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FDA - CONSULTANT
MARTHA M. BENNETT

August 9, 2001

Dockets Management Branch
Food and Drug Administration
Dockets Management Staff, HFA-305
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Citizen Petition

The undersigned submits this Petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.93, to request the Commissioner of Food and Drugs to accept the submission of an abbreviated new drug application for a new drug which has a different strength from the listed drug.

A. Action Requested

The undersigned requests permission to file an abbreviated new drug application for sodium tetradecyl sulfate injection in strengths of 0.5% and 0.2%. The strengths of the listed drug are 1% and 3% (NDA # 005970, Elkins Sinn).

B. Statement of Grounds

The proposed drug product meets the criteria for submission of an abbreviated new drug application as described in section 505(j)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act.

The proposed drug product and the listed drug product contain the same active ingredient and have the same injectable dosage form. This Petition seeks permission to submit an ANDA for two additional strengths (0.5% and 0.2%).

Since the proposed drug product and the listed drug product have the same active ingredient and route of administration, the safety and effectiveness of the proposed drug product is not expected to be different from that of the listed drug product.

CP1

01P-0351

The labeling for the proposed drug product will be consistent with the most recently approved labeling for the listed drug product. (See attached proposed labeling and current labeling for the listed drug.)

C. Environmental Impact

The undersigned claims a categorical exclusion for submission of an environmental assessment in accordance with 21 CFR 25.31(a). This claim is based upon the fact that the proposed drug product has a chemical structure and composition with known pharmacological properties and indications for use that are identical to a drug product which is already on the market.

D. Economic Impact

A statement of the economic impact of the requested action will be supplied at the request of the Commissioner.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petitioner relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Sincerely,

Martha M. Bennett

Martha M. Bennett, R.A.C.

1. Proposed Labeling

PACKAGE INSERT

NAME OF PRODUCT
FIBRO-VEIN*.

PRESENTATION
FIBRO-VEIN is a sterile aqueous solution of sodium tetradecyl sulphate available in four strengths 3%, 1%, 0.5% and 0.2% and is buffered to pH 7.6. The solution also contains: benzyl alcohol, di-sodium hydrogen phosphate, potassium di-hydrogen phosphate and water.

USE
The solution is for intravenous use as a sclerosant in the treatment of varicose veins of the leg by compression sclerotherapy. The action of sodium tetradecyl sulphate in this technique is considered to be that of irritation to the intima of the vein wall, so that on compression of the vein, fibrosis takes place and the vein is permanently occluded by the development of fibrosis in the wall of the compressed vein.
The strength of FIBRO-VEIN selected depends on the size of the veins to be treated. FIBRO-VEIN 3% is for the treatment of large superficial varicose veins, FIBRO-VEIN 1% for the treatment of small varicose veins and the larger venules. Minor venules and spider veins (venous flares) should be treated with FIBRO-VEIN 0.5% or 0.2%.

DOSAGE AND ADMINISTRATION
ADULTS AND THE ELDERLY (NOT RECOMMENDED FOR USE IN CHILDREN)
FIBRO-VEIN 3%.
Dosage 0.5-1ml at each of four sites (maximum 4ml).
A dose of 0.5 to 1ml of FIBRO-VEIN 3% is injected intravenously into the lumen of an isolated segment of emptied superficial vein, followed by immediate continuous compression. A maximum of four sites (4ml total) may be injected during one treatment session.

FIBRO-VEIN 1%.
Dosage 0.25-1ml at each of 10 sites (maximum 10ml).
A dose of 0.25 to 1ml of FIBRO-VEIN 1% is injected intravenously into the lumen of an isolated segment of emptied superficial vein, followed by immediate continuous compression. A maximum of ten sites (10ml total) may be injected during one treatment session.

FIBRO-VEIN 0.5%.
Dosage 0.25-1ml at each of 10 sites (maximum 10ml).
A dose of 0.25 to 1ml of FIBRO-VEIN 0.5% is injected intravenously into the lumen of an isolated segment of emptied superficial vein, followed by immediate continuous compression. A maximum of ten sites (10ml total) may be injected during one treatment session.

FIBRO-VEIN 0.2%.
Dosage 0.1-1ml at each of 10 sites (maximum 10ml).
A dose of 0.1 to 1ml of FIBRO-VEIN 0.2% is injected intravenously into the lumen of an isolated segment of emptied superficial vein, followed by immediate continuous compression. A maximum of ten sites (10ml total) may be injected during one treatment session.

COMPRESSION THERAPY TECHNIQUE AND AFTERCARE
The treatment of varicose veins by compression sclerotherapy is directed towards the restoration of the efficiency of the synchronised pumping systems within the leg by permanently destroying the leaking points rather than in the eradication of the superficial tortuous veins which may, in many cases, be capable of reverting to normal pattern of pressure within the veins of the limb. Localisation of the incompetent perforating veins is the supremely important object of diagnosis.
Treatment comprises the permanent blocking of the offending leak by producing a short fibrotic segment of vein involving the area of the junction of the perforating and superficial veins. This can be achieved by carrying out the following procedure:

1. *The first injection should be given at the most distal chosen site.* The following needle sizes are recommended:-
   FIBRO-VEIN 3% 25 gauge needle; FIBRO-VEIN 1% 27 gauge needle; FIBRO-VEIN 0.5% 30 gauge needle;
   FIBRO-VEIN 0.2% 30 gauge needle. Compression should be applied immediately and before the adjacent site is injected.
2. The sclerosant should be introduced into the vein after it has been emptied.
3. The sclerosant should be maintained within the empty and isolated segment of the vein for approximately 30 seconds.
4. Compression should be applied immediately. It should be uninterrupted and it must be adequate and maintained for 6 weeks after the last chosen site is injected. One should feel quite confident that when the patient stands erect, the internal pressure of the blood in the adjacent unobliterated vein cannot reopen the segment; otherwise compression should be re-applied. The segment of the veins should have become a palpable, firm, fibrous cord and there should be no sign of tenderness.
5. Application of compression is most suitably obtained by firm bandaging with a number of strong cotton crepe bandages and by incorporating therein shaped rubber pads over the sites of injection.

A class 1 elastic stocking applied over the bandage aids compression and the retention of the bandage in position.
For FIBRO-VEIN 1% the compression regime may be replaced by the use of class 2 or 3 graduated compression elastic stocking at an earlier stage. It must, however, be remembered that the process of fibrosis is not shortened for smaller veins and adequate compression must be maintained for 6 weeks. Walking should commence as soon as possible after the completion of treatment and last for at least one hour. Subsequent daily walking of one hour's duration is essential.
Patients must be advised to avoid even short periods of standing still.
The injection of FIBRO-VEIN 0.5% and FIBRO-VEIN 0.2% should be made slowly so that the blood content of these veins is expelled. In the treatment of spider veins and fine spider veins an air block technique may be used, for this a shaken foam, or a small amount of air (0.05ml) is first injected into the venous flare followed by the sclerosant which is then seen to flow around the veins with immediate blanching. Even with FIBRO-VEIN 0.5% and FIBRO-VEIN 0.2%, extra vascular injection should be avoided. Injected sites should be compressed with a bandage within half a minute of injection and this pressure continued whilst other sites are injected at the same session. The bandage may be replaced by a class 2 graduated elastic stocking at the end of the session and this compression maintained throughout the ensuing 2 to 3 weeks. Periods of inactive standing should be avoided.
The use of a small dose, the isolation of the injection within the vein segment and the application of immediate adequate and lasting compression are of supreme importance in obtaining a good result.

CONTRA-INDICATION, WARNINGS, ETC.
The use of FIBRO-VEIN is not recommended for the treatment of varicose veins by compression sclerotherapy when any of the following factors are present:

1. Allergy to sodium tetradecyl sulphate or any component of the preparation.
2. Patients unable to walk due to any cause.
3. Patients currently taking oral contraceptives.
4. Significant obesity.
5. Acute superficial thrombophlebitis.
6. Local or systemic infection.
7. Varicosities caused by pelvic or abdominal tumours.
8. Uncontrolled systemic disease eg diabetes mellitus.
9. Significant valvular incompetence requiring surgical treatment.

SIDE EFFECTS

1. Local: Pain or burning. Skin pigmentation. Tissue necrosis and ulceration may occur with extravasation. Paraesthesia and anaesthesia m occur if an injection effects a cutaneous nerve.
2. Vascular: Superficial thrombophlebitis. Deep vein thrombosis and pulmonary embolism are very rare. Inadvertent intra-arterial injection is very rare but may lead to gangrene. Most cases have involved the posterior tibial artery above the medial malleolus.
3. Systemic reactions: Allergic reactions are rare, presenting as local or generalised rash, urticaria, nausea or vomiting, asthma, vascular collapse. Anaphylactic shock, which may potentially be fatal, is extremely rare.

PRECAUTIONS

1. FIBRO-VEIN should only be administered by practitioners familiar with an acceptable injection technique. Thorough pre-injection assessment for valvular competence and deep vein patency must be carried out.
   Extreme care in needle placement and slow injection of the minimal effective volume at each injection site are essential for safe and effici use.
2. A history of allergy should be taken from all patients prior to treatment. Where special caution is indicated a test dose of 0.25 to 0.5ml FIBRO-VEIN should be given up to 24 hours before any further therapy.
3. Treatment of anaphylaxis may require, depending on the severity of attack, some or all of the following: Injection of adrenaline, injection of hydrocortisone, injection of antihistamine, endotracheal intubation with use of a laryngoscope and suction.
   The treatment of varicose veins by FIBRO-VEIN should not be undertaken in clinics where these items are not readily available.
4. Extreme caution in use is required in patients with arterial disease such as severe peripheral atherosclerosis or thromboangiitis obliterans (Buerger's disease).
5. Special care is required when injecting above and posterior to the medial malleolus where the posterior tibial artery may be at risk.
6. 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.
7. Do not use with heparin in the same syringe.
8. Safety for use in pregnancy has not been established. Use only when clearly needed for symptomatic relief and when the potential benefits outweigh the potential hazards to the foetus.
9. It is not known whether sodium tetradecyl sulphate is excreted in human milk. Caution should be exercised when used in nursing mothers.

PHARMACEUTICAL PRECAUTION
Store below 25°C, away from direct sunlight.
The in use period of each 5ml multidose vial is a single session of therapy and for use in the treatment of a single patient. Unused vial content should be discarded immediately afterwards.

LEGAL CATEGORY
Prescription only.

PACKAGE QUANTITIES.
FIBRO-VEIN 3% 10 x 5ml Multidose Vials
FIBRO-VEIN 3% 5 x 2ml Single Dose Ampoules
FIBRO-VEIN 1% 5 x 2ml Single Dose Ampoules
FIBRO-VEIN 0.5% 5 x 2ml Single Dose Ampoules
FIBRO-VEIN 0.2% 10 x 5ml Multidose Vials

PRODUCT LICENCE NUMBERS

FIBRO-VEIN 3%	PL 0398/5000
FIBRO-VEIN 1%	PL 0398/0003
FIBRO-VEIN 0.5%	PL 0398/0002
FIBRO-VEIN 0.2%	PL 0398/0004

SOLD AND SUPPLIED BY: S.T.D PHARMACEUTICAL PRODUCTS LTD., FIELDS YARD, PLOUGH LANE, HEREFORD HR4 OEL. ENGLAN

MANUFACTURED BY: CP PHARMACEUTICALS LTD, WREXHAM INDUSTRIAL ESTATE, WREXHAM, CLWYD LL13 9UE

*Trade Mark

Date of leaflet: 19 June 1995

Fibro-Vein

Patient Information Leaflet

FIBRO-VEIN 3%, 1%, 0.5% AND 0.2%

containing sodium tetradecyl sulphate

Please read this leaflet carefully. It contains important information about your treatment. If you have any doubts or questions, or if you are not sure about anything, ask your doctor or pharmacist.

It is important that you follow the instructions before and after administration of FIBRO-VEIN. Look at the label on the pack and this leaflet for details.

What is in the pack?

The name of your medicine is FIBRO-VEIN. It comes in the form of a glass ampoules or glass vials containing a clear sterile solution. FIBRO-VEIN contains the active ingredient, sodium tetradecyl sulphate at either 3%, 1%, 0.5% or 0.2% strength. The solution also contains the inactive ingredients: benzyl alcohol, di-sodium hydrogen phosphate, potassium di-hydrogen phosphate and water.

FIBRO-VEIN 3%, 1% and 0.5% is packed as 5 x 2ml glass ampoules, with a different colour label for each strength. In addition FIBRO-VEIN 3% also comes in 10 x 5ml rubber packed glass vials. FIBRO-VEIN 0.2% is only packed as 10 x 5ml rubber capped glass vials.

What is FIBRO-VEIN?

FIBRO-VEIN contains sodium tetradecyl sulphate which is one of the group of medicines known as sclerosants.

Who supplies FIBRO-VEIN?

The product licence holder is STD Pharmaceutical Products Limited, Hereford, HR4 0EL, UK and the manufacturer is CP Pharmaceuticals, at Wrexham LL13 9UF, UK.

What is FIBRO-VEIN used for?

FIBRO-VEIN is used in a procedure called compression sclerotherapy in the treatment of varicose veins.

Before receiving FIBRO-VEIN

Before you start treatment:

- Are you pregnant, trying to become pregnant or breast feeding?
- Have you previously experienced a reaction to FIBRO-VEIN or a product containing sodium tetradecyl sulphate?
- Do you suffer from asthma or any other allergic disease?
- Are you currently taking oral contraceptive tablets?
- Are you taking medicines for thrombosis?

If the answer is YES to any of these questions, tell your doctor before you are treated with FIBRO-VEIN.

You should inform medical staff that you expect to be treated with FIBRO-VEIN; for example if you go into hospital or see a dentist or doctor for another matter.

100307/3

How to take FIBRO-VEIN

Because FIBRO-VEIN is administered by injection into the vein it is always administered by a medically competent person. The normal dose administered is up to 1ml. For the 3% strength, a maximum of 4 sites (total 4ml) should be treated and for 1%, 0.5% and 0.2% strengths a maximum of 10 sites (total 10ml) should be treated. It is not supplied for self administration.

After taking FIBRO-VEIN

To obtain a satisfactory result from your treatment you should follow the following instructions:

- You should walk for 30-60 minutes immediately after treatment, as much as you can, but at least for three miles a day.
- The stocking and bandages must not be removed for at least six weeks after your last injection and then only when specified by your doctor.
- You should not stand still unless strictly necessary, and only then for very short periods of time, when you should change weight from one foot to the other by alternating the raising of each heel.
- When you bath or shower you should keep the bandages and stockings dry.
- If you are a sportsperson you may continue with your sport providing the bandages and stockings do not get wet.
- When your treatment is completely finished, elastic stockings should still be worn if your legs feel tired or if your occupation requires long periods of standing.
- It is important to continue to exercise your legs daily.

Tell medical staff that you have taken FIBRO-VEIN; for example, if you go into hospital or see a dentist or doctor.

Side Effects

FIBRO-VEIN can sometimes cause side-effects in some people. The most often reported side-effects are:

- Allergy (eg rash) and anaphylaxis (hypersensitivity)
- Urticaria (severe itching)
- Pain at the injection site

If you get any of these, or any other unusual effects, it is very important that you tell your doctor before receiving any further treatment.

How to store FIBRO-VEIN

- FIBRO-VEIN is stored at the treatment centre below 25°C away from direct sunlight, you will not be asked to take it home. As with all medicines it should be kept out of the reach of children.
- FIBRO-VEIN should not be used after the expiry date.

REMEMBER: This medicine is for you. Only your doctor can prescribe it for you.

FIBRO-VEIN is a trade mark.

Date of leaflet: 21 August 1995

100307/3

2. Labeling for listed drug

151408

J-1514H

ELKINS-SINN

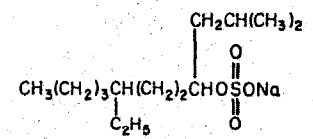
SOTRADECOL®

(Sodium Tetradecyl Sulfate Injection)

For Intravenous Use Only

DESCRIPTION

Sodium tetradecyl sulfate is an anionic surfactant which occurs as a white, waxy solid. The structural formula is as follows:



$C_{14}H_{29}NaSO_4$ 7-Ethyl-2-methyl-4-hendecanol sulfate sodium salt MW 316.44

Sotradecol® (Sodium Tetradecyl Sulfate Injection) is a sterile nonpyrogenic solution for intravenous use as a sclerosing agent. Each mL contains sodium tetradecyl sulfate 10 mg or 30 mg, benzyl alcohol 0.02 mL and dibasic sodium phosphate, anhydrous 0.72 mg in Water for Injection, pH 7.9; monobasic sodium phosphate and/or sodium hydroxide added, if needed, for pH adjustment.

CLINICAL PHARMACOLOGY

Sotradecol® (Sodium Tetradecyl Sulfate Injection) is a mild 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.

INDICATIONS AND USAGE

Indicated in the treatment of small uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves. The benefit-to-risk ratio should be considered in selected patients who are great surgical risks.

CONTRAINDICATIONS

Contraindicated in previous hypersensitivity reactions to the drug; in acute superficial thrombophlebitis; significant valvular or deep vein incompetence; huge superficial veins with wide open communications to deeper veins; phlebitis migrans; acute cellulitis; allergic conditions; acute infections; varicosities caused by abdominal and pelvic tumors unless the tumor has been removed; bedridden patients; such uncontrolled systemic diseases as diabetes, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases.

WARNINGS

Since severe adverse local effects, including tissue necrosis, may occur following extravasation, Sotradecol® (Sodium Tetradecyl Sulfate Injection), should be administered only by a physician familiar with proper injection technique. Extreme care in needle placement and using the minimal effective volume at each injection site are, therefore, important.

Allergic reactions, including anaphylaxis, have been reported that led to death. Therefore, as a precaution against anaphylactic shock, it is recommended that 0.5 mL of Sotradecol® be injected into a varicosity, followed by observation of the patient for several hours before administration of a second or larger dose. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat it appropriately. In extreme emergencies, 0.25 mL of 1:1000 Epinephrine Injection (0.25 mg) intravenously should be used and side reactions controlled with antihistamines.

PRECAUTIONS

GENERAL

The drug should only be administered by physicians who are familiar with an acceptable injection technique. Because of the danger of thrombosis extension into the deep venous system, thorough preinjection 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. In particular, deep venous patency must be determined by angiography and/or the Perthes test before sclerotherapy is undertaken. Venous sclerotherapy should not be undertaken if tests, such as the Trendelenberg and Perthes, and angiography show significant valvular or deep venous incompetence. The physician should bear in mind that injection necrosis is likely to result from extravascular injection of sclerosing agents.

Extreme caution must be exercised in the presence of underlying arterial disease such as marked peripheral arteriosclerosis or thromboangiitis obliterans (Buerger's Disease).

Embolism may occur as long as four weeks after injection of sodium tetradecyl sulfate. The incidence of recurrence is low if the patient wears elastic stockings.

No well controlled studies have been performed on patients taking antiovulatory drugs. Therefore, use judgment and evaluate any patient taking antiovulatory drugs prior to initiating treatment with Sotradecol®. (See ADVERSE REACTIONS.)

Heparin should not be included in the same syringe as Sotradecol®, since the two are incompatible.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

When tested in the L5178YTK +/− mouse lymphoma assay, sodium tetradecyl sulfate did not induce a dose-related increase in the frequency of thymidine kinase-deficient mutants and, therefore, was judged to be non-mutagenic in this system. However, no long-term animal carcinogenicity studies with sodium tetradecyl sulfate have been performed.

PREGNANCY

Teratogenic Effects–Pregnancy Category C. Animal reproduction studies have not been conducted with Sotradecol®. It is also not known whether Sotradecol® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sotradecol® should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sotradecol® is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Local reactions consisting of pain, urticaria or ulceration may occur at the site of injection. A permanent discoloration, usually small and hardly noticeable but which may be objectionable from a cosmetic viewpoint, may remain along the path of the sclerosed vein segment. Sloughing and necrosis of tissue may occur following extravasation of the drug.

Allergic reactions such as hives, asthma, hayfever and anaphylactic shock have been reported. Mild systemic reactions that have been reported include headache, nausea and vomiting. (See WARNINGS.)

Four deaths have been reported with the use of Sotradecol®. One death has been reported in a patient who received Sotradecol® and who had been receiving an antiovulatory agent. Another death (fatal pulmonary embolism) has been reported in a 36-year-old female treated with sodium tetradecyl *acetate* and who was not taking oral contraceptives. Two cases of anaphylactic shock leading to death have been reported in patients who received Sotradecol®. One of the patients reported a medical history of asthma, a contraindication to the administration of Sotradecol®.

DOSAGE AND ADMINISTRATION

For intravenous use only. Do not use if precipitated or discolored. The strength of solution required depends on the size and degree of varicosity. In general, the 1% solution will be found most useful with the 3% solution preferred for larger varicosities. The dosage should be kept small, using 0.5 to 2 mL (preferably 1 mL maximum) for each injection, and the maximum single treatment should not exceed 10 mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Sotradecol® (Sodium Tetradecyl Sulfate Injection)

1%—2 mL DOSETTE® ampuls packaged in 5s (*NDC* 0641-1514-34)

3%—2 mL DOSETTE® ampuls packaged in 5s (*NDC* 0641-1516-34)

STORAGE

Store at controlled room temperature 15°-30°C (59°-86°F).

ANIMAL TOXICOLOGY

The intravenous LD_{50} of sodium tetradecyl sulfate in mice was reported to be 90 ± 5 mg/kg.

In the rat, the acute intravenous LD_{50} of sodium tetradecyl sulfate was estimated to be between 72 mg/kg and 108 mg/kg.

Purified sodium tetradecyl sulfate was found to have an LD_{50} of 2 g/kg when administered orally by stomach tube as a 25% aqueous solution to rats. In rats given 0.15 g/kg in drinking water for 30 days, no appreciable toxicity was seen, although some growth inhibition was discernible.

J-1514H — Revised November 1996
Manufactured by **ELKINS-SINN**, Cherry Hill, NJ 08003-4099
A division of A. H. Robins Company

Sotradecol