 hour study period was found to be very low. The compound was not found to be persistent. HPLC analyses indicated that the urinary radiolabel co-chromatographed with 3H-STS. However, the hydrolysed STS product (tetradecanol) also co-chromatographs with STS.
No pharmacokinetic studies have been conducted in elderly patients, children or patients with renal or hepatic impairment. The Applicant stated that the normal dosing regimen may be used in the elderly and in patients with renal or hepatic impairment on the basis of the available pharmacokinetic data and well-established clinical use of injectable formulations of STS. Neither pharmacokinetic drug interactions studies nor drug compatibility investigation studies have been conducted and therefore the product should not be mixed with other medicinal products.
Pharmacodynamics Pharmacodynamics/Mechanism of Action
Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is indicated for the treatment of all sizes of varicose veins, from small thread veins to large truncal veins, by injection sclerotherapy. The recommended maximum dosage in a treatment session suggested by the manufacturer (STD Pharmaceutical Products Limited, Hereford) is 4 mL of a 3% solution. Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is available in a range of concentrations. Concentrations of 0.1% to 0.3% are commonly used for the treatment of telangiectatic veins 0.2 to 1.0 mm in diameter; 0.5% to 1% for treatment of uncomplicated varicose veins 2 to 4 mm in diameter; and 1.5% to 3% for the treatment of larger varicose veins, incompetent perforating veins, or an incompetent sapheno-femoral junction (SFJ). The treatment is based on the recommendations given in the proposed SmPC. Dosing of Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is typically based on multiple discrete administrations.
The mechanism of sclerosis for intravascular STS has been elucidated in human varicose veins (***Schneider 1964, Schneider 1965***) and in rabbit (***Dietrich 1968, Imhoff 1969***). The inter-cellular "cement" is disrupted, resulting in desquamation of endothelial cells in plaques. With STS, endothelial damage is concentration dependent and occurs immediately after injection, with resulting rapid thrombus formation leading to vascular sclerosis. Sclerosis with STS produced similar results in a concentration-dependent manner (***Martin 1990, Goldman 1987***). Endothelial damage occurred within 1 hour followed by the rapid onset of vascular thrombosis with subsequent organisation. Histological recanalisation occurred after 30 days with solution concentrations of 0.1% to 0.5%. The histological findings explained the clinical appearance that demonstrated initial thrombosis followed by partial reappearance of the vessel injected with STS 0.1%. Therefore, there may be a concentration gradient in which an ideal concentration depends on many factors, including vessel diameter, rate of blood flow, animal model, and anatomical region within each animal model.
Optimal clinical results occur when sclerotherapy-induced thrombosis is minimised. Factors predisposing to thrombus formation include decreased velocity of blood flow, hypercoagulability, and endothelial cell damage. The velocity of blood flow is unaffected by the sclerosing agent itself, but flow in general is usually slower in varicose veins and telangiectasia. This relative decrease in blood flow may predispose to thrombus formation in varicose veins and may be a significant, contributing factor to the increased incidence of thrombophlebitis and deep vein thrombosis (DVT) in patients with varicose veins. Hypercoagulability also predisposes one to thrombus formation. MacGowan (***MacGowan 1972***) combined STS with whole normal blood, resulting in a homogeneous red cell lysate without the formation of thrombin. *In vivo* studies have also demonstrated a lack of hypercoagulability from sclerosing solutions. Platelet aggregation occurs only at the site of the sclerosing solution injection, with aggregation-inhibiting effects occurring in the efferent deep veins distally to the femoral vein. Therefore the tendency to thrombosis is confined to the region of injection and is not spread throughout the venous system. It is the result of endothelial injury and not to thrombotic changes in the blood. This lack of hypercoagulability also correlates with clinical experience. The addition of heparin to STS has no effect on the sclerotherapy results in a paired comparison of 100 patients (***Kanter 1992***). The mechanism of action of STS depends principally on the production of endothelial damage rather than promoting thrombus formation associated with platelet aggregation (***Klein-Fein 1977***).
Excessive thrombosis is also detrimental to the production of endofibrosis because it may lead to recanalisation of the vessel and excessive intravascular and perivascular inflammation and its resulting sequelae. This can be prevented or at least minimised with the application of compression therapy immediately after sclerotherapy and continued for 1 to 3 weeks post-therapy using compression hosiery and/or bandaging. The object of compression is to compress the vein so that the resulting thrombus is kept to the minimum and the subsequent formation of scar tissue within the vein produces a fibrous cord and permanent obliteration. Histological examinations of sclerosed varices have shown that the strongest fixation of a thrombus occurs in areas where the entire endothelium is destroyed (***Schneider 1965***). Therefore, endothelial damage must be complete and should result in minimal thrombus formation with subsequent organization and fibrosis (***Green 1993***).
Clinical efficacy/Safety Overview of Clinical Efficacy
The efficacy of STS compression sclerotherapy has been compared with:
-surgical treatment of varicose veins,

-with other sclerosants and
-with compression therapy.
The use of STS at low concentrations in the management of small varices and telangiectases has also been demonstrated.
Comparison of sclerotherapy and surgery
Compression sclerotherapy with 3% STS (n=182 patients) was compared with surgery (n=149 patients) in a trial described as a random series Doran and White (***Doran 1975***). The results showed that in patients with incompetence at the sapheno-femoral junction and who underwent surgery, 49.6% of the limbs on which long saphenous stripping was done required injections at the end of the first year compared with 23.7% of those who received sclerotherapy as their primary treatment. When comparing all limbs treated, fewer limbs treated by sclerotherapy required additional treatment at the end of the first year, than those operated upon, irrespective of site. The investigators concluded that the initial response of varicose veins to STS sclerotherapy is better than surgery. They did not investigate the long term results due to the difficulty of maintaining the efficiency of follow-up.
Chant (***Chant 1972***) compared sclerotherapy (n=215 patients) with surgery (n=100 patients) in the treatment of varicose veins. The patients were seen at periods up to three years after treatment started. No significant difference between the treatments was found during the whole of the study period; no further treatment was required for 78 to 89% of the patients receiving sclerotherapy and 86 to 93% of those patients receiving surgery. Hobbs (***Hobbs 1968***) compared the efficacy of injection sclerotherapy using 3% STS (211 patients) with surgery (207 patients) as an effective treatment of varicose veins. The results after 12 months showed that for groups I (Long saphenous system only) and II (Short saphenous system only) injection sclerotherapy was comparable to surgery (approximately 50 to 60% cured using either technique). For those patients in groups III (Long saphenous system plus incompetent perforating veins) and IV (Lower leg perforating vessels only), injection sclerotherapy (56 to 59% cured) appeared to be significantly superior to surgery (12 and 13% cured). There were fewer complications in the sclerotherapy groups (n-14 of 211) vs surgical groups (40 of 207 patients). The investigators concluded that for the treatment of diffuse dilated superficial veins, injection sclerotherapy was most effective and results from surgery less so. **Hobbs** (**1974)** reviewed the results of surgical treatment and sclerotherapy of varicose veins over a 6 year follow up, including those patients reported in the above mentioned study. In total 404 legs had been treated by injection and 275 legs by surgery. The results showed that whilst injection sclerotherapy was superior to surgery up to 2 years post treatment, the failure rate increased over the next 4 years to achieve a level greater than that seen following surgery. The cure rate was not particularly high for either treatment at 6 years (7% sclerotherapy and 20% surgery).
Freedman 1980 Reported a controlled clinical trial involving patients with below-knee saphenous varicose veins, without clinical evidence of sapheno-femoral incompetence were treated either by surgery (n = 195) or by STS 3% sclerotherapy (n = 74). Examination of the legs 2 to 3 years after treatment showed that surgery was significantly ($p<0.01$) more successful than sclerotherapy. In all patients the success rate for surgery was 71% compared to 47% for sclerotherapy.
There have been several cochrane reviews on use of sclerosants for variacose veins. A Cochrane Collaboration review of the medical literature concluded that "the evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins following surgery and thread veins." A second Cochrane Collaboration review comparing surgery to sclerotherapy concluded that sclerotherapy has greater benefits than surgery in the short term but surgery has greater benefits in the longer term. Sclerotherapy was better than surgery in terms of treatment success, complication rate and cost at one year, but surgery was better after five years with the caveat that the quality of evidence was less than exceptional. A Health Technology Assessment found that sclerotherapy provided less benefit than surgery, but is likely to provide a small benefit in varicose veins without reflux from the sapheno-femoral or saphenopopliteal junctions. It did not study the relative benefits of surgery and sclerotherapy in varicose veins with junctional reflux.
Liquid STS sclerotherapy versus other sclerosants in the treatment of varicose veins
The efficacy of 3% STS in compression sclerotherapy of varicose veins was compared with 5% ethanolamine sulphate in 974 patients (***Reid 1968***). They grouped various types of varicose veins together according to their clinico-anatomical appearance. A good response to treatment was seen in 85% or more of the patients treated in most groups. There were no significant reactions immediately following the injection. Ulceration occurred in a number of patients receiving STS. Ulceration was not seen in those patients receiving ethanolamine oleate.
Cochrane review (*Tisi 2006*); In this Cochrane review four studies were included which compared STS with other sclerosants. **Schadeck 1995** showed that 4% polidocanol (Aetoxysclerol, Kreussler, Germany) resulted in more venous spasm following sclerotherapy than 3% STS (RR7.50, 95% CI 2.06 to 27.25), although the disappearance of superficial venous reflux following sclerotherapy was not statistically significant (RR 1.30, 95% CI 0.86 to 1.96). **Goldman 2002** was not able to show a difference in photographic appearance of varicose veins following sclerotherapy with polidocanol (Aethoxysklerol) compared to STS (varying concentrations according to vein diameter). In contrast, **Labas 2003**, showed that STS improved cosmetic appearance of varicose veins and achieved greater symptomatic improvement at six months (RR 0.85, 95% CI 0.78 to 0.92), although this effect was non-significant at five years follow-up. For thread veins, 10% hypertonic dextrose had similar efficacy in terms of sclerosis to 0.15% STS (**Prescott 1992** cited in the Cochrane review). Complication rates in terms of pain, matting and pigmentation were not significantly different. The haemodynamic benefit from sclerotherapy was demonstrated by **Kahle 2003**. Sclerotherapy with 3% polidocanol reduced venous by arterial flow (as assessed by Duplex ultrasound) to essentially normal levels in comparison to placebo (normal saline). This study did not assess any clinical parameters.
Liquid STS sclerotherapy versus compression therapy in the treatment of varicose veins

A single randomised, clinical trial compared sclerotherapy to graduated compression stockings in 101 pregnant women with varicose veins, 45 receiving 3% STS sclerotherapy and 56 being given elastic hosiery (***Abramowitz 1973***). Sclerotherapy was more effective in terms of symptomatic improvement and cosmetic appearance (RR 1.61, 95% CI 1.19 to 2.18). The results showed that sclerotherapy was far superior, 32 (71 %) achieving a good result, compared with 5 (9%) using elastic hosiery. No serious complications arose following the use of STS.

Liquid STS sclerotherapy in the treatment of small varices and telangiectases

Good results were reported in virtually all 144 patients with spider angiomata who were treated with 1% STS solution (***Tretbar 1978***). An unspecified number of episodes of epidermal necrosis without significant sequelae and a 30% incidence of post-sclerosis pigmentation were reported which resolved within a few months. The efficacy of 1% STS solution for microsclerosis of telangiectases has also been demonstrated in 105 patients (***Shields 1982***). Only 1 episode of necrosis was reported in more than 600 treatments in vessels less than 5 mm in diameter. There were no systemic reactions, and the majority of post-sclerosis skin pigmentation resolved in 3 to 4 months. Excellent results with minimal adverse sequelae were reported in a 2 year prospective trial which used minimally effective sclerosing concentrations of STS to treat varicose veins and telangiectases in 2665 patients (***Thibault 1999***). A 0.15 % incidence of significant or severe pigmentation was found that was identical to the rate reported with polidocanol sclerosing solution. Four patients (0.15%) developed anaphylactoid reactions with two patients (0.07 %) developing urticaria.

Foam sclerotherapy versus liquid sclerotherapy

Administration of STS as a foam has been used as a means of improving the efficacy of sclerotherapy. Foam sclerotherapy has also been investigated in the management of small varices, including reticular veins and telangiectases. ***Henriet*** reported his results in 10,000 patients with reticular varices and telangiectases of the lower limb treated between the years 1995-8 (***Henriet 1999***). A series of authors ***(Monfreux 1997, Sadoun 1998, Frullini 2000)*** have described methods of preparing foam which may be used for ultrasound guided sclerotherapy but the method of Tessari is one most often used (***Tessari 2001***).

A number of clinical series and a few randomised clinical trials have assessed the immediate efficacy of foam treatment by duplex ultrasonography (***Coleridge Smith 2009***). The majority of published studies used polidocanol. Ouvry compared the efficacy of 3% polidocanol foam or liquid (***Ouvry 2008***). The volume injected was limited to 2 to 2.5 mL. Early elimination of reflux was 35% in the liquid group and 85% in the foam group at 3 weeks. By 2 years only 12% of veins had remained obliterated in the liquid sclerosant group compared to 53% in the foam group. These authors also published a randomised controlled trail (RCT) comparing the efficacy of 1% and 3% polidocanol foam (***Hamel Desnos 2007***). Up to 3 injections of foam were permitted with a maximum volume of 7.5 mL (A mean volume of approximately 4.5 mL foam per session was given to each study group when treating the great saphenous vein (GSV)). The 3 week occlusion rates were 96% in the 3% group and 88% in the 1% group, falling to 69 and 68% respectively at 2 years follow-up. A similar study was reported by Ceulen (***Ceulen 2007***) in which the main outcome measure was the occlusion rate of the GSV on duplex ultrasonography 1 year following treatment with either 1% or 3% polidocanol foam. The 1% foam group showed a 70% occlusion rate and the 3% foam group an 80% occlusion rate at one year but the numbers of patients included in the study was too small for this to reach statistical significance. Another RCT comparing the outcome of 4 mL of 3% polidocanol liquid versus 5 mL 3% polidocanol foam injected into saphenous trunks (***Rabe 2008***). This achieved 69% obliteration of the saphenous vein at 3 months in the foam group compared to 27% in the liquid group.

Gonzalez-Zeh (***Gonzalez-Zeh 2008***) reported the outcome of a cohort study in which patients with truncal saphenous incompetence were treated either by endovenous laser ablation or foam sclerotherapy. An injection of 3% polidocanol foam was used (volume not stated) but was assessed as 1 mL of foam per 1 mm diameter of saphenous trunk. The mean saphenous trunk diameter treated was about 8 mm. At one year 77% of saphenous trunks remained obliterated after foam sclerotherapy and 93% following laser ablation. The author undertook an analysis to assess the influence of diameter of the saphenous vein on the likelihood of successful obliteration. He estimated that with ultrasound guided foam sclerotherapy (UGFS), 93% efficacy of treatment could be achieved in saphenous veins of less than 8 mm diameter compared to 33% in veins of more than 12 mm diameter veins. In those patients treated by endovenous laser ablation, failure of obliteration of the vein was seen only in saphenous veins greater than 12 mm diameter. Similar falls in venous clinical severity score (VCSS) were found one year after foam and endovenous laser ablation of saphenous trunks.

Coleridge Smith (***Coleridge Smith 2006***) reported the outcome at 11 months of follow-up showed 88% occlusion of the GSV with 10 mL of sclerosant foam (1% and 3%) and concomitant treatment of associated varices. Cabrera reported that in his group of 500 patients treated by UGFS, 81% of saphenous trunks remained obliterated after 3 years follow-up (***Cabrera 1993***). Approximately 10% of patients underwent additional sclerotherapy after their initial treatment to achieve this outcome. He used 15-30 mL of 1% polidocanol foam to achieve this outcome in the initial treatment session.

Myers studied the outcome of foam sclerotherapy by duplex ultrasonography 3 years following treatment (***Myers 2007***). The treatment method involved injecting a median of 5 mL of foam per session. After three years, ultrasonography showed that 83% of tributaries, 53% of GSVs and 36% of SSVs had remained obliterated. He analysed the factors which were associated with treatment failure. The risk of recurrence was greatest in saphenous veins with a diameter of more than 6 mm. Injection of more than 12 mL of foam was associated with double the success rate in patients where less than 6 mL had been injected.

Wright (***Wright 2006***) compared surgery with polidocanol foam sclerotherapy ('Varisolve ®' (Provensis/BTG PLC, London UK) in a randomised multi-centre study involving 654 patients. Two separate studies were conducted: a surgical part undertaken by surgeons who randomised patients to saphenous stripping or ultrasound guided foam sclerotherapy. In addition,

sclerotherapists randomised patients to ultrasound guided sclerotherapy conducted using either home-made foam or liquid sclerosant. Up to 4 sessions of UGFS were allowed over a 3 months to obliterate the saphenous trunks. The outcome was assessed by duplex ultrasonography. After 12 months the surgeons had eliminated truncal saphenous reflux in 130 of 176 patients (74%) by UGFS (mean foam volume: 25 mL, range 5 – 55 mL) and in 84/94 (88%) by surgery. In comparison, sclerotherapists had eliminated reflux in 239 of 254 patients (91%) by Varisolve foam (mean foam volume: 15 mL, range: 2 –60 mL) and 104/125 (83%) by home-made foam and liquid sclerotherapy. Large volumes of foam (up to 60 mL) were permitted in this study, but the surgeons who were naïve to UGFS at the start of the study obtained slightly less satisfactory results than the sclerotherapists.

A 10-year, prospective RCT involving over 800 patients conducted by vascular surgeons in Europe compared 6 treatment options: A: Sclerotherapy; B: High-dose sclerotherapy; C: Multiple ligations; D: Stab avulsion; E: Foam-sclerotherapy; F: Surgery (ligation) followed by sclerotherapy (***Belcaro 2003***). The paper concluded that when performed correctly, all treatments were similar with no statistical difference between them. Foam sclerotherapy (higher dose) appears to be more effective than standard-dose liquid sclerotherapy, and results were comparable to surgery. Interestingly, this study also looked at lung scintigraphy in select patients who received foam. The investigators found no perfusion defect even after injections of up to 10 mL of foam. Although foam sclerotherapy is effective for veins of all sizes, some researchers have noted slightly higher rates of minor adverse effects such as pigmentation, inflammation, and minimal necrosis when foam is used for small reticular veins and telangiectases (***Belcaro 2003***).

While these data do not form the most robust evidence for use of the foam, as they come from clinical series, the RCTs that have been included clearly show the **superiority of foam** over liquid sclerosants. However, it is clear that in the studies where a total of 5 mL or less foam was injected into a saphenous trunk, failure to occlude the saphenous trunk was common. In the clinical series of Coleridge Smith (***Coleridge Smith 2006***) and of Cabrera (***Cabrera 1993***) where much larger volumes of foam were used and saphenous varices were treated on the same occasion, far higher proportions of saphenous trunks were obliterated. Many phlebologists have based their practice on the **Tegernsee Consensus Conference recommendations in 2006** (***Breu 2008***). In the survey conducted by these authors 87% of respondents limited the total dose of foam to 10 mL or less in a single session. A recommendation of a maximum of 10 mL per session was made on the basis of the majority opinion. Safety of treatment was one of the main considerations in reaching this conclusion. The content of this publication is based on medical opinion and not on clinical trials and it must be treated as such.

Management of recurrent varicose veins:

Coleridge Smith used this in his clinical series in the management of residual saphenous trunks and tributaries, including those patients with neovascularisation (***Coleridge Smith 2006***). The overall data showed no difference in the ultrasound determined recurrence rate at 11 months between primary and recurrent varices, which formed 30% of this series. **Myers'** comes to the same conclusion following analysis of his data (***Myers 2007***). In contrast, the outcome of surgical management includes a substantial complication rate post-operatively and a 30% duplex ultrasound recurrence rate at 1 year following surgery for recurrence at the saphenofemoral junction (SFJ) (***Winterborn 2008***).

Quality of life after Foam therapy:

Little has been published on quality of life indicators and patient satisfaction after foam sclerotherapy. Barrett investigated the outcome of a range of varicose veins greater and less than 10 mm diameter (***Barrett 2004***). Assessment at one year was undertaken using clinical criteria (presence of visible varices, assessment of quality of life, patient assessment of symptoms) as well as ultrasound imaging. The majority of patients (94%) with <10 mm diameter saphenous trunks were free of varices and 96% with saphenous trunks ≥10 mm diameter. For veins in the <10 mm diameter group 88% of saphenous trunks were obliterated compared with 69% in the ≥10 mm diameter group. This series employed a mean of 8.4 mL of 3% STS foam in the <10 mm group and
13.4 mL in the ≥10 mm diameter group. Recognised quality of life questionnaires were not used in this study, but assessment of patient satisfaction showed that >94% of patients experienced improvement in symptoms.

Main results from a recent Cochrane review (2009):

Seventeen studies were included in review. One study comparing sclerotherapy to GCS in pregnancy found that sclerotherapy improved symptoms and cosmetic appearance. Three studies comparing sodium tetradecyl sulphate (STD) to alternative sclerosants found no significant differences in outcome or complication rates; another study found that sclerotherapy with STD led to improved cosmetic appearance compared with polidocanol, although there was no difference in symptoms. Sclerosant plus local anaesthetic reduced the pain from injection (one study) but had no other effects. Two studies compared foam- to conventional sclerotherapy; one found no difference in failure rate or recurrent varicose veins; a second showed short-term benefit from foam in terms of elimination of venous reflux. The recanalisation rate was no different between the two treatments. One study comparing Molefoam and Sorbo pad pressure dressings found no difference in erythema or successful sclerosis. The degree and duration of elastic compression had no significant effect on varicose vein recurrence rates, cosmetic appearance or symptomatic improvement.

The review authors concluded that **"e**vidence from RCTs suggests that the choice of sclerosant, dose, formulation (foam versus liquid), local pressure dressing, degree and length of compression have no significant effect on the efficacy of sclerotherapy for varicose veins. The evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins following surgery and thread veins.

Additional data was requested during the procedure;

The applicant provided additional evidence relating to the efficacy and safety of the use of the foam formulation during sclerotherapy.

Efficacy of foam over liquid STS

Two prospective randomised studies directly comparing liquid STS with foam treating a total of 541 legs. A prospective randomised study in France treated 300 great saphenous veins (GSV) with 3% liquid or foam and 100 small saphenous veins (SSV) with 1.5% liquid or foam (**Demagnay 2002**). In another randomised clinical trial (**Martimbeau 2003**) 141 veins were treated with 1% STS liquid or foam. In both these studies, the results with 1 and 3% foam were deemed to be marginally superior to the liquid form. The SmPC has been modified to include the use of foam for the 3% and 1% solutions only because the data described here only supports those strengths. The SmPC for 0.2% and 0.5% Fibrovein will only include use as a liquid. The SmPC has also been revised to include a clear description of how to make foam using the standard Tessari method.

Foam sclerotherapy using both sodium tetradecyl sulphate (STS) and polidocanol has been very widely used to treat varicose veins successfully for over ten years. A systematic review of foam sclerotherapy for varicose veins was published in 2007 (Jia et al)[1]. These are supported by the two big studies that treated nearly 3000 legs with varicosities with an overall occlusion rate of 60-89% .

Support for the Tessari method of Foam generation; The applicant argues that the Tessari method is used commonly (refer to earlier response relating to the systematic review of foam use and methods adopted; ***Jia X et al., 2007***). Moreover, based on the results of their own analysis of consistency of foam generation using the Tessari method, the applicant has recommended this in the SmPC. Such a recommendation would obviate / reduce use of other methods. The description of a particular method in the product literature and this being the commonest method used in clinical practise supports the applicant's arguments.

The safety information relating to the use of the Foam has been updated in the SPC and the main difference is small and only in terms of frequency when compared to the liquid form. The Risk Management Plan (RMP) has been updated.

Safety of foam STS

Issues relating to the safety of foam use were raised citing a few references about hypotheses relating to apparent neurologiocal and cardiac consequences. The issues relevant to the regulatory application should be limited to safety issues that have actually been identified and structurally related to use of the foam. While the hypotheses of increased endothelin secretion and Pulmonary arteriovenous (AV) shunts are interesting scientific aspects, the hard evidence linking neurological events with changes in computed tomography (CT) or magnetic resonance imaging (MRI) are negligible. Therefore, it is prudent to view the reports and available evidence carefully rather than rely on hypotheses.

Gillet JL, 2011 [Phlebology 2011; 26:277-279] states this very clearly and indeed the title is " Neurological complications of foam sclerotherrapy; Fears and reality". The review is timely and highlights the controversy in a balanced fashion; several sentences from the article are extracted below to emphasize the points;

That the clinical significance of microemboli are unclear and a diffusion weighted MRI performed on two occasions failed to show any cerebral lesions in 57 patients (Gibson et al).

With millions of foam sclerotherapy session have been undertaken only few cases of cerbrovascular accident (CVAs) have been reported and these related to paradoxical air

[1] Jia X et al. Systematic review of foam sclerotherapy for varicose veins. Br. J Surg. 2007; 94: 925-936.

embolism. Additionally only few cases of CVA are reported. It is important to note that CVA/transient ischaemic attack (TIA) have been reported with use of solution as well.

Last but not the least, it was implied that patent foramen ovale (PFO) screening and targeting those with PFO has not decreased the ADR frequency, and that other hypothesis need to be addressed by the applicant. This is also discussed by Gillet in the review in phlebology. With an estimated prevalence rate of PFO ~30% in the adult population with the rate for all types of right to left shunts ~70% the risk of strokes following foam sclerotherapy is very low.

While it is well known that some patients experience neurological symptoms including visual disturbances that provide the basis for the hypotheses and will be the focus of further research, the belief that this occurs at high frequency is questioned. In this context, the RMS stands by its observation that the strength of evidence relating these events to the foam is very small. *Indeed strokes have been reported after liquid sclerotherapy*. Moreover, injection of agitated echocontrast has been used during transesophageal echocardiography but again without increased frequency of neurological symptoms and in this case the injections are administered even closer to the superior vena cava (SVC) (without anatomical filters such as natural valves or distance) and therefore are seen in the right atrium and right ventricle. At the very least, these would be subject to the same considerations or as the sclerotherpy injections (such as pulmonary A-V shunts etc). However, the evidence for stroke here is also very limited in the absence of a PFO. So while the endothelin and pulmonary Av shunt hypotheses is of great scientific interest, the evidence to support them is weak. In this context, the RMS warns against overinterpretation of a few reports and drastic regulatory steps.

Pharmacovigilance system

The Applicant has provided a pharmacovigilance system is considered satisfactory.

Risk Management Plan

The Applicant has provided a plan for management of risk. While request for RMP might be considered valid, the applicant's approach based on the available data from observational studies is considered relevant in determining the stringency of the

RMP and proportionate. In this case the RMS considers that the applicant's response is appropriate as this product has been on the market for a number of years and the use of the foam is almost routine practice.

Periodic Safety Update Report (PSUR)

A Periodic Safety Update Report (PSUR) for STS for the period May 2001-Dec 2005 concluded that there was no change in the benefit-risk for the use of STS as a sclerosant of varicose veins. No new safety findings were reported and therefore no proposals were made to change the SmPC for Fibro-Vein.

The active substance is a well known active substance which has been marketed for many years throughout the EU. In line with the current legislation, the applicant has agreed to monitor the RMP and provide PSURs as relevant.

V. OVERALL CONCLUSIONS

There is evidence of extensive clinical experience with STS which has shown it to be an effective sclerosant in the treatment of varicose veins. The extensive worldwide safety data from published information and from post-marketing surveillance demonstrate that injectable formulations of STS have a predictable safety profile.

The pharmacology of the compound in human is limited and the risks associated with its use are well known. Although there is limited human pharmacokinetic data on STS, it is known that onset of action is immediately after injection and the very short half-life permits achieving the desired clinical response within minutes. The magnitude of effect can be titrated by adjusting the concentration and volume, so that small veins and spider veins can be treated effectively and safely. To facilitate titration of dose, Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is provided in a range of concentrations. STS becomes rapidly bound and inactivated by albumin in the blood plasma and its short duration of action results in rapid dissipation of effects. Therefore the rapid onset and short half-life of STS enhance the efficacy and safety of its use.

There is a great deal of clinical experience on the use of sclerosants administered as foam and potential advantage in using STS as foam. The evidence for the claim that administration of foam allows lower and likely safer doses of the active ingredient to be injected with improved results is not ideal but based on existing clinical practise as evidenced by the summary statement from the **Consensus Conference recommendations in 2006** (***Breu 2008***). The pattern and frequency of adverse reactions do not seem any different from those of conventional liquid sclerotherapy, but with less perioperative morbidity than surgery. Evidence from few randomised controlled trials (RCT) suggests that the choice of sclerosant, dose, formulation (foam versus liquid), local pressure dressing, degree and length of compression have no significant effect on the efficacy of sclerotherapy for varicose veins. In the Cochrane Collaboration reviews comparing sclerotherapy to other forms of therapy including surgery and liquid and foam sclerotherapy concluded that sclerotherapy has greater benefits than surgery generally in the short to medium term and that foam performs as well if not better than the liquid form. Fibrovein 3.0%, 1.0%, 0.5%, 0.2% Injection is identical to the Fibro-Vein which has been marketed since 1992 in several EU countries. The applicant has addressed the issues of efficacy and safety by providing available evidence that supports the clinical use of the foam although this would be considered only modest from the observational studies. Ideally this should have been from RCTs but in the context of established clinical use, an RCT may not be feasible due to many reasons.

PRODUCT INFORMATION: Summary of Product Characteristics (SmPCS)

The approved SmPCs are consistent with that for existing liquid formulations of sodium tetradecyl sulphate. The product literature is in-line with suggestions made that foam formulations are only recommended for use for larger veins and for the 3% and 1% concentrations.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

Based on the clinical evidence presented by the applicant and that the use of sodium tetradecyl sulphate is well established in clinical practice; it is considered that these applications are clinically satisfactory and that these applications can be granted. However; as part of the approval of these applications it was agreed, at Day 195 of the procedure that the applicant should commit to the following 5 follow-up measures within 30 days of the completion of the procedure:

1. The SmPC is not the appropriate document to provide all the recommendations regarding sclerotherapy. Additional measures to ensure the safety of this practice is therefore necessary. The Applicant should ensure that training sessions are proposed to physicians to ensure the correct preparation and administration of the foam. The training program should focus on gesture learning and should follow the main messages:

i. Need for appropriate and specialised training on sclerotherapy before use

ii. Management of patients – before and after sclerotherapy iii. Conditions for good practice-the place and material for sclerotherapy should be of good level of asepsia, the material needed should be described

iv. Instructions for foam preparation

v. Instructions for injection Videos for foam preparations should be proposed to the potential users of FibroVein. The applicant committed to submit proposals for these educational tools within 30 days following completion of this procedure.

1. A targeted follow-up questionnaire should be developed to further characterise the identified and potential risks associated with FibroVein. The applicant committed to submitting proposed targeted questionnaires for assessment within 30 days following procedure completion.
2. A recent review of the references highlights the risk of ischemic damage seen both in rats and humans which therefore constitutes a signal. Since the product is already used and the risk has already been identified, a large observational study should be conducted to better characterise adverse events (AEs), their incidence and its predictive factors. The applicant has committed to conducting such a study.
3. A drug utilisation study should also be conducted in order to describe the use of FibroVein in real-life conditions. One large cohort could answer both the safety and in-use objective. The safety profile of FibroVein could be potentially dependant of product access conditions and foam preparation methods, which will be different between countries. The study should be conducted in a sample of countries ensuring a representativeness of results. The Applicant has committed to provide a full detailed protocol with a proposal of case report form for assessment within a month following completion of this procedure and before the study starts.
4. A Direct Healthcare Professional Communications (DHPC) to inform physicians that this product must be used only by trained physicians and to warn them of ischemic risk. The letter should remind prescribers' of their obligation of reporting adverse events (AEs) and to encourage patient participation on the large observational study that is to be conducted at the Competent Authority's request. The Application has committed to submitting a DHPC proposal within a month of the procedure closing.

OVERALLCONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Fibrovein 0.2%, 0.5%, 1% & 3% Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

Medicinal products containing sodium tetradecyl sulphate have been available in the UK for many decades. Its use is well-established with recognised efficacy and acceptable safety.

No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE

The SmPCs and PILs are acceptable. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sodium tetradecyl sulphate is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk ratio is considered to be positive.

VI. REVISION DATE

SEPTEMBER 2026

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From CZ/H/0944/001-004 to IE/H/1502/001-004	NA	NA	September 2026