Public Assessment Report

UKPAR

Aethoxysklerol 2.5 mg/ml solution for injection
Aethoxysklerol 5 mg/ml solution for injection
Aethoxysklerol 10 mg/ml solution for injection
Aethoxysklerol 20 mg/ml solution for injection
Aethoxysklerol 30 mg/ml solution for injection

(Lauromacrogol 400)

UK Licence No: PL 20685/0042, 0039-0040, 0043 and 0041

Ferndale Pharmaceuticals Ltd
LAY SUMMARY

Aethoxysklerol 2.5 mg/ml solution for injection
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(Lauromacrogol 400)

This is a summary of the Public Assessment Report (PAR) for Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml solution for injection (PL 20685/0042, 0039-0040, 0043 and 0041). For ease of reading, the products may be collectively referred to as 'Aethoxysklerol'. The lay summary explains how the applications for Aethoxysklerol were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Aethoxysklerol.

For practical information about using Aethoxysklerol, patients should read the package leaflets or contact their doctor or pharmacist.

What is Aethoxysklerol and what is it used for?
Aethoxysklerol is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Aethoxysklerol is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Aethoxysklerol is used to treat varicose veins of the lower extremities and may be injected either as a liquid or as a microfoam. Aethoxysklerol is only for use in adults (including the elderly).

How does Aethoxysklerol work?
Aethoxysklerol is a sclerosing agent for local injection whose active substance is lauromacrogol 400. It is available in five strengths. Aethoxysklerol works by causing the lining of the blood vessel to break up and also stops the flow of blood through that vein. The affected leg is then squeezed by application of compression which helps to complete closure of the varicose vein.

How is Aethoxysklerol used?
Aethoxysklerol is available in the pharmaceutical form solution for injection. Aethoxysklerol should always be given by injection into the varicose vein by a doctor, who will select the appropriate dose and method of administration.

Dosage
Aethoxysklerol may be used either as liquid or as microfoam. The patient's doctor has access to more detailed information in the Summary of Product Characteristics for healthcare professionals. Depending on the size of the varicose vein to be treated, the patient's doctor will decide which treatment must be applied. In case of doubt the lower dose should be chosen.

Generally, the dose of 2 mg/kg/day of lauromacrogol 400 should not be exceeded. For a patient weighing 70 kg, this is corresponding to a dose of up to:

<table>
<thead>
<tr>
<th>Aethoxysklerol</th>
<th>2.5 mg/ml</th>
<th>5 mg/ml</th>
<th>10 mg/ml</th>
<th>20 mg/ml</th>
<th>30 mg/ml</th>
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<td>140 mg lauromacrogol 400</td>
<td>56ml</td>
<td>28 ml</td>
<td>14 ml</td>
<td>7 ml</td>
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When administered as a microfoam, it is recommended not to exceed the total dose of 10 ml microfoam (the sum of the liquid and air components) per session and day – irrespective of body weight and strength of Aethoxysklerol.

Aethoxysklerol is not for use in children and adolescents.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Aethoxysklerol can only be obtained on prescription.

What benefits of Aethoxysklerol have been shown in studies?
As lauromacrogol 400 is a well-known substance, and its use in the proposed indication is well-established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of lauromacrogol 400 in the proposed indication.

What are the possible side effects of Aethoxysklerol?
Like all medicines, Aethoxysklerol can cause side effects, although not everybody gets them.

Serious side effects are very rare. If the patient experiences a serious side effect, he/she should immediately stop treatment and contact your doctor. The most serious side effects that have been reported are:

- anaphylactic shock (a sudden life-threatening allergic reaction, symptoms are sudden breathing difficulties, dizziness, blood pressure drop),
- blockage of lung artery (pulmonary embolism),
- stroke or transient ischaemic attack (TIA) (cerebrovascular accident).
- stress heart attack (cardiomyopathy - Tako Tsubo), heart attack(cardiac arrest)

The most commonly reported side effects are temporary in most cases and include short-term injection site pain, injection site intravaricose blood clots and temporary skin discolouration after treatment.

The following common adverse reactions were observed, with the frequency stated estimated from published data and world-wide reports:

Common (may affect up to 1 in 10 people)

- occurrence of blood vessels in the area of sclerosation which were not visible prior to treatment (neovascularisation), bruise (haematoma)
- discolouration of the skin (hyperpigmentation), cutaneous haemorrhage (ecchymosis)
- pain at the injection site (short-term), thrombosis at the injection site (local intravascular blood clots).

For the full list of all side effects reported with Aethoxysklerol, see section 4 of the package leaflets.

For the full list of restrictions, see the package leaflets for Aethoxysklerol.

Why is Aethoxysklerol approved?
The use of Aethoxysklerol in the proposed indications is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Aethoxysklerol outweigh the risks and the grant of Marketing Authorisations were recommended.

What measures are being taken to ensure the safe and effective use of Aethoxysklerol?
A Risk Management Plan has been developed to ensure that Aethoxysklerol is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets (PLs) for Aethoxysklerol, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about Aethoxysklerol
Marketing Authorisations for Aethoxysklerol were granted in the UK to Ferndale Pharmaceuticals Ltd on 24 December 2018.

The full PAR for Aethoxysklerol follows this summary.

For more information about treatment with Aethoxysklerol, read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in February 2019.
SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Ferndale Pharmaceuticals Ltd Marketing Authorisations for the medicinal products Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml solution for injection (PL 20685/0042, 0039-0040, 0043 and 0041) on 24 December 2018. The products are Prescription Only Medicines (POM) and are indicated for sclerotherapy of varicose veins of the lower extremities. For ease of reading, the products may be collectively referred to as ‘Aethoxysklerol’ or ‘Aethoxysklerol solution for injection’ in this scientific discussion.

The applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance (lauromacrogol 400 (also known as polidocanol (former INN)) of well-established use (in clinical use for more than 10 years).

Aethoxysklerol was first registered in Germany in May 1966 by Kreussler & Co. GmbH. Aethoxysklerol has since been licenced and marketed across Europe; in Austria since 1968, in Belgium since 1978, in the Czech Republic since 1971, in Denmark since 1977, in Finland since 1976, in France since 1996, in Hungary since 1986, in Italy since 1971, in the Netherlands since 1970, in Poland since 2002, in Portugal since 2016, in Slovakia since 1971, in Spain since 1983, in Sweden since 1975 and in Switzerland since 1967. Furthermore, it is registered and marketed in USA (2010), Australia (2001), Japan (2006) and other non-EU countries. At the time of assessment, lauromacrogol 400 was not licensed in the UK.

Lauromacrogol 400, also known as polidocanol (former INN), is a sclerosing agent that has been used for many decades for sclerotherapy of varices. Lauromacrogol 400 is a detergent and forms micelles in aqueous solution which interact with the lipid double layer of cell membranes. After intravascular administration, this induces damage of the vessel endothelium and a locally restricted thrombus formation. This in turn leads to replacement of the treated vein by fibrous tissue (“sclerosis”) and to obliteration of the vessel.

No new non clinical or clinical studies were conducted to support these applications, which is acceptable given that these are bibliographic applications for products containing an active ingredient of well-established use.

The current clinical dossier includes data from clinical studies with Aethoxysklerol as well as published literature on medicinal products (mainly Aethoxysklerol) containing lauromacrogol 400 as active substance. The literature focusses on sclerotherapy of leg varices. No formal paediatric development programme has been submitted. This is accepted for this generic product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Aethoxysklerol outweigh the risks and Marketing Authorisations were granted.

II. QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The products are clear, colourless to very faintly greenish yellow sterile solutions for injection, packaged in ampoules each containing 2 ml of solution for injection.
Each ml of Aethoxysklerol 2.5 mg/ml contains 2.5 mg lauromacrogol 400; each 2 ml ampoule contains 5 mg lauromacrogol 400.
Each ml of Aethoxysklerol 5 mg/ml solution for injection contains 5 mg lauromacrogol 400; each 2 ml ampoule contains 10 mg lauromacrogol 400.

Each ml of Aethoxysklerol 10 mg/ml solution for injection contains 10 mg lauromacrogol 400; each 2 ml ampoule contains 20 mg lauromacrogol 400.

Each ml of Aethoxysklerol 20 mg/ml solution for injection contains 20 mg lauromacrogol 400; each 2 ml ampoule contains 40 mg lauromacrogol 400.

Each ml of Aethoxysklerol 30 mg/ml solution for injection contains 30 mg lauromacrogol 400; each 2 ml ampoule contains 60 mg lauromacrogol 400

The products also contain pharmaceutical excipients, namely ethanol 96%, potassium dihydrogen phosphate, disodium phosphate dihydrate and water for injections

Aethoxysklerol 2.5 mg /ml solution for injection is packaged in 2 ml ampoules (Type I glass), each marked with 2 red stripes.

Aethoxysklerol 5 mg /ml solution for injection is packaged in 2 ml ampoules (Type I glass), each marked with two white stripes and one red stripe.

Aethoxysklerol 10 mg/ml solution for injection is packaged in 2 ml ampoules (Type I glass), each marked with one yellow stripe and one red stripe.

Aethoxysklerol 20 mg /ml solution for injection is packaged in 2 ml ampoules (Type I glass), each marked with one green stripe and one red stripe.

Aethoxysklerol 30 mg /ml solution for injection is packaged in 2 ml ampoules (Type I glass), each marked with one blue stripe, one red stripe and one white stripe.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCE

Lauromacrogol 400

INN: Lauromacrogol 400
Chemical name: Polyethylene glycol monododecyl ether
Molecular formula: \( \text{CH}_3\text{(CH}_2\text{)}_{11}\text{(OCH}_2\text{CH}_2\text{)}_n\text{OH} \) where \( n \) = an average of nine
Structure: \( \text{CH}_3\text{-(CH}_2\text{)}_{10}\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-(CH}_2\text{-CH}_2\text{O)}_{n-2}\text{-CH}_2\text{-CH}_2\text{-OH} \)
Mean M.: Approximately 600
Mean degree of polymerisation: Approximately 9
Appearance: White or almost white, unctuous and hygroscopic mass, melting at 24 °C into a colourless or yellowish, viscous liquid
Solubility: Freely soluble in water, very soluble in acetone and in ethanol (96 per cent).

Lauromacrogol 400 is the subject of a European Pharmacopoeia monograph.

Synthesis of the active 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.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

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.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

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.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious sterile solutions for injection which contained 2.5 mg/ml (5 mg/2ml), 5.0 mg/ml (10 mg/2 ml), 10 mg/ml (20 mg/2ml), 20 mg/ml (40 mg/2ml) or 30 mg/ml (60 mg/2ml) of the active substance lauromacrogl 400 in 2 ml ampoules. Suitable pharmaceutical development data have been provided for these applications.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of each strength of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specifications have been provided.

Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions has been approved. The ampoule is intended for single use. After first opening, the medicinal product should be used immediately. Any residual amount must be discarded.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary for applications of this type.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for these applications, from a quality point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
The non-clinical pharmacodynamic, pharmacokinetic and toxicological properties of lauromacrogl 400 (also referred to as polidocanol) are well-known, hence, the applicant has not provided additional
studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

A brief summary of the non-clinical aspects of pharmacokinetics of lauromacrogol 400 presented is provided in the sections below; further detail is provided in the non-clinical overview.

III.2 Pharmacology
Primary pharmacology
Lauromacrogol 400 is a detergent based sclerosant that disrupts the phospholipid bilayer through micelle formation resulting in endothelial damage, and induces a locally restricted thrombus with subsequent fibrosis. The efficacy of the sclerosing therapy is dependent on the type and size of the varices and the dose; thus, five strengths of aethoxysklerol are proposed: 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml.

In vitro tests have shown that polidocanol, at 1.6 to 3.9 mg/mL, induced irreversible platelet aggregation when applied to human plasma samples. Conversely, 0.3 mg/mL resulted in inhibition of platelet aggregation. The concentrations expected in vivo within the efferent deep veins of the lower extremity were estimated by tracking the dilution of indocyanine into the femoral veins of patients. The authors suggested that sclerosants likely caused induction of platelet aggregation and that this was localised solely to the sclerotized vein. However, a short lasting inhibitory effect on aggregation may be observed (because of the major dilution of the agents with circulating blood) in efferent deep veins and may potentially reduce thrombotic complications caused by the sclerosant.

As demonstrated in vivo, effects are rapid with extensive intima damage evident at the injection site 10 minutes post-injection with a 4% Polidocanol solution. A subsequent platelet thrombus and fibrin network at the injection site can be formed within 30 minutes and 1 hour after treatment, respectively. Typically, sclerosant-induced thrombi are accompanied by necrotic or absent endothelium and cellular infiltrate. As demonstrated in the dorsal rabbit ear model, 1% polidocanol results in histologic fibrosis within the vessel which completely replaces vessel structure with a fibrous cord by Day 30 but with no recanalization at Day 60. However, recanalization with polidocanol has been demonstrated at 0.25% and 0.5%.

Secondary pharmacology
In cultured human endothelial cells and in canine mesenteric veins, the extent of cell damage and cytotoxicity observed with polidocanol was shown to increase with dose and duration of exposure. The length of ethylene oxide chains within structure of polidocanol was also shown to affect the degree of cytotoxicity, where the largest chain length (n=12) were less cytotoxic when compared to those with shorter chain lengths (n=6 or n=8).

Inflammation and cell viability of human endothelial cells were assessed following exposure to polidocanol. At 0.00125%, polidocanol did not induce significant ICAM-1 expression, at 0.0125% there was a rapid decline in cell number and at 0.025% almost all cells died. Cell death was a consequence of the disruption to the cell membranes and cytoplasm, leaving behind only the nucleus. ICAM-1 expression was not observed.

In cultured bovine aortic endothelial cells, within 15 minutes of treatment (at 0.3% polidocanol), activation of nitric oxide pathways, calcium signalling and subsequent cell death was observed. The time to cell death was increased by reducing the concentrations; whereby at 0.003%, cells remained viable after 60 mins. In this study, the relationship between the degree of cellular toxicity and exposure time was non-linear. The effects were similar those observed with another sclerosant, sodium tetradeyl sulfate.
To investigate the effects of polidocanol foam in rat pulmonary parenchyma, a 0.4 ml (equivalent to 120 ml in humans) injection of 1% polidocanol tessari foam was injected into the lateral saphenous vein of rats and the lungs were removed for histological examination at 24 hours, 7 days, or 28 days post-injection. Alveolar oedema was observed at 24 hours. Vessel thickening was observed at 7 and 28 days and interstitial fibrosis in some animals at 28 days group. There was no evidence of venous or arterial thrombosis. The Applicant has adequately discussed the relevance of the findings of this study to investigate the effects of polidocanol foam in rat pulmonary parenchyma and have included a discussion of the available literature relevant to the potential for respiratory effects. The dose used in this study was over twice that used clinically on a mg/kg basis, and the volume of foam was well in excess of that used clinically. As no lower doses were included in the study is not possible to determine the no-effect level or if these findings would be apparent at clinically relevant doses/volumes.

However, given the clinical experience with polidocanol and the relative rarity of adverse effects to the respiratory system in humans, this concern can be adequately addressed by means of information within the Summary of Product Characteristics (SmPC) and package leaflet (PL); the information within the current SmPC and PL is considered to be sufficient.

**Safety pharmacology**

In guinea-pig Langendorff hearts, treatment with polidocanol (2.6x10⁻⁶ mol/L) was associated with a significant decrease in beating frequency (~27%) and (at constant frequency) a significant delay of intraventricular conduction, increased in PQ and QRS intervals; however, QT remained near constant. Effects were only slightly reversible after a 30 min wash out period. Polidocanol at 1 x 10⁻⁵ mol/L decreased both the duration and V_max of the action potential by 10%. At this concentration, the spontaneous beating frequency in the isolated sinus node was decreased by 8% due to a -18% reduction in diastolic depolarisation rate. These effects were attributed to the inhibition of both fast sodium channels and calcium or potassium conductance.

In the dog, haemolysis, reduced platelet count, and a slight decrease in fibrinogen were observed following administration of 1% (1 mL/kg) polidocanol. A reversible transient decrease in cardiac index, pulmonary artery pressure, and pulmonary artery resistance was observed. In comparison to other sclerosing agents, polidocanol had the least pronounced effect on these parameters.

In the rabbit, a polidocanol infusion of 1 mg/kg/min produced a reduction in heart rate (14%), mean arterial pressure (11%), cardiac output (41%), stroke volume (16%) and contractility (43%) at 5 minutes following administration. At 15 minutes an increase in thromboxane B₂ and 6-ketoPGF₁α were also observed which was attributed to a systemic reaction produced by cardiogenic shock. The aethoxysklerol SmPC, states that safety pharmacology studies showed negative chronotropic, inotropic and dromotropic effects, with a blood pressure drop. Additional proarrhythmic effects were seen when concomitantly administered with other local aesthetics.

The cardiac effects of polidocanol in rabbits were comparable to those in rats. Additionally, in rats exposed to a continuous polidocanol infusion of 2 mg/kg/min lethality was 100% at approximately 40 minutes. Pre-treatment with indomethacin and methylprednisolone had no effect on survival time; however, a concomitant infusion of positive inotropic agents prolonged survival.

After administration of 6% polidocanol to the common carotid artery or the external iliac artery of rats, it was found that under this pressurised system platelets and vessel components could be shunted away from the arterial system, the site of injection, and into smaller vessels. This suggests that there is an increased risk of peripheral embolism if polidocanol was inadvertently administered to the arterial system. The ability to induce thrombogenesis is decreased when administered with anti-coagulants.

The no effect level for systemic toxicity of polidocanol has proven to be 2 mg/kg or more throughout all the species examined in the single-dose and multiple-dose toxicological animal studies included in the USA FDA polidocanol review. The systemic exposure of maximal 2 mg/kg body weight through polidocanol in the course of sclerotherapy is well established within worldwide clinical practice and shows a safety profile which is very well known and does not impose any concern with respect to the safety of the drug.
Pharmacodynamic drug interactions
There was no discussion regarding pharmacodynamic drug interactions; however, given the products and the proposed use, this could be accepted.

III.3 Pharmacokinetics
No pharmacokinetic data relating to polidocanol were located in the literature; hence, the applicant refers to the FDA review of Asclera (polidocanol) 0.5% & 1.0% solution for injection.

Polidocanol, and its metabolites, undergo rapid and widespread distribution at the site of administration. In the rat, the apparent t\(_{1/2}\) is 1.3 h and 15 h at 4 h and 6-72 h, respectively.

No data on the metabolism of polidocanol are reported. Data from the FDA review indicate that in the rat, 100% is eliminated within 48 hours of administration, primarily in urine but with a substantial amount also found in faeces. In the dog, approximately 97% of an administered dose was eliminated within 72 hours, with about 2/3 of the activity in the urine and the remainder in the faeces.

Overall, given the well-established clinical use of polidocanol, the lack of pharmacokinetic data could be accepted.

III.4 Toxicology
Single-dose toxicity
No data was provided.

Repeat-dose toxicity
Limited data are found in the literature; hence, the applicant refers to the FDA review of polidocanol and the SmPC of the German product aethoxysklerol, which indicate that the primary effects involve damage at or near the injection site, including discoloration, necrosis, scarring, and ulceration, and that acute toxicity is relatively low.

Upon repeat dosing, histological alterations in the intestine, adrenal gland and liver were noted in all species evaluated. Rabbits showed additional alterations in the kidneys. Lauromacrogol 400 caused haematuria in all species investigated. At ≥4 mg/kg/day for seven days, an increase in liver weight was observed and at ≥14 mg/kg/day, increases in AST and ALT were apparent.

In the rat, repeated administration of polidocanol at 1, 3, or 9 mg/kg for 13 weeks produced discoloration, necrosis, scarring, and ulceration at the injection site; severity was proportional to increased exposure duration and dose. Decreased red blood cell count, haemoglobin, and haematocrit levels were attributed to haemolysis. Increases in white blood cells and plasma proteins were attributed to the activation of the inflammatory response. The no-observed effect level (NOEL) for systemic toxicity was 1 mg/kg weekly for 14 doses which is 0.17 times the maximum human dose based on body surface area.

In the dog, following repeated intravenous administration every other day for 13 weeks, the NOEL was 3 mg/kg. Above this concentration reversible emesis and salivation was noted. Perivenous fibrosis localised to the injection site was noted in all treated animals and at ≥3 mg/kg this persisted throughout the 28-day recovery period.

Genotoxicity
The genotoxic potential of polidocanol has been assessed in a series of in-vitro and in vivo studies. The Applicant has provided publications found within the literature and the FDA assessment report. The data from the literature suggest that no mutagenic activity was seen in Ames test, bone marrow micronucleus test, and a mouse lymphoma cell mutation assay.

Polidocanol was considered to be weakly clastogenic in-vitro and not genotoxic in-vitro and in vivo (rat) up to 27 mg/kg, above the proposed clinical dose. The genotoxic findings are summarised within Section 5.3 of the SmPC.
Carcinogenicity
No carcinogenicity studies were reported in the literature.

Reproductive and developmental toxicity
No data relating to the reproductive and developmental toxicity of lauromacrogol 400 in animals were found in the literature.

The applicant cites the FDA review which states that the NOEL for both maternal effects and fetal effects was 10 mg/kg for the rat and 2 mg/kg for the rabbit. Polidocanol did not cause skeletal or visceral abnormalities in rabbits but at > 2 mg/kg mean fetal weight and fetal survival were reduced. The fetal toxicity observed in rabbits was attributed to maternal toxicity, however, it was concluded that an embryocidal effect in rabbits was produced by polidocanol. There was no effect to rat fertility or ability to deliver and rear pups.

The applicant quotes the German SmPC for Aethoxysklerol which states that the embryotoxic and fetotoxic effects (increased embryo/foetal mortality, reduced foetal weights) were seen in the maternal toxic dose range. However, no maternal toxicity or embryotoxic/fetotoxic effects were seen when polidocanol administration was restricted to the organogenesis phase (when animals were dosed for 4 consecutive days).

When polidocanol was administered intravenously every other day during late gestation and in the lactation period, peri- and postnatal development or behaviour and reproduction was not impaired in offspring.

Data within the FDA review and SmPC therefore demonstrate that at doses below those associated with maternal toxicity, no direct effect on reproductive performance or embryofetal development was observed.

Local tolerance
Local irritation is expected given the pharmacological mode of action of the product.
When 1% polidocanol was administered in the femoral vein of rats, both intravenously and perivenously at the same site, severe inflammation and necrosis of the tissues surrounding the injection site, including nerve lesions and focal necrosis of the muscle, was observed; for this reason, i.v. combined with perivenous administration is not recommended. Further, degenerative damage to axon of peripheral nerves, especially those that were myelinated, was observed following 0.1% or 0.2% polidocanol paravascular injections in rats and rabbits. These effects were reversible in most cases.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. Lauromacrogol 400 is a mixture of lauryl alcohol (dodecanol) monoethers of mixed macrogols. It is a well-established substance in several countries worldwide, as such it’s chemical, physical and biological properties, and environmental fate are well characterised. In addition to its pharmaceutical use, lauromacrogol 400 is used as non-ionic surfactant in laundry detergents. In 2009, a Human and Environmental Risk Assessment (HERA) of ingredients in household products suggested that alcohol ethoxylates do not constitute a risk to the aquatic environment, sediment or soil, or sewage treatment plants, and that no risk to the atmosphere is expected. Thus, it is not expected that environmental exposure of Lauromacrogol 400 will increase following approval of the Marketing Authorisations for the proposed products. Hence, it is agreed that an environmental risk assessment is not necessary.

III.6 Discussion of the non-clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of lauromacrogol 400 administered via the proposed routes are well known. Aethoxysklerol is already been approved for intravenous bolus administration; therefore, no additional non-clinical data were considered necessary for these applications.

In conclusion, there are no objections to the approval of these applications, from a non-clinical point of view.
IV. CLINICAL ASPECTS

IV.1 Introduction

These are national applications for Marketing Authorisations for Aethoxysklerol solution for injection. The legal basis of these applications is a well-established medicinal use applications according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic references only.

The liquid form of lauromacrogol 400 has been in use for many decades. However, its use as foam is more recent and the Applicant has indicated that this was approved by the German competent authority, BfArM, only in October 2009. Published data (see Table 1 and Section 2 ‘Clinical Assessment’ below) suggest that polidocanol foam started being used in clinical studies and was introduced into clinical practice much earlier. On that basis, and taking into account the overall experience with polidocanol over the years, it is accepted that “well-established use” (for more than 10 years) is also applicable to the foam form.

No new clinical studies have been submitted in support of these applications.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

The clinical dossier includes a large number of publications on the clinical pharmacology, efficacy and safety of lauromacrogol 400 and a critical discussion on the available evidence. The bibliographic search strategy is also adequately described and is considered acceptable.

Data on the safety and efficacy of polidocanol come from 50 published clinical studies.

All published randomised clinical trials (RCTs), controlled clinical trials (CCTs) and case series where at least 100 patients were evaluated in order to capture the best quality data series were included. To assess the quality of the cited publications the following system was used by the Applicant based on the classification system of the Agency for Healthcare Research and Quality (AHRQ) and Cochrane, for the classification of published studies which will be applied during the subsequent paragraphs:

• Category A: Meta-analysis.
• Category B: Randomized controlled clinical trial or Good Clinical Practice (GCP) conform randomized study.
• Category C: Controlled clinical trial distinguishing more than one treatment group, no indication for a randomization.
• Category D: Non-interventional studies (case series, observational study (cohort and case control study) or registry), no randomization, no control group.
• Category E: Case presentation.
• Category F: Systematic review, guideline, consensus paper, expert opinion.

Twenty four RCTs (B), 9 CCTs (C) and 17 clinical series (D) have been published for polidocanol sclerotherapy (liquid only: 9 RCTs, 2 CCTs and 8 clinical series; liquid and foam: 5 RCTs and 3 CCTs; foam: 10 RCTs, 4 CCTs and 9 clinical series). All these studies have been performed after the initial registration of Aethoxysklerol in Germany in 1966. Overall, 7783 patients (and additionally 17,304 limbs) were included in these studies: 3361 patients (and additional 16,804 limbs) were treated with liquid sclerotherapy and 4422 patients (and additional 500 limbs) were treated with foam sclerotherapy. An overview of the clinical studies performed with polidocanol is provided in Table 1.
Table 1: Studies identified in the literature analysing polidocanol sclerotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Type of vein</th>
<th>Subject of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1979)</td>
<td>B</td>
<td>3% POL (N = 516/453 analysed; sclerotherapy = 157 analysed; surgery = 161 analysed; mild surgery + sclerotherapy = 165 analysed)</td>
<td>GSV, SSV</td>
<td>Comparison of radical surgery, a combination of mild surgery and sclerotherapy and sclerotherapy.</td>
</tr>
<tr>
<td>(1989)</td>
<td>C</td>
<td>0.25%, 0.5%, 0.75% and 1% POL (N = 20/16 analysed, max. 2 mL /visit, max. 6 visits)</td>
<td>Telangiectasia</td>
<td>Efficacy (clearing of involved veins) and safety (itching, hyperpigmentation, neovascularization, patient satisfaction)</td>
</tr>
<tr>
<td>(1993)</td>
<td>C</td>
<td>3% POL; POL: 78; surgery: 74 surgery = POL 60</td>
<td>GSV</td>
<td>To compare the long-term value of different forms of treatment (compression sclerotherapy or compression sclerotherapy with high tie under local anaesthesia)</td>
</tr>
<tr>
<td>(1995)</td>
<td>D</td>
<td>0.5%, 1%, 3% POL (N = 15,504 limbs)</td>
<td>Telangiectasia, smaller veins, varicose veins</td>
<td>- Efficacy: Any complications that occurred as a result of the injections.</td>
</tr>
<tr>
<td>(1999)</td>
<td>B</td>
<td>1% POL, (N = 81; POL: 81, STS: 81)</td>
<td>Telangiectasia and Reticular veins</td>
<td>Patient satisfaction, efficacy (improvement variables) and safety (adverse events; patients rated pain of injection, immediate reactions (either local or systemic) or within the 2-months follow-up)</td>
</tr>
<tr>
<td>(2000)</td>
<td>B</td>
<td>3%</td>
<td>SFJ, GSV</td>
<td>Efficacy and costs of endovascular sclerotherapy and surgery</td>
</tr>
<tr>
<td>(2000)</td>
<td>D</td>
<td>3% POL (N = 895/895 analysed; POL = 695; STS = 1293; POL + STS = 876)</td>
<td>Varices (perforating veins, GSV, SSV, ulcers)</td>
<td>Disappearance of varices and eczemas, reduction of oedemas, healed ulcers and relief of symptoms (pain, fatigue, tiredness) with STS in comparison to POL</td>
</tr>
<tr>
<td>(2000)</td>
<td>D</td>
<td>3% POL (N = 247)</td>
<td>GSV</td>
<td>Efficacy and safety</td>
</tr>
<tr>
<td>(2002)</td>
<td>B</td>
<td>0.5%, 1%, 3% POL (N = 129; POL = 60, STS = 69)</td>
<td>Telangiectasia, reticular veins, varicose veins, without incompetence at the SFJ or SPJ</td>
<td>- Disappearance of veins in all size categories in comparison to STS - recording of adverse events</td>
</tr>
<tr>
<td>(2003)</td>
<td>B</td>
<td>3% POL (N = 62/75 analysed, sclerotherapy = 49/49; phlebectomy</td>
<td>Tributary</td>
<td>Recurrence rates of varicose veins and complications after compression sclerotherapy and ambulatory phlebectomy</td>
</tr>
</tbody>
</table>

Study Type of study Treatment Type of vein Subject of the study

- (2003) | D | 2%, 3% POL (N = 117/106 analysed) | Reticular veins GSV, SSV | Vein recurrence after compression sclerotherapy |
- (2004) | B | 2%, 3% POL (N = 14 sclerotherapy, N = 11 placebo) | Medium sized with competent SFJ or popliteal junction | Efficacy of POL sclerotherapy in comparison to placebo |
- (2005) | D | 2%, 1% (N = 296; POL = 30, stripping = 192; ligation = 74) | GSV | - recurrence-free rate after sclerotherapy in comparison to stripping or SFJ |
- (2010) | B | 0.5%, 1% POL (N = 316/269 analysed) | Telangiectasia Reticular veins | - improvement of veins - adverse events |
- (2012) | B | 0.5%, 1% POL (N = 63/63 analysed) | Telangiectasia and reticular legs | Safety and efficacy of POL and hypertonic saline |
- (2012) | D | 0.5% POL (30/30, POL: 30/30; laser: 30/30, RFA: 30/30) | Telangiectasia | Clinical improvement, pain intensity and adverse events. |
- (2012) | B | 0.5%, 1%, 3% POL (Ne POL: 216/206; Placebo: 72/69) | Telangiectasia, reticular veins/smaller sized veins, medium or large non-saphenous veins | Efficacy and safety of POL in Chinese patients |
- (2012) | D | 1 - 3% POL (N = 354) | Multiple treatment sessions | Tributaries, Anterior accessory saphenous vein, SSV, GSV | Efficacy of sclerotherapy with a preliminary saline flush |

Studies using liquid and foam polidocanol

- (2003) | B | 3% (liquid or foam; N = 88/88 analysed; liquid: 43, foam: 45) | GSV | Elimination of pathological reflux in the GSV, as assessed by a Doppler (Duplex) ultrasonography after liquid and foam treatment. The secondary criteria were the length of the parietal reaction, the time of recanalization, and the incidence of side effects. |
- (2004) | C | 1%, 3% POL (N = 77/77 analysed, liquid = 40, foam = 37) | GSV | Safety and efficacy of dupilux-guided foam sclerotherapy in comparison to dupilux guided liquid sclerotherapy |
- (2005) | B | 0.5% | 1% (1% foam) (N = 20, POL = 18; STS: 19) | Telangiectasia Reticular veins (Small varicose veins) | Comparison of liquid and foam sclerotherapy |

GSV = Great saphenous vein, n.a. = not available, POL = polidocanol, SFJ = sapheno-femoral junction, SPJ = sapheno-popliteal junction, SSV = Small saphenous vein, STS = Sodium Tetradecy Sulphate; UGFS = ultrasound-guided foam sclerotherapy

NOTE: Where relevant, study references include information on the above classification, for example: (2011; D)
### Pharmacokinetics

The pharmacokinetic (PK) properties of polidocanol are well known and are adequately described in the applicant's clinical overview.

### Note

NOTE: Where relevant, study references include information on the above classification, for example: (2011; D)
Pharmacokinetic studies
The information presented in this dossier is based on relatively recent studies (1990, 2003 and 2015) as first marketing authorisation for Aethoxysklerol was granted over 50 years ago, when neither pharmacodynamic nor pharmacokinetic information was required. The first two studies investigate the PK properties of Aethoxysklerol in liquid form, and the last study concerns polidocanol as foam.

In the first study (1990), radioactively labelled \(^{14}\)C-Aethoxysklerol was used for the determination of polidocanol general PK in six healthy subjects who received a single intravenous dose of a 0.5% polidocanol solution in the great saphenous vein. Since Aethoxysklerol was injected directly into the vein a complete bioavailability of the active ingredient polidocanol was assumed, although the degree of polidocanol mixing with the intravascular blood may vary. The time course of the concentration in whole blood was bi-exponential, showing a rapid disposition phase with a half-life of 19 minutes, and an elimination phase with a half-life of 4 hours. The volume of distribution was 24.5 litres and the total clearance was 11.7 litres per hour. The mean protein binding value was 64% at 1 hour after administration. \(^{14}\)C radioactivity determined in whole blood was only 31% of the recorded plasma level, which suggests that almost no polidocanol penetrated into erythrocytes.

Renal clearance was 2.43 litres per hour and biliary clearance was 3.14 litres per hour. There was a recovery of radioactivity of 21% in urine and 27% in faeces, while the overall recovered radioactivity during the first 48 hours post application was 97% in urine and 81% in faeces. The study authors explained that the reason for the unbalanced urinary and faecal excretion could be due to autoradiolytic formation of degradation products of low molecular weight that are excreted via respiration before they could be detected in excretion products.

The PK, safety and tolerability of polidocanol after a single dose were also assessed in 19 patients with varicose veins of a lower extremity (2003). After an injection of polidocanol with 1.62-1.88 mg/kg the maximum plasma concentration was 6.645 to 10.319 μg/ml. The elimination phase ranged between 0.94 to 1.27 hours. The authors also concluded that polidocanol at doses of up to 2 mg/kg, in patients with varicose veins of a lower extremity, was safe and well tolerated.

A later PK study (2015) was conducted by using polidocanol Endovenous Microfoam (PEM) at 1% and 2% strengths in patients with GSV vein incompetence. The weight-adjusted polidocanol \(C_{max}\) levels (serum) were lower than those reported in both of the liquid polidocanol PK studies. Doubling the polidocanol foam dose appears double the serum \(C_{max}\) levels (e.g. 1% foam: 840.7 ng/mL vs. 2% 1189.6 ng/mL). The levels obtained in this study following administration of polidocanol in the foam form were within the expected range based on results obtained previously for the liquid form.

Drug interactions
The active substance polidocanol acts as a local anaesthetic. When combined with other anaesthetics, there is a risk of an additive effect of these anaesthetics on the cardiovascular system. This is stated in the currently approved German product SmPC of Aethoxysklerol.

IV.3 Pharmacodynamics (PD)
The submitted review of the available PD data is adequate; a summary is provide below:

The general goal of sclerotherapy in leg varices is obliteration of the targeted vein. From its chemical mode of action, polidocanol acts as a detergent since the molecule contains both a lipophilic and a hydrophilic part. Following contact with the vessel endothelium polidocanol results in a breakdown of the lipid double layer of the cellular wall. The destruction of the endothelium was demonstrated (1993) by treating human saphenous vein segments, obtained during cardiac bypass procedures, in vitro with sclerosing agents. The result of intima epithelial damage is the starting point for the subsequent physiological processes leading to vein occlusion (1991 and 2006).

Studies have also shown that sclerotherapy has an effect (enhance) coagulation and fibrinolysis. However, it seems that high concentrations of polidocanol achieve some anticoagulant activity and prevent clot formation, whereas low concentrations induce the release of procoagulant platelet-derived microparticles and strong clots were initiated (2011).
Conversely, foam sclerotherapy seems to act differently on endothelial cells and peripheral blood cells compared to the liquid form: in a randomised, open, prospective study (2011) blood samples on day 1, 7, 14 and 28 after foam sclerotherapy of the ‘great saphenous vein’ (GSV) and ‘small saphenous vein’ (SSV) with 1% polidocanol were analysed and compared to blood samples just prior to sclerotherapy. Apart from a moderate increase in D-dimers at Day 1-Day 14, no significant biological change was observed. The authors concluded that in terms of inflammation and coagulation, foam sclerotherapy appeared to have a minimal effect on systemic activation of vascular endothelium, platelets and plasma coagulation.

In one study, the in vivo effects of 3% foam sclerosants in GSV and SSV, in the adjoining deep veins and in the systemic circulation of 13 patients aged between 18 and 75 years, were investigated (2014). The authors found a distance-dependent increase in pro-coagulant activity following infusion of foam, shortening of clotting times in the adjoining deep veins within minutes of the procedure and a systemic rise in the D-dimer levels, but no effect on systemic coagulation pathways.

There has been considerable discussion on further underlying physiological mechanisms that result in the subsequent vein obliteration following sclerosant administration in either form. Although it has been proposed that fibrin within the vascular wall is responsible for the onset of thrombus formation (1990), this has been questioned by other authors who found fibrin within the vein lumen (1990).

Studies by several investigators have demonstrated the very complex nature of the reaction between polidocanol and the vascular endothelium, as well as the haemostatic system. However, it is certain that a sclerosant induces significant alterations of the vessel wall resulting in injuring the intima leading to the formation of an immobile sclerus adhering firmly to the vein wall (1999). In larger veins treated with polidocanol, the progress in vein obliteration can be assessed and documented using color-coded duplex-ultrasonography (1990). The results show, that complete obliteration is not always achieved and that complete organization of the thrombus takes some time. Recanalization of the vein may be seen in some cases; therefore, compression treatment seems advisable after sclerotherapy of larger veins (1986). The compression narrows the vein lumen leading to a closer contact between the vein walls and supports the development of small-diameter thrombi and scleri. This reduces the probability of recanalization of the sclerus and promotes its development into fibrous tissue which usually achieves persistent obliteration of the vein.

Overall, the appropriate action of a sclerosant depends on its concentration. Administering too little of the drug will result in an insufficient effect on the vein wall to start the sclerosing process and will lack efficacy, whereas too high a concentration may result in significant damage to the tissue. In order to achieve an optimal clinical outcome and minimize adverse events, the polidocanol concentration administered as a liquid or foam should be considered in relation to the location and size of the varicose veins being treated (1998). Thus, the proposed dosage regimen is adjusted for each concentration of Aethoxysklerol solution for injection.

**IV.4 Clinical Efficacy**

The following review is summarised from the submitted Clinical Overview and Clinical Summaries, and the cited literature.

**IV.4.1 Sclerotherapy**

The standard clinical methodology for sclerotherapy of leg varices with sclerosants like Aethoxysklerol is injection into the targeted vessel with subsequent compression hosiery when appropriate. Approaches to increase the success rate of sclerotherapy and to decrease adverse drug reactions resulting from paravasal and intra-arterial injections include ultrasound guidance during the injection procedure.

Several publications have demonstrated the clinical benefits of Aethoxysklerol injections under ultrasound control. As a consequence of the results of these studies it is recommended that application of Aethoxysklerol microfoam into non visible veins is guided by duplex ultrasound. It is recommended, that the time between foam production and injection should be as short as possible to prevent foam degeneration.
IV.4.2 Study population
A total of 3361 patients treated with liquid polidocanol and 4422 patients treated with foam were included in the studies reviewed as part of the efficacy analyses. In all studies, more female patients were included than men, which may be explained by a higher genetic disposition of women for leg varices. The majority of patients were between 40 and 55 years of age (mean). Aethoxysklerol is not indicated for use in the paediatric population.

For the treatment of leg varices with Aethoxysklerol liquid or foam in special population groups two publications have investigated whether sclerotherapy in elderly patients is effective and can increase the quality of life in this patient group (these are further discussed in the sections below). No other specific results from clinical trials or literature can be derived concerning other special populations. However, populations with comparatively young members are found among Klippel-Trenaunay patients or patients suffering from other congenital venous malformations. Several authors investigated the efficacy of foam sclerotherapy in patients with such concomitant conditions. Currently, the use of Aethoxysklerol for these conditions is not proposed as part of this application.

IV.4.3 Efficacy results
The success of sclerotherapy in the treatment of leg varices mainly depends on two key factors: (1) The size/diameter of the treated vessel and (2) the concentration and volume of the applied sclerosing agent. This is due to the fact that the pharmacodynamic action of polidocanol depends on the contact with the endothelial wall. Hence a higher concentration increases the magnitude of contact of the sclerosing agent with the endothelial wall and consequently the chances of a positive effect. However, the concentration should not be too high for the specific vessel, which may increase the risk of adverse reactions. For these reasons treatment regimens need to be adapted to the size of the targeted veins. Telangiectasias in general refer to varicose veins of a diameter of 1 mm or smaller whereas reticular veins refer to vein diameters of 1 to 3 mm. Veins of larger diameters more than 3 mm are often specified according to the anatomic classification and comprise truncal veins such as the GSV and the small saphenous vein (SSV), collateral veins, and perforating veins. This rough classification of vein sizes according to mm units has been previously used, but a proper classification is difficult – the vein size can vary from one location to another, standardising the measurement is difficult, and choosing the most precise methodology for determination of the vein size is problematic. Therefore, in clinical practice veins are often differentiated according to vein type (telangiectasias, reticular veins, collateral veins, perforating veins, and truncal veins) than according to exact vein size. This aspect is also acknowledged in the current German SmPC of Aethoxysklerol, the European guidelines for sclerotherapy in chronic venous disorders (F), and the German guideline for sclerotherapy of varicose veins (2012; F), in which veins are differentiated by vein type and not by vein size. Thus the treatment regimens for Aethoxysklerol are specified in relation to vein type (for smaller veins) as well as vein size (for varicose veins).

Comparison of liquid and foamed polidocanol
Published medical literature, particularly concerning medium or large sized veins, assessing polidocanol sclerotherapy as liquid or foam favours use of foam.

This is acknowledged by relevant guidelines recommending the use of polidocanol foam in larger varicose veins but pointing out that liquid polidocanol is the gold standard for treatment of spider veins and reticular veins (C1 varicose veins). Although the European guidelines for sclerotherapy in chronic venous disorders mention foam sclerotherapy as an alternative method for ablation of telangiectasias and reticular veins, they also mentioned liquid sclerotherapy as the method of choice (2014; F). These recommendations are substantiated by efficacy data derived from clinical trials comparing polidocanol foam with the liquid formulation. Thus, Aethoxysklerol foam is now proposed for treatment of medium to large veins whereas the liquid form is suggested for all sizes from telangiectasias up to large veins.

Seven studies compared the efficacy of liquid and foamed sclerotherapy. Three studies analysed the differences in smaller varices. Two of the three studies could demonstrate better results for foam treatment (2006 and 2011; B) while one study found no differences (2010; C). For larger varicose veins, four RCTs and one CCT analysed the efficacy of foam versus liquid sclerotherapy. In all studies foam sclerotherapy was superior in comparison to liquid sclerotherapy in respect to occlusion of the treated
vein (2003, 2004, 2008 and 2008). The above publications demonstrated the efficacy of Aethoxysklerol liquid and foam in the treatment of varices of different sizes but for large varicose veins it was shown that foam is more effective in comparison to liquid.

Comment:
It is true that clinical guidelines recommend foam sclerotherapy mostly for larger veins while liquid sclerotherapy may be more appropriate for telangiectasias and reticular veins. The most recent (2014) European guidelines for sclerotherapy in chronic venous disorders, recommends: “Liquid sclerotherapy is considered to be the method of choice for the treatment of C1 (clinical, aetiological, anatomical and pathological elements [CEAP] classification) varicose veins (reticular varicose veins and telangiectasias)”. although it is still noted that “Foam sclerotherapy is an additional treatment option for C1 varicose veins”.

For larger veins the Guideline suggests: “In the treatment of incompetent saphenous veins, thermal ablation or surgery are well established methods. Nevertheless, treatment of saphenous veins by sclerotherapy is also a good and cost-effective treatment option. This applies in particular to foam sclerotherapy, as has been demonstrated by case-control studies and prospective randomized controlled studies conducted in recent years.”

The proposed use of Aethoxysklerol in liquid form alone for telangiectasias and reticular veins, with both forms (foam or liquid) suggested for small-large varicose veins is in line with the SmPC of the German Aethoxysklerol product; also, consistent with the relevant advice in the currently approved SmPC of Fibrovein which recommends use of foam only for the treatment of larger veins.

**Telangiectasias and reticular veins (treatment with liquid polidocanol)**

In the clinical, aetiological, anatomical and pathological elements (CEAP) classification of venous disease spider veins and reticular veins are classified as C1 varicose veins, whereas C0 means no visible or palpable signs of venous disease. Telangiectasias are commonly seen in various patterns, labelled as linear, cartwheel or sunburst varicosities (spider veins) (1949). Spider veins have a central reddish area which is visible because it lies closer to the skin, with smaller veins spreading out from this central point in the shape of spider’s legs. Guidelines indicate that sclerotherapy is the treatment of choice for spider veins. A recent Cochrane review investigating sclerotherapy treatment options for telangiectasias also comments that sclerotherapy has been used for centuries to treat this condition (2011; F).

In one study (2008), the epidemiology of telangiectasias (CEAP category 1, diameter < 1 mm) and its association with trunk varices and symptoms was investigated. In this study participants were divided into three groups (Grades 1-3) according to the degree and extent of tortuosity and prominence of veins in their right legs. A total of 1139 patients were classified as having Grade 1 telangiectasias (494 men, 645 women), while a further 74 subjects had Grade 2 or 3 telangiectasias. The study reported a correlation between the severity of the trunk varicose veins and the percentage frequency of telangiectasias, although the authors further comment that there is no intimate connection between the saphenous system and the reticular network which feeds telangiectatic veins. These results were confirmed by a later study by the same authors in 2012 (2012). In summary, spider veins (telangiectasias) are often a visible sign of an underlying venous disease and/or associated with symptoms which may affect the quality of life of the patient. The data support that telangiectasias is a medical condition, and furthermore that polidocanol sclerotherapy is a potential treatment method.

The following studies treating telangiectasias or reticular veins with liquid sclerotherapy (Table 2) were reviewed as part of the polidocanol efficacy evaluation in this setting.
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj. PL 20685/0042, 0039-0040, 0043 and 0041

Table 2: Studies investigating the treatment of telangiectasias and reticular veins with liquid polidocanol and their key characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Liquid Concentration</th>
<th>Diameter (mm) mean/range</th>
<th>Volume (mL) Mean/Range</th>
<th>Liquid ≤ 6 month</th>
<th>Foam ≤ 6 month</th>
<th>Liquid &gt; 6 &lt; 24 month</th>
<th>Foam &gt; 6 &lt; 24 month</th>
<th>Liquid ≥ 24 month</th>
<th>Foam ≥ 24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1989)</td>
<td>Telangiectasia</td>
<td>0.25%, 0.5%, 0.75% and 1%</td>
<td>0.2 - 1</td>
<td>Max. 2 mL</td>
<td>0.25%: 38.3 0.5%: 70.6 0.75%: 58.3 1%: 62.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(1999)</td>
<td>Telangiectasia and Reticular veins</td>
<td>1%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>scores</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(2002)</td>
<td>Telangiectasia Reticular veins Varicose veins without incompetence at the SFJ or popliteal junctions</td>
<td>0.5%</td>
<td>1%</td>
<td>1-3</td>
<td>3-8</td>
<td>n.a.</td>
<td>70 -72</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(2005)</td>
<td>Telangiectasia Reticular veins (Small varicose veins)</td>
<td>0.5%</td>
<td>1% (1% foam)</td>
<td>&lt; 1</td>
<td>1-3</td>
<td>3-8</td>
<td>n.a.</td>
<td>In average</td>
<td>63%</td>
<td>-</td>
</tr>
<tr>
<td>(2010)</td>
<td>Telangiectasia Reticular veins</td>
<td>0.5%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Max 4.8</td>
<td>Max 2.4</td>
<td>64</td>
<td>88</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2010)</td>
<td>Telangiectasia Reticular veins small veins</td>
<td>0.25%, 0.5% 1.0%</td>
<td>&lt; 1</td>
<td>1-2</td>
<td>&gt; 2 &lt; 4</td>
<td>n.a.</td>
<td>72</td>
<td>84</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2011)</td>
<td>reticular veins &gt; 2 mm</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Liquid: n.a. Foam: 2 mL</td>
<td>76</td>
<td>92</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2012)</td>
<td>Telangiectasia Reticular veins</td>
<td>0.5%</td>
<td>1%</td>
<td>&lt; 1</td>
<td>1-3</td>
<td>1.43/n.a. 1.83/n.a.</td>
<td>Scores</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(2012)</td>
<td>Telangiectasia</td>
<td>0.5%</td>
<td>1-2</td>
<td>1</td>
<td>56.6 (50 – 100 improvement)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

(Only RCTs, controlled clinical trials or non-interventional studies of 100 or more patients were included. Efficacy of the treatment means occlusion of the treated veins. n.a. = not available)

The majority (7 out of 9 studies) used 0.5% polidocanol for the treatment of telangiectasias; in one study 0.25% was used and 3 studies reported the use of 1%. Reticular veins were treated with 1% polidocanol in all studies while 0.5% polidocanol was mentioned in 2 of 7 studies.

Two RCTs analysed the efficacy in comparison to placebo and demonstrated significant higher efficacy for polidocanol. The prospective randomised, placebo and comparator controlled, double blind, multicentre EASI trial (2010) investigated the efficacy and safety of Aethoxysklerol (0.5% and 1%) compared to placebo (isotonic saline) but also STS, for the treatment of reticular veins and spider veins. The primary analysis revealed statistically significant superiority of the treatment with Aethoxysklerol versus placebo in the assessment of the improvement of the veins according to a 5-grade scale (p<0.0001). The same comparison between Aethoxysklerol and STS showed no significant differences. Patient satisfaction with the treatment after 12 (± 2) weeks and after 26 (± 4) weeks showed superiority of the treatment with Aethoxysklerol compared to STS.

Table 3: Summary of Aethoxysklerol vs. placebo efficacy results obtained in the EASI study.

<table>
<thead>
<tr>
<th></th>
<th>Aethoxysklerol</th>
<th>STS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>155</td>
<td>105</td>
<td>53</td>
</tr>
<tr>
<td><strong>12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein improvement</td>
<td>Mean 4.5 SD 0.65</td>
<td>Mean 4.5 SD 0.74</td>
<td>Mean 2.2 SD 0.68</td>
</tr>
<tr>
<td>Treatment success?</td>
<td>96% Yes (P &lt; 0.0001 vs. placebo)</td>
<td>92% Yes (P &lt; 0.0001 vs. placebo)</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>26 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein improvement</td>
<td>Mean 4.5 SD 0.67</td>
<td>Mean 4.5 SD 0.77</td>
<td>Mean 2.2 SD 0.72</td>
</tr>
<tr>
<td>Treatment success?</td>
<td>95% Yes (P &lt; 0.0001 vs. placebo)</td>
<td>91% Yes (P &lt; 0.0001 vs. placebo)</td>
<td>5.7% Yes</td>
</tr>
<tr>
<td>Patient satisfaction – satisfied/very satisfied</td>
<td>88%</td>
<td>63%</td>
<td>13%</td>
</tr>
</tbody>
</table>

(Efficacy of the treatment means occlusion of the treated veins. Scale: 1=worse than before treatment, 2=same as before treatment, 3=moderate improvement, 4=good improvement, 5=complete success. no. = number, n.a. = not available)

Comparison of Aethoxysklerol to placebo in the treatment of telangiectasias, reticular veins and/or small varicose veins and larger veins in Chinese patients (ESA-China study2012; B) showed a
significantly higher treatment success in each of the vein-type groups when Aethoxysklerol was used (Table 4). Moreover, Aethoxysklerol significantly decreased symptoms which were caused by varicose veins and improved the quality of patients’ daily life.

Table 4: Key results obtained in the ESA-China study. Efficacy of the treatment means occlusion of the treated veins. no. = number

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Mean treatment dose (mL)</th>
<th>Vein occlusion and/or absence of reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (0.5% Aethoxysklerol)</td>
<td>70</td>
<td>1.97</td>
<td>87.1%</td>
</tr>
<tr>
<td>B (1% Aethoxysklerol)</td>
<td>22</td>
<td>2.62</td>
<td>13.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>66</td>
<td>2.11</td>
<td>86.4%</td>
</tr>
<tr>
<td>C (3% Aethoxysklerol)</td>
<td>24</td>
<td>5.49</td>
<td>12.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>70</td>
<td>2.21</td>
<td>88.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>23</td>
<td>4.58</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Group A: Spider veins (< 1 mm), treated with 0.5% Aethoxysklerol; Group B: Recicular veins and/or small varicose veins 1-5 mm, treated with 1% Aethoxysklerol; Group C: Medium sized and/or large non-saphenous subcutaneous varicose veins of > 5 mm with reflux > 0.5 s, treated with 3% Aethoxysklerol.

Several studies compared the efficacy of polidocanol with other sclerosants (hypertonic saline and STS) or with other methods (laser, radiowave). In comparison to hypertonic saline plus 1 - 2% lidocaine and 1% polidocanol in the treatment of leg telangiectasias and reticular feeding veins no significant difference between hypertonic saline and polidocanol was found in one study when clinical or photo assessments were analysed (1999; B). However, patients reported significantly greater satisfaction with sites treated with hypertonic saline. On the other hand, the injection with hypertonic saline was rated significantly more painful than polidocanol, although 1 - 2 % lidocaine was already added to hypertonic saline.

Investigators compared polidocanol (0.5% and 1%) with hypertonic saline (11.7% and 23.4%) in patients with telangiectasias and reticular veins (2012; B). Again, hypertonic saline was equally effective for clinical improvement in telangiectasias, although the treatment with hypertonic saline was associated with significant discomfort during the procedure; patients also judged hypertonic saline to be more painful and was associated with two episodes of tissue necrosis. Both above studies demonstrated that polidocanol and hypertonic saline produced good results, but treatment with hypertonic saline caused more discomfort and was painful.

Three studies compared the efficacy of polidocanol to STS. As noted above, in EASI trial Aethoxysklerol was found to be as effective as STS, but patient satisfaction was higher in the Aethoxysklerol group; also fewer adverse drug reactions occurred with Aethoxysklerol (see Table 3 above). Similar results had been reported in another study 2002; B). The treatment of varicose and telangiectatic leg veins with Aethoxysklerol (0.5%, 1% and 3%) and STS (0.25%, 0.5% and 1.5%) were equally effective in treating veins smaller than 1 mm, veins with a diameter between 1 and 3 mm and veins with a diameter of 3 and 6 mm. All patients had an average 70% improvement and expressed 70 – 72% satisfaction in all vein categories treated with either solution. However, polidocanol caused less localised urticaria and skin necrosis than STS.

Another study (2012; D) compared the efficacy of sclerotherapy, laser and radiowave coagulation in the treatment of telangiectasias. The most efficient method identified in this study, giving a high significant statistical difference in efficacy compared with the other treatments, was sclerotherapy followed by laser and finally radiowave coagulation. Again, only minimal sense of pain (10% of patients) was associated with sclerotherapy, while the strongest pain was reported by 23.33% of patients receiving radiowave coagulation therapy.

Overall, many of the studies discussed above have shown polidocanol liquid 0.5% to be one of the most effective and best tolerated sclerosing agents for treatment of telangiectasias (1989;
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj. PL 20685/0042, 0039-0040, 0043 and 0041

2000, 20052010 (and 2010). Also relevant guidelines indicate that sclerotherapy is the treatment of choice for telangiectasias.

Comment:
It is agreed that there is sufficient evidence to support the efficacy of polidocanol sclerotherapy in the treatment of telangiectasias and reticular veins. Studies have shown that polidocanol is superior to placebo and generally comparable (and in some cases better) to other sclerosants or other forms of treatment.

A Cochrane review published in 2011 on sclerotherapy for lower limb telangiectasias including 10 studies involving 484 patients, concluded there was no evidence suggesting superior efficacy of anyone sclerosant over another, but the data indicated superiority of sclerotherapy to placebo in general. There was some evidence suggesting that for telangiectasias a lower polidocanol concentration (0.5%) was less likely to cause adverse reactions. There was also some evidence suggesting that polidocanol was less painful than STS and no more painful than placebo.

As discussed above, liquid sclerotherapy is also mentioned as the treatment of choice for reticular varicose veins and telangiectasias in the most recent (2014) European guidelines for sclerotherapy in chronic venous disorders where polidocanol, together with STS, are considered the main sclerosing agents. For telangiectasias a polidocanol concentration of 0.25-0.5% is advised and for reticular veins 0.5%-1%, 0.5-1% for central veins of telangiectasias and 1% for reticular veins. This issue (evidence on recommended posology) is further discussed below.

Another general point that deserves further consideration is to what extent telangiectasias are more a cosmetic issue rather than a medical problem requiring specific intervention, and how this affects the benefit:risk balance of polidocanol in this indication. The Applicant has submitted some evidence from published studies and reports supporting that telangiectasias are often associated with incompetence in other parts of the venous system and that a significant percentage of patients with telangiectasias have symptoms requiring medical treatment. Yet, this is still a matter of debate and some experts in the field still do not support medical treatment especially of mild telangiectasias suggesting that the risks may outweigh the benefits. Nevertheless, the principle (and a positive benefit:risk) of treating spider veins with a sclerosant has already been accepted for STS (Fibrovein), implying that the medical need for such therapy has been recognised.

Small varicose veins (treatment with liquid or foamed polidocanol)

Liquid sclerotherapy

Three studies have published data on the treatment of small varices with liquid polidocanol:

Table 5: Clinical trials treating small varicose veins with liquid sclerotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Liquid Concentration</th>
<th>Diameter (mm) mean/range</th>
<th>Volume (mL) Mean/range</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1995)</td>
<td>Telangiectasias and smaller varicose veins</td>
<td>0.5% or 1%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Liquid ≤ 6 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Foam ≤ 6 month</td>
</tr>
<tr>
<td>(2010)</td>
<td>Telangiectasias Reticular veins small veins</td>
<td>0.25%, 0.5%, 1.5%</td>
<td>&lt; 1 mm 1-2 mm &gt;2 &lt; 4</td>
<td>n.a.</td>
<td>Liquid &gt; 6 ≤ 24 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Foam &gt; 6 &lt; 24 month</td>
</tr>
<tr>
<td>(2012)</td>
<td>Telangiectasia Reticular veins/small sized veins Medium or large non-saphenous veins</td>
<td>0.5% 1% 3%</td>
<td>&lt; 1 1-5 &gt;5</td>
<td>1.97/n.a. 2.11/n.a. 2.21/n.a.</td>
<td>Liquid ≥ 24 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Foam ≥ 24 month</td>
</tr>
</tbody>
</table>

Efficacy of the treatment means occlusion of the treated veins. n.a. = not available

In these trials the small varices were generally treated with liquid 1% polidocanol. All three studies
demonstrated high efficacy with 1% polidocanol.

One study (1995; D) reported the results of a total of 16,804 limbs injected with polidocanol liquid. Sclerotherapy was performed with polidocanol 0.5% or 1% for telangiectasias or smaller venules and with polidocanol 3% for larger varicose veins. The effectiveness of polidocanol (over a 2 year period) was 85% (no separation between the different types of varicose veins) and superior to comparators STS and hypertonic saline.

In the most recent and larger study, the prospective, multicentre, randomised, and double-blind ESA-China (also mentioned above in the previous section ‘Telangiectasias and reticular veins (treatment with liquid polidocanol’), investigators assessed the efficacy and safety of liquid Aethoxysklerol in comparison to placebo in 285 Chinese patients aged between 18 and 75 years old. The patients were allocated to three treatment groups (spider veins, reticular and/or small varicose veins, and medium sized and/or large non-saphenous veins). 66 subjects with reticular veins and/or small varicose veins were treated with 1% Aethoxysklerol and 2.11 mL (mean) was used. Vein occlusion and/or absence of reflux was obtained in 86.4% of the patients (Table 4 above). The difference in efficacy between the treatments with 1% vs. placebo group was statistically significant (P < 0.001). Both investigators’ satisfaction and patients’ satisfaction were significantly higher with polidocanol than with placebo (P > 0.001). For reticular and smaller varicose veins 85.7% of the investigator and 90.5% of the patients’ with polidocanol treatment and 38.1% of the investigator and patients’ were satisfied or very satisfied with the placebo treatment at 12 weeks.

**Foam sclerotherapy**

Although liquid sclerotherapy can be used for treatment of smaller varicose veins, today mostly foam is used for such veins (e.g. tributaries). These frequently occur in combination with incompetent GSVs or SSVs. Thirteen studies are published where treatment of smaller varicose veins was investigated.

**Table 6: Treatment of smaller varicose veins (tributaries, perforating, recurrent veins, smaller SSVs) with foam sclerotherapy.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Concentration</th>
<th>Diameter (mm) mean/range</th>
<th>Foam method</th>
<th>Foam volume (mL) Mean/range</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Foam &lt; 6 month</td>
<td>Foam &gt; 6 &lt; 24 month</td>
<td>Foam &gt; 24 month</td>
</tr>
<tr>
<td>(2000)</td>
<td>GSV tributaries</td>
<td>1 - 3% 1 - 3%</td>
<td>n.a. / 9 - 32</td>
<td>n.a.</td>
<td>n.a. / 15 - 25</td>
<td>-</td>
</tr>
<tr>
<td>(2004)</td>
<td>GSV tributaries</td>
<td>3% (liquid or foam) 1% (liquid or foam)</td>
<td>n.a.</td>
<td>Tessari</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>(2005)</td>
<td>GSV SSV tributaries</td>
<td>n.a. n.a.</td>
<td>n.a.</td>
<td>DSS</td>
<td>n.a.</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>tributaries reticular vein small veins</td>
<td>0.5% liquid 1% liquid 1% foam</td>
<td>n.a.</td>
<td>n.a.</td>
<td>DSS</td>
<td>At the beginning up to 30; later on 10</td>
</tr>
<tr>
<td>(2005)</td>
<td>GSV SSV tributaries recurrent</td>
<td>0% 1% 1%</td>
<td>GSV: 6.3 ± 8 - 14 GSV: 6.3 ± 4 - 8</td>
<td>DSS</td>
<td>n.a.</td>
<td>83</td>
</tr>
<tr>
<td>(2006)</td>
<td>reticular veins recurrent veins</td>
<td>1 - 1.25% (liquid); 0.5 - 0.65% (foam) 1.5 - 2.5% (liquid); 0.75% - 1.25% (foam)</td>
<td>reticular veins: n.a. / 1 - 3 recurrent veins: n.a. / 3 - 6</td>
<td>Tessari</td>
<td>n.a. / max:2.0</td>
<td>94.4</td>
</tr>
<tr>
<td>(2008)</td>
<td>GSV SSV tributaries recurrent veins</td>
<td>3% 1% 3% 1% 1%</td>
<td>GSV: n.a. / 3.8 - 10.5 GSV: n.a. / 4.4 - 10.2 recurrent: n.a. / 3.2 - 7.5</td>
<td>Tessari</td>
<td>GSV: median 6 / 2 - 6; max: 14; SSV: median 3 / 2 - 4; max: 14</td>
<td>GSV: 96 (single); SSV: 86 (two); SSV: 95.7%</td>
</tr>
<tr>
<td>(2009)</td>
<td>CE (ulcers)</td>
<td>3% 3% 1% 3% 1%</td>
<td>GSV: n.a. / max: 10 SSV: n.a. / max: 5 tributaries: n.a. / max: 5 Perforating: n.a. / max: 2</td>
<td>Tessari</td>
<td>GSV: n.a. / max: 10 SSV: n.a. / max: 5</td>
<td>78</td>
</tr>
</tbody>
</table>
In 7 of the 13 studies, 1% polidocanol was used (2004; 2005; 2006; 20092011; 2012a), while in three studies 1% or 3% polidocanol foam was mentioned (2000; 2012; 2012b). In one study, investigators used foam concentration around 1% (2006). A single trial (2011) mentioned the use of 3% foam for the treatment of tributaries or recurrent veins and one study did not mentioned the used concentration (2005).

Tributaries are often treated during the control visits, after the treatment of larger veins is carried out. Results specifically relating to the preliminary tributary treatment are consequently not always identified in the literature reports. The efficacy of polidocanol foam specifically for the treatment of tributaries has, however, been analysed in two of the afore-mentioned studies (2000; 2006). Investigators reported disappearance of all superficial branches in 96.5% of the cases at least 3 years after treatment with 1% - 3% polidocanol microfoam (2000; D). Similarly, in another study it was found that 33 out of 38 limbs treated with 1% polidocanol microfoam were completely occluded after just one treatment, giving an efficacy of 86.84% (2006; D).

Three studies mentioned the foam volume used for sclerotherapy of tributaries, or tributaries/recurrent veins. In one study using 2 mL 1% polidocanol foam; efficacy at 1 year follow-up was 67.6% (GSV & tributaries) following foam treatment (2004; C). In another study, less than 0.5 mL polidocanol 1% foam per injection, total <10 mL (including subsequent GSV treatment), was used and the efficacy at 6 months was 58.8% (GSV & tributaries) (2012a; B). The third study mentioned 4.8 - 8.2 mL polidocanol foam for the treatment of tributaries/recurrent veins. The volume depended on the polidocanol concentration (1 - 3%) (; D). The efficacy at 6 months was 88.9% for the treatment of GSV and tributaries and 81.5% for SSV and tributaries. Hence a volume range of 4 – 6 mL Aethoxysklerol foam for the treatment of tributaries is currently proposed.

The findings discussed above are consistent with advice from the guidelines of the German Society of Phlebology (2012) and the European guidelines for sclerotherapy in chronic venous disorders (2014), recommending the use of liquid polidocanol in the therapy of smaller varicose veins (as well as telangiectasias and reticular veins), and the use of polidocanol foam therapy for the treatment of small (tributaries) to larger blood vessels.

Comment:
The submitted study data generally support the efficacy of polidocanol sclerotherapy (in both liquid and
foam form) in the treatment of small varicose veins.

Also the use of the currently proposed concentration of 1% appears consistent with the one used in most studies for this type of veins and the recommendations of the relevant Guidelines.

**Medium size varicose veins**
Relevant clinical guidelines as well as the German Aethoxysklerol SmPC recommend use of a 2% or 3% solution for the treatment of medium-sized varicose veins; the proposed SmPC is consistent with this recommendation.

**Large varicose veins (treatment with liquid and foamed polidocanol)**
It is generally suggested in the literature that treatment of varicose veins of larger diameters should either be treated with liquid Aethoxysklerol 2% and 3% or Aethoxysklerol foam 1% to 3% (2000; 2006; 2010, 2012).

**Liquid sclerotherapy**
A total of 16 studies have been published to date presenting results regarding polidocanol liquid treatment in larger varices (e.g. SSV and GSV).
### Table 7: Clinical trials treating large saphenous veins with liquid sclerotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Liquid Concentration</th>
<th>Diameter (mm) mean/range</th>
<th>Volume (mL) Mean/range</th>
<th>Liquid ≤ 6 month Foam ≤ 6 month</th>
<th>Liquid &gt; 6 &lt; 24 month Foam &gt; 6 &lt; 24 month</th>
<th>Liquid ≥ 24 month Foam ≥ 24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1979)</td>
<td>GSV, SSV</td>
<td>3%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>84.7 (visible) 99.2 (inconvenience)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(1993)</td>
<td>GSV</td>
<td>3%</td>
<td>n.a.</td>
<td>0.5 – 0.75 at different points</td>
<td>99 (patient) 89 (surgeon)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2000)</td>
<td>SFJ, GSV</td>
<td>3%</td>
<td>n.a.</td>
<td>n.a./5 - 10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2003)</td>
<td>Varices (perforating veins, GSV, SSV, iters)</td>
<td>3%</td>
<td>n.a.</td>
<td>Max. 2</td>
<td>78.53 ± 7.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2000)</td>
<td>GSV</td>
<td>3%</td>
<td>5.7/2-14</td>
<td>Max. 3</td>
<td>46.8 (after 1 session) 67.5 (after 2 sessions)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2002)</td>
<td>Telangiectasia Reticular veins Varicose veins without incompetence at the SFJ or popliteal junctions</td>
<td>0.5%</td>
<td>&lt; 1</td>
<td>n.a.</td>
<td>70 - 72</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2003)</td>
<td>Tributary</td>
<td>3%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>-</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>(2003)</td>
<td>GSV</td>
<td>3%</td>
<td>n.a./2 - 2.5</td>
<td>40</td>
<td>84</td>
<td>25.56</td>
<td>80</td>
</tr>
</tbody>
</table>

### Efficacy of the treatment means occlusion of the treated veins. GSV = great saphenous vein; SSV = small saphenous vein; SFJ = sapheno-femoral junction; n.a. = not available

In comparison with placebo, one study (2004; B) demonstrated the superiority of Aethoxysklerol liquid in the treatment of larger veins. Veins of 3 to 4 mm in diameter were treated with 2% and those of 5 to 6 mm with 3%. In comparison to the placebo group, 76.8% of the veins treated with polidocanol were completely occluded (P < 0.0001). Overall, in the polidocanol group the venoarterial flow index decreased from 1.45 ± 0.66 to 1.06 ± 0.2 (P = 0.05) at 12 weeks post-injection, compared to 1.24 ± 0.27 in the placebo group.

Long term efficacy of liquid sclerotherapy (with mostly 3% concentrations) of the anterolateral thigh vein (lateral accessory saphenous vein, without SFJ incompetence) were published (2003; D). In 5 patients additional 2% polidocanol was used and treatment could be repeated if necessary. In 24 cases a
second session after one week was necessary. Recurrent varicose veins were found after 6 months in 6% of cases, after one year in 18% (cumulative percentage), after two years in 28%, after three years in 36%, after four years in 46%, and after five years in 54%. Comparing the recurrence group with the non-recurrence group, after five years a significant difference was found only for the diameter of the original varicose vein and not for the length of the varicose vein, total amount of polidocanol used, amount of polidocanol used per cm varicose vein, number of injections, or circumference of the leg or patient age.

Four studies compared liquid sclerotherapy with foam sclerotherapy. The efficacy rate in three studies was relatively low: 40% after 3 weeks (2003; B), 17.5% after 1 year follow-up (2004; C), 35% at 3 weeks and 12% at 2 years (2008; B). However, foam efficacy was 84% after 3 weeks (2003; B), 67.6% after 1 year follow-up (2004; C), 85% at 3 weeks and 53% at 2 years (2008; B). The low success rates for liquid polidocanol in comparison to the previous described publications could be explained by the fact that no reinjections were allowed in these studies.

In comparison to another sclerosant (STS) a single treatment with 3% polidocanol resulted in an average success rate of 78.53 ± 7.39% in the polidocanol group and 82.38 ± 6.58% in the STS group after 6 months (2000; D). A significant difference was found in disappearance of varices (P = 0.0005), while reduction of oedemas, reduction of eczemas, healed ulcers, relief of night cramps and relief of pains, fatigue, heaviness was not significantly different between groups. Yet, more significant complications were observed with STS (local necrosis, hyperpigmentation and telangiectasias). In another study by the same authors (2003; D), the average cure rate for polidocanol was 67.47% after 6 months and 60.3% after 5 years. In the STS group this rate was 83.6% after 6 months and 78.54% after 5 years. Statistically significant differences (P < 0.05) were found only for the disappearance of varices and reduction of pain in favour of STS. Again, more significant complications (P < 0.001) were found with STS (local necrosis, hyperpigmentation and telangiectasias). Both studies demonstrated, that polidocanol leads to generally comparable results with STS but with fewer adverse events.

In comparison to surgery (ligation plus stripping or ligation alone), saphenous varices treated with 3% liquid Aethoxysklerol with a single session led to significant better results for surgery (1979; B). However, in all three treatment groups the results were worse after 3 years than after 3 months. Further analyses demonstrated that 70.5% of the patients were satisfied with the sclerotherapy treatment in comparison to 93% for the group 1 (radical surgery) and 84.8% for group 2 (mild surgery in combination with sclerotherapy). This is still considered a relatively good result for a single sclerotherapy treatment of large varicose veins.

Comparable results but with higher closure rates were found by Belcaro and colleagues in the treatment of incompetent GSV (2000; B). Surgery (ligation) leads to higher occlusion rates in comparison to a single treatment with 3% polidocanol. At 10 years, in the sclerotherapy group 18.8% of the SFJ were patent and incompetent, i.e. 81.2% of the veins were closed. In 43.8% of limbs the distal (below-knee) venous system was still incompetent.

Generally clinical trials comparing sclerotherapy with surgery showed that surgery leads to higher occlusion rates in comparison to a single treatment with polidocanol. However, if more sclerotherapy treatments are performed, the occlusion rates after sclerotherapy are higher and the difference to surgery is less pronounced. Nevertheless, better occlusion rates could be reached if polidocanol foam instead of liquid polidocanol is used (see below).

**Foam sclerotherapy of the GSV**

A total of 27 studies have been published to date discussing polidocanol treatment of the GSV (Table 8).
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Concentration</th>
<th>Diameter in mm Mean/Range</th>
<th>Foam volume in mL Mean/Range</th>
<th>Efficacy (%)</th>
<th>Foam &gt; 6 &lt; 24 month</th>
<th>Foam &gt; 24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2000)</td>
<td>GSV tributaries</td>
<td>1 - 3%</td>
<td>n.a. / 9 - 32</td>
<td>n.a. / 15 - 25</td>
<td>-</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>(2003)</td>
<td>GSV</td>
<td>3%</td>
<td>n.a. / 4 - 8</td>
<td>n.a. / max. 2.5</td>
<td>84</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>(2004)</td>
<td>GSV tributaries</td>
<td>3%</td>
<td>n.a. / 1%</td>
<td>3 / n.a.</td>
<td>-</td>
<td>-</td>
<td>67.6</td>
</tr>
<tr>
<td>(2005)</td>
<td>GSV telangiectasia</td>
<td>n.a. / n.a.</td>
<td>n.a. / n.a.</td>
<td>n.a. / n.a.</td>
<td>97</td>
<td>92.5</td>
<td>83.05</td>
</tr>
<tr>
<td>(2005)</td>
<td>GSV SSV tributaries</td>
<td>n.a. / n.a.</td>
<td>n.a. / n.a.</td>
<td>n.a. / max. 10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2006)</td>
<td>GSV SSV tributaries</td>
<td>3%</td>
<td>GSV: 8.5 / 6 -14</td>
<td>At the beginning up to 30 later on 10</td>
<td>90</td>
<td>89</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>SSV tributaries</td>
<td>1%</td>
<td>GSV: 6.5 / 6 - 14</td>
<td>SSV: 5.0 / 4 - 8</td>
<td>-</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td></td>
<td>recurrent veins</td>
<td>1%</td>
<td>GSV: 5.3 / 6 - 14</td>
<td>SSV: 5.0 / 4 - 8</td>
<td>-</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td>(2007)</td>
<td>GSV</td>
<td>1%, 3%</td>
<td>1%: 6.1 / 4, n.a.</td>
<td>1%: 5.3 / 1 - 10</td>
<td>-</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%: 6.4 / 4, n.a.</td>
<td>1%: 6.1 / 1 - 10</td>
<td>-</td>
<td>-</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td>(2008)</td>
<td>GSV</td>
<td>3%</td>
<td>7.6 ± 3.0 / n.a.</td>
<td>1 ml per mm diameter = max. 10.6</td>
<td>90.6</td>
<td>77.4</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of vein</th>
<th>Polidocanol Concentration</th>
<th>Diameter in mm Mean/Range</th>
<th>Foam volume in mL Mean/Range</th>
<th>Efficacy (%)</th>
<th>Foam &gt; 6 &lt; 24 month</th>
<th>Foam &gt; 24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2008)</td>
<td>GSV</td>
<td>3%</td>
<td>5.5 ± 1.2 / 4 - 8</td>
<td>n.a. / max. 2.5</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2008)</td>
<td>GSV</td>
<td>3%</td>
<td>7.5 ± 10 - 10.9</td>
<td>3.8 ± max. 5</td>
<td>69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2009)</td>
<td>GSV (ulcers)</td>
<td>3%</td>
<td>3%</td>
<td>n.a. / n.a.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>n.a. / n.a.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>n.a. / n.a.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2009)</td>
<td>GSV SSV tributaries perforating veins</td>
<td>0.5 - 3%</td>
<td>GSV: 6.3 ± 1.9 / 4 -16</td>
<td>4.5 ± 2.5 / 1 - 18</td>
<td>90.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 - 3%</td>
<td>SSV: 5.6 ± 1.9 / 4 - 12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2010)</td>
<td>GSV</td>
<td>1%</td>
<td>2%</td>
<td>n.a. / n.a.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% (10 % of treatments)</td>
<td>1%: 6.1 / 1 - 10</td>
<td>-</td>
<td>-</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>3%: 8.4 / max. 10</td>
<td>79.78</td>
<td>69.6</td>
<td>69.6</td>
<td>69.6</td>
</tr>
<tr>
<td>(2010)</td>
<td>GSV tributaries recurrent veins</td>
<td>3%</td>
<td>GSV: 5.8 ± 1.1 / 3.5 - 8.0</td>
<td>SSV: 5.1 ± 1.0 / 3.5 - 7.5</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>2% (10 % of treatments)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2011)</td>
<td>GSV tributaries recurrent veins</td>
<td>3%</td>
<td>GSV: 6.3 ± 1.7 / n.a.</td>
<td>GSV: 4.1 / 2.5 - 7.5, max. 8</td>
<td>-</td>
<td>-</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>recurrent veins: 0.05</td>
<td>SSV: 3.6 ± 1.2 / 2.5, max. 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(2011)</td>
<td>GSV SSV tributaries recurrent veins</td>
<td>3%</td>
<td>GSV: 5.8 ± 4 / 6</td>
<td>SSV: 5.8 ± 3.5 - 6.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>3%</td>
<td>7 / 8 - 10</td>
<td>-</td>
<td>GSV: 69 SSV: 69</td>
<td>-</td>
</tr>
<tr>
<td>(2012)</td>
<td>GSV SSV tributaries recurrent veins</td>
<td>3%</td>
<td>GSV: 5.6 ± 2.7 / 0.5-11</td>
<td>GSV: 5.6 ± 2.7 / 0.5-11</td>
<td>82.7/87</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>3%</td>
<td>SSS: 2.9 ± 1.5 / 4 - 8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>n.a. / n.a.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Efficacy means closure rate of varicose veins after the treatment and is given in %. GSV = great saphenous vein; SSV = small saphenous vein)
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj. PL 20685/0042, 0039-0040, 0043 and 0041

Polidocanol 3% foam or liquid was used in 21 of the studies, 1% polidocanol in 8 of the studies, and 2 studies did not mention the used polidocanol concentration. Independent of the used concentration, the foam volume for the treatment of the GSV ranged from 1 to 20 mL (mean 5.19). The maximum volume of polidocanol used in 18 out of 27 studies was restricted to 10 mL. In three studies the maximum foam volume did not exceed 15 mL and in three other studies it was below 20 mL. The proposed Aethoxysklerol SmPC is currently recommending a maximum foam dosage of 10 mL.

Four of the 27 studies listed above investigated the efficacy of 1% polidocanol foam versus 3% foam in the treatment of the GSV (2010, 2007, and 2012b). It was found at 6 months that abolition of venous reflux occurred in 69% of the patients in the polidocanol 1% foam group and in 85% of the patients in the polidocanol 3% foam group (2010). The respective positive outcome at 3 years was 79% for the 1% group and 78% for the 3% group (including additional injections at 6 months). It was concluded that 1% polidocanol can be as effective as 3% if additional injections are used. Using a single injection 3% was superior to 1% polidocanol (2010; B).

Another study found no significant difference in effectiveness between 1% and 3% polidocanol foam after a single treatment for unilateral GSV reflux (2012b; C). Three months after the treatment complete occlusion was demonstrated in 56.3% of the 1% foam patients and 66.7% of the 3% foam patients. Additionally, partial recanalization with no reflux was observed in 25.0% of the 1% foam patients and 27.7% of the 3% foam group. Although no significant difference in effectiveness between the two foam strengths was demonstrated in this study, the 3% polidocanol foam strength appeared to better facilitate occlusion and elimination of reflux. The authors concluded that 3% polidocanol foam may be a better sclerosant than the 1% strength, even though both, the 1% and 3% strengths are effective for treatment of superficial venous insufficiency.

Overall, the studies have demonstrated the efficacy of polidocanol foam 1% and 3% in the treatment of the GSV, with slightly better occlusion rates obtained in the short term after using polidocanol 3% foam compared with 1% foam. Three out of the four studies found no significant difference between the two concentrations, although two of these concluded that overall 3% polidocanol foam gave better results than the 1% strength. This is also reflected by the high number of studies using 3% instead of 1% polidocanol foam for the treatment of the GSV (20 studies and 8 studies respectively).

Additional compression therapy after sclerotherapy with polidocanol 1% or 2% in patients with incompetent GSVs and SSVs showed no difference in occlusion rate in one study (2010; B). However, the abolition of venous reflux and occlusion of the vein was seen in 100% of the cases in both groups.

In terms of timing, in general, analysis of the published studies listed above investigating the use of polidocanol for the treatment of GSV incompetence shows that the majority of the polidocanol-treated GSV were occluded within the first 6 months, with good success rates continuing after 24 months post-treatment. 17 studies provided short term efficacy results (Table 9). 11 studies showed efficacy of more than 80% (2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012 and 2013). Apart from one study (2012b) the occlusion of the treated veins in the other studies was greater than 65%.
However, the occlusion rate can be further improved by additional treatments (2006; C). Complete occlusion of the GSV (defined as closure of saphenous trunk or at least 85% of the varicosities) 6 weeks after ultrasound-guided polidocanol 3% treatment was 66% after a single treatment and 85.6% after two treatments.

Table 9: Short-term (≤ 6 months) and mid-term efficacy (> 6 < 24 months) after foam treatment of the GSV.

<table>
<thead>
<tr>
<th>Study</th>
<th>POL concentration</th>
<th>Follow-up</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term (≤ 6 months) efficacy results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2003)</td>
<td>3%</td>
<td>3-weeks</td>
<td>84</td>
</tr>
<tr>
<td>(2005)</td>
<td>n.a.</td>
<td>6 weeks</td>
<td>97</td>
</tr>
<tr>
<td>(2006)</td>
<td>1% 3%</td>
<td>6 months</td>
<td>90</td>
</tr>
<tr>
<td>(2007)</td>
<td>1% 3%</td>
<td>6 weeks</td>
<td>66 (single), 85.6 (two)</td>
</tr>
<tr>
<td>(2008)</td>
<td>3%</td>
<td>3 weeks</td>
<td>86</td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>6 months</td>
<td>90.6</td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>3 weeks</td>
<td>89</td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>6 months</td>
<td>78</td>
</tr>
<tr>
<td>(2009)</td>
<td>0.5 - 3%</td>
<td>3 weeks</td>
<td>90.3</td>
</tr>
<tr>
<td>(2010)</td>
<td>1% 3%</td>
<td>6 months</td>
<td>69</td>
</tr>
<tr>
<td>(2010)</td>
<td>1% or 2% (10 % of treatments)</td>
<td>1 month</td>
<td>100</td>
</tr>
<tr>
<td>(2011)</td>
<td>1%</td>
<td>1 month</td>
<td>100</td>
</tr>
<tr>
<td>(2012)</td>
<td>1%, 2%, 3%/ 1%, 2, 3%</td>
<td>6 weeks</td>
<td>82.7 (air) 87.3 (CO₂)</td>
</tr>
<tr>
<td>(2012a)</td>
<td>1%</td>
<td>6 months</td>
<td>58.8</td>
</tr>
<tr>
<td>(2012b)</td>
<td>1% 3%</td>
<td>3 months</td>
<td>66.3 66.7</td>
</tr>
<tr>
<td>(2013)</td>
<td>3%</td>
<td>2 weeks</td>
<td>97.9</td>
</tr>
<tr>
<td><strong>Mid-term (&gt; 6 &lt; 24 months) efficacy results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2003)</td>
<td>3%</td>
<td>1 year</td>
<td>80</td>
</tr>
<tr>
<td>(2004)</td>
<td>3%</td>
<td>1 year</td>
<td>67.6</td>
</tr>
<tr>
<td>(2005)</td>
<td>n.a.</td>
<td>1 year</td>
<td>92.5</td>
</tr>
<tr>
<td>(2005)</td>
<td>1% 3%</td>
<td>1 year</td>
<td>89</td>
</tr>
<tr>
<td>(2007)</td>
<td>1% 3%</td>
<td>1 year</td>
<td>69.5 80.1</td>
</tr>
<tr>
<td>(2008)</td>
<td>3%</td>
<td>1 year</td>
<td>77.4</td>
</tr>
<tr>
<td>(2010)</td>
<td>1% 3%</td>
<td>1 year</td>
<td>82 90</td>
</tr>
<tr>
<td>(2012)</td>
<td>3%</td>
<td>1 year</td>
<td>69</td>
</tr>
<tr>
<td>(2013)</td>
<td>3%</td>
<td>1 year</td>
<td>72.2</td>
</tr>
<tr>
<td>(2013)</td>
<td>3%</td>
<td>1 year</td>
<td>86</td>
</tr>
<tr>
<td>(2013)</td>
<td>3%</td>
<td>1 year</td>
<td>83.7</td>
</tr>
</tbody>
</table>

Efficacy of the treatment means occlusion of the treated veins. n.a. = not available; POL = polidocanol, single = single treatment; two = two treatments

Investigators (2009; B) compared the efficacy of polidocanol foam sclerotherapy with surgical treatment after 6 months. Severity scores of pain, oedema and inflammation were statistically significantly reduced in both patient groups at 180 days after treatment compared with pre-treatment (P < 0.005). The saphenous vein was obliterated in 90% of the surgery group compared to 78% in the foam sclerotherapy group without a statistically significant difference between the two groups. Overall, all studies demonstrated very good closure rates in the short term.
Efficacy results after 1 year after treatment of the GSV were demonstrated in 11 studies. In 6 studies the efficacy was equal or above 80% (2003, 2005, 2005, 2010, 2013, 2011 and 2013). In the other 5 studies, the efficacy was above 65% (2004, 2007, 2008, 2012 and 2013).

One study demonstrated an occlusion rate for ultrasound-guided foam sclerotherapy after one year of 72.7%, which, however, was significant lower than the occlusion rates found for endovenous laser ablation (88.5%) and surgery 88.2% (P < 0.001) (2013; B). No differences in reported quality of life between the three groups was found at one year post-treatment. The lowest number of adverse events was found in the sclerotherapy group (5 cases), followed by ablation (7 cases) and surgery (11 cases).

Long-term results must also be considered when discussing efficacy of Aethoxysklerol treatment in order to minimise the need for repeat treatments. Nine studies identified in the literature have analysed the long-term efficacy of polidocanol treatment (Table 10).

Table 10: Long-term efficacy results (≥ 24 months) after foam treatment of the GSV

<table>
<thead>
<tr>
<th>Study</th>
<th>POL concentration</th>
<th>Follow-up</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2000)</td>
<td>1% and 3%</td>
<td>3-years</td>
<td>81 (GSV and SSV)</td>
</tr>
<tr>
<td>(2005)</td>
<td>n.a.</td>
<td>2-years</td>
<td>83.05 (superficial branches)</td>
</tr>
<tr>
<td>(2005)</td>
<td>3%</td>
<td>2-years</td>
<td>88</td>
</tr>
<tr>
<td>(2007)</td>
<td>1%</td>
<td>2-years</td>
<td>68</td>
</tr>
<tr>
<td>(2007)</td>
<td>3%</td>
<td>3-years</td>
<td>69</td>
</tr>
<tr>
<td>(2008)</td>
<td>3%</td>
<td>2-years</td>
<td>53</td>
</tr>
<tr>
<td>(2010)</td>
<td>1%</td>
<td>3-years</td>
<td>79</td>
</tr>
<tr>
<td>(2011)</td>
<td>1% and 3%</td>
<td>2-years</td>
<td>76 (one vessel was treated)</td>
</tr>
<tr>
<td>(2012)</td>
<td>3%</td>
<td>2-years</td>
<td>65</td>
</tr>
<tr>
<td>(2011 and 2013)</td>
<td>3%</td>
<td>3-years</td>
<td>76</td>
</tr>
</tbody>
</table>

Efficacy of the treatment means occlusion of the treated veins. GSV = great saphenous vein; POL = polidocanol; SSV = small saphenous vein

The closure rates after 2 years or longer were generally slightly below the rates obtained after 6 months, but still high. Three studies could demonstrate occlusion rates above 80% (2000, 2005, 2005) and only 2 studies found occlusion rates smaller than 65%, but still above 50% (2008, 2011). One study analysed the efficacy of 3% foam vs. 3% liquid polidocanol sclerotherapy for the single treatment of incompetent saphenous veins (2008; B). Success rate (no recanalization) at 2 years was 53%. This low success rate after 2 years is in contrast to all other studies published and was suggested by the authors to be due to the fact that no reinjections were allowed and only a low total dosage of 2.5 mL was administered.

Overall, all studies with foam sclerotherapy demonstrate good efficacy results after a single treatment. However, the occlusion rate can be greatly increased when patients receive multiple injections. Furthermore, with respect to long term effects of sclerotherapy, it has to be considered that varicose veins are a chronic disease; further treatment sessions will usually be necessary to control the condition. Repeated treatments are possible with liquid or foam sclerotherapy.

Foam sclerotherapy of the SSV

The efficacy of polidocanol foam sclerotherapy for SSV treatment has been investigated in 10 studies found in the literature. In 3 of the 10 studies 3% polidocanol was used; 3 studies used 1% polidocanol and 1 study did not mention the polidocanol concentration tested. In 3 studies both 1% and 3% polidocanol was used. Independent of the used concentration, the foam volume across all studies for the treatment of the SSV ranged from 1 to 18 mL. However, the mean volume recorded in those studies in which the foam volume was specified was 4.25 mL. 6 out of 10 studies used not more than 10 mL of foam. In one study the maximum foam volume did not exceed 15 mL and another study used up to 20 mL. The efficacy results from the studies are summarised in Table 11.
Table 11: Short-term (≤ 6 months), mid-term (> 6 < 24 months) and long-term (≥ 24 months) efficacy results of treated SSVs with polidocanol foam.

<table>
<thead>
<tr>
<th>Study</th>
<th>POL concentration</th>
<th>Follow-up</th>
<th>Efficacy in %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term</strong> ≤ 6 months efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2006)</td>
<td>1% and 3%</td>
<td>6-weeks</td>
<td>95.6</td>
</tr>
<tr>
<td>(2009)</td>
<td>3</td>
<td>6 months</td>
<td>90%</td>
</tr>
<tr>
<td>(2009)</td>
<td>0.5 - 3%</td>
<td>3 weeks</td>
<td>93.4</td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>6-weeks</td>
<td>85.1%</td>
</tr>
<tr>
<td>(2010)</td>
<td>1% and 2%</td>
<td>4 weeks</td>
<td>100</td>
</tr>
<tr>
<td>(2011)</td>
<td>1% (1 patient received 2%)</td>
<td>4 weeks</td>
<td>100</td>
</tr>
<tr>
<td>(2012)</td>
<td>3%</td>
<td>6 weeks</td>
<td>85.7%</td>
</tr>
<tr>
<td><strong>Mid-term</strong> &gt; 6 &lt; 24 months efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>1 year</td>
<td>77.7%</td>
</tr>
<tr>
<td>(2012)</td>
<td>3%</td>
<td>1 year</td>
<td>58 complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 near-complete</td>
</tr>
<tr>
<td><strong>Long-term</strong> ≥ 24 months efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2005)</td>
<td>n.a.</td>
<td>2 years</td>
<td>83.05</td>
</tr>
<tr>
<td>(2005)</td>
<td>1%</td>
<td>2 years</td>
<td>88</td>
</tr>
<tr>
<td>(2009)</td>
<td>3%</td>
<td>2 year</td>
<td>74.4%</td>
</tr>
</tbody>
</table>

Efficacy of the treatment means occlusion of the treated veins. n.a. = not available; POL = polidocanol

All seven studies describing short term (< 6 months) occlusion rates for the sclerotherapy of the SSV reported rates above 85% (2006, 2009, 2009, 2009, 2010, 2011 and 2012). As with the treatment of the GSV, the efficacy declines after 1 and 2 years follow-up but with exception of the 1 study describing mid-term (> 6 < 24 months) occlusion rates (2012; C), all studies showed occlusion rates above 70%. However, the single study describing mid-term (> 6 < 24 months) occlusion rates, reported 58% complete and 16% near complete obliteration of 49 SSVs one year after catheter-directed polidocanol 3% foam sclerotherapy (2012; C).

Overall, efficacy of the sclerotherapy procedures investigated in these studies was very high at 6 months, and still very good at 24 months. Further on, these studies showed that the efficacy of SSV treatment with polidocanol foam was comparable with the efficacy of GSV treatment.

Comparison of therapeutic options for treatment of varicose veins

Several meta-analyses and reviews have been published over the past few years that have investigated the efficacy of polidocanol sclerotherapy (foam or liquid) in comparison with other treatment methods.

One Cochrane systematic review aimed to determine whether sclerotherapy is effective in terms of symptomatic improvement, recurrence and cosmetic appearance (2006; F). Evidence from randomised clinical trials suggested 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 of different sizes. In this review, the authors concluded that the evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to treatment of recurrent varicose veins and thread veins. However, only studies published up to October 2006 were considered and more recently published studies were not included in this systematic review.

Other authors (2011; F) assessed the effectiveness and safety of sclerosing agents in the treatment of telangiectasias of the lower limbs. It included randomised or quasi-randomised controlled trials comparing (liquid) sclerotherapy with a normal saline placebo, no treatment or an alternative sclerotherapy regimen. There was no evidence suggesting superior efficacy of any one sclerosant over another, but there was evidence of superiority of sclerotherapy to placebo.
A systematic review and meta-analysis, (2015; A) investigated and compared the anatomical success rates and complications of various treatments for SSV incompetence. The review included 49 articles (5 randomized controlled trials, 44 cohort studies) and reported a pooled success rate of 58.0% (95% CI 40.9% to 75.0%) for surgery in 798 SSVs, 98.5% (95% CI 97.7% to 99.2%) for EVLA in 2950 SSVs, 97.1% (95% CI 94.3% to 99.9%) for Radiofrequency ablation (RFA) in 386 SSVs, and 63.6% (95% CI 47.1% to 80.1%) for UGFS in 494 SSVs. One study reported results of Mechanochemical endovenous ablation (MOCA), with an anatomical success rate of 94%. Neurologic complications were most frequently reported after surgery and thermal ablation. Deep venous thrombosis was a rare complication (0% to 1.2%). It was advised that endovenous thermal ablation (EVLA/RFA) should be preferred to surgery and foam sclerotherapy in the treatment of SSV incompetence. However, the authors concluded that although the data on nonthermal techniques in SSV are still sparse, the potential benefits, especially the reduced risk of nerve injury, might be of considerable clinical importance.

Different endovenous therapies of lower extremity varicosities were analysed in another meta-analysis (2009; A). After 3 years, the estimated pooled success rates (with 95% confidence intervals [CI]) for stripping, foam sclerotherapy, radiofrequency ablation, and laser therapy were found around 78% (70%-84%), 77% (69%-84%), 84% (75%-90%), and 94% (87%-98%), respectively. After adjusting for follow-up, foam therapy and radiofrequency ablation were as effective as surgical stripping. Endovenous laser therapy was significantly more effective compared with stripping, foam therapy, and radiofrequency ablation. The authors concluded that in the absence of large, comparative randomised clinical trials, the minimally invasive techniques appear to be at least as effective as surgery in the treatment of lower extremity varicose veins.

In general, the reviews confirmed the role of polidocanol foam sclerotherapy as therapeutic alternative in the treatment of varicose veins. Particularly, sclerotherapy in general has the advantage over surgical procedures or endovenous laser therapy that it can be repeated several times and can reach areas that are difficult to treat surgically, for example regions of the limb affected by lipodermatosclerosis, where incisions tend to heal slowly.

Clinical information relevant to dosing recommendations
The publications discussed in the above sections are the basis for the dosage regimens for Aethoxysklerol liquid and foam treatment stated on the proposed SmPC.

The recommended posology in section 4.2 of the SmPC reflects the findings of the relevant studies, although it is noted that there was significant variation in the doses and methods used across trials.

The findings discussed above are also in line with advice from the guidelines of the German Society of Phlebology (2012) and the European guidelines for sclerotherapy in chronic venous disorders (2014), recommending the use of liquid polidocanol in the therapy of smaller varicose veins (as well as telangiectasias and reticular veins), and the use of polidocanol foam therapy for the treatment of larger blood vessels and tributaries.

Concerning the foam formulation a maximum application of 10 mL foam per session and day is considered as the maximum dose, based on the second European consensus meeting on foam sclerotherapy and guidelines (2012, 2014). However, many studies used lower dosage which were considered safe at the time of study design (which was set at 6-8 mL foam per session and day according to the first European consensus meeting on foam sclerotherapy, 2004). However, results of later studies demonstrated that higher volumes might lead to better long-term results; particularly when considering the very good results of comparable studies which applied higher volumes of foam and still displaying equally good safety profiles.

IV.5 Clinical Safety
The safety review is based on the available literature, also supported by analysis of relevant spontaneous case reports collected by Kreussler & Co. GmbH, the current product licence holder in several countries worldwide.
When reviewing and assessing the relevant publications with regards to safety information on the use of polidocanol in liquid or foam sclerotherapy treatment, the obtained literature sources have been grouped according to their specific objectives and content. Most concern published randomised clinical trials or controlled clinical trials.

**Extent of exposure**
For treatment with liquid sclerotherapy 19 studies (including those, where efficacy and safety of liquid and foamed polidocanol was compared) were available for review. A total of 2172 individuals were exposed to liquid polidocanol in different concentrations and volumes. Additionally, in one study 16,804 limbs were treated with liquid sclerotherapy (1995). The maximum amount of polidocanol applied did not exceed the recommended maximal dose of 2 mg/kg body weight for the liquid form.

For treatment of foam sclerotherapy 27 studies (including those, where efficacy and safety of liquid and foamed polidocanol was compared) are available for dosage analyses. A total of 4291 individuals were exposed to polidocanol foam in different concentrations and volumes. Additionally, in one study 500 limbs were treated with foam sclerotherapy (2000). The maximum amount of polidocanol applied exceeds the recommended maximal dose of 10 mL of foam in 7 studies.

**Demographics and other characteristics of the study population**
With the exception of one study where the patient age ranged from 17 years to 78 years (2012), all subjects in the studies were 18 years or older. Also patients had a mean body weight ranging from 55.75 to 77.5 kg and a BMI ranging from 22.4 to 26.3. There was a higher proportion of female patients in all studies, which may reflect a genetic disposition of women for leg varices.

In most studies, subjects were excluded if they had a history of DVT or active DVT, superficial thrombosis, suffered from thrombophlebitis, were taking anticoagulants or had a hypercoagulable states/thrombophilia. They were also ineligible if they were pregnant or had severe allergies/hypersensitivity to polidocanol. Patients with a history of heart abnormalities/cardiac diseases or arterial diseases were also often excluded.

**Adverse reactions**
The relevant European guidelines (2012 and 2014) provide comprehensive information regarding the general adverse reactions with sclerotherapy treatment with polidocanol liquid or foam, mainly derived from the clinical practice and published literature. According to those, the main adverse reactions and risks associated with polidocanol sclerotherapy comprise anaphylaxis, allergic reactions, stroke and Transient Ischemic Attack (TIA, isolated cases), headaches and migraines, skin necrosis, hemotoma, ecchymosis, superficial phlebitis, (hyper)pigmentation, matting, urticaria, nerve damages, scintillating scotomas, deep vein thrombosis, pulmonary embolism (isolated cases), chest tightness (very rare), dry cough (very rare), visual disturbances (very rare), pain on injection, vaso-vagal reactions, nausea, metallic taste, inductions, and Embolia cutis medicamentosa (very rare). All these reactions can occur to different extent with most cases exhibiting just minor reactions. Overall, the authors emphasise that the complications and adverse reactions are in general mild and that the general risk for serious adverse reactions is very low.

The adverse reactions more often observed after microfoam sclerotherapy (compared with liquid sclerotherapy) are transient neurological symptoms, visual disturbances, migraine, distal deep vein thrombosis, sensory nerve injury, and skin necrosis (2008, 2014). It was demonstrated, in a prospective multicentre study, that the transient visual disturbances occurring after foam sclerotherapy correspond to migraine with aura (2010).

Published data from an extensive safety registry in France evaluated the polidocanol safety profile in a large patient population. In the course of this registry, approximately 12,173 sessions of sclerotherapy, were analysed: 5,434 performed with liquid, 6,395 with foam and 344 using both (2005). The results showed a very low number of adverse reactions (in 49 out of 12,173 sessions), of which 12 were with liquid and 37 with foam sclerosants. Regarding the sclerosing agent it has to be clarified that there are only three sclerosing agents in common use in France [Aethoxysklerol (polidocanol), Trombovar (STS), and Scleremo (chromated glycerine)] with polidocanol holding a market share of 75%. Therefore, it is
reasonable to assume that most of the sclerotherapy sessions were conducted with polidocanol. Out of the 49 reported adverse events the most frequent events were 20 cases of visual disturbances (16 cases with foam and 4 cases with liquid administration) all resolving without sequelae. A femoral vein thrombosis was the only serious adverse. The results of this registry led to the conclusion that sclerotherapy with foam and liquid polidocanol is a safe treatment option for all types of varicose veins.

A follow-up registry initiated by Kreussler & Co. GmbH recorded the long term adverse reactions in patients of the first registry over a period of 4 years (2010). Among 1,605 patients having received at least one Aethoxysklerol injection (foam or liquid) and 6,284 treatment sessions (4,298 with foam) only 51 adverse reactions were reported (less than 1% of the treatment sessions). 5 adverse reactions observed after injection with liquid polidocanol were 1 cramp, 2 inflammatory reactions, 1 case of pigmentation, and 1 visual disturbance. Of the 46 adverse reactions which occurred after the application of polidocanol foam the most common reactions were 13 cases of visual disturbances. 8 muscular vein thromboses were recorded as well as 1 DVT occurring in a patient with thrombophilia (heterozygote Factor V Leiden). The patient’s medical history revealed a second DVT with no relation to any sclerosing agent and despite the prescription of anticoagulants the patient stopped his medication while sclerotherapy was performed. Overall polidocanol foam and liquid confirmed the good safety profile shown in the initial registry.

In general, adverse events reported for liquid sclerotherapy in studies include pain, injection site warmth, haematoma, injection site erythema, neovascularization, phlebitis/thrombophlebitis, induration/mild tension, bullous lesion, tender clots, cramping, soreness, pigmentation/hyperpigmentation, itching/urtication, dyspnoea/respiratory difficulties, transient ischemia, injection site discomfort, tingling, paraesthesia, visual disturbances/scotoma, headache/migraine, dry cough, chest pressure, vaginal discomfort, circulatory problems, dizziness and nausea.

Deaths
In the reviewed published studies, no subject died after treatment of varicose veins with polidocanol.

Other serious adverse events (SAEs)
The following SAEs were reported in the published studies with polidocanol liquid: allergic reactions, DVT and hyperventilation. For foam sclerotherapy reported SAEs were DVT, pulmonary embolism, dyspnoea/respiratory difficulties, transient ischemia attack (TIA), stroke and anaphylaxis/allergic reactions.

Allergic reactions. Authors estimated the probability of allergic reactions during and after sclerotherapy with polidocanol to 1:10000 (quoting other investigators) and pointed out that three out of four patients developing an allergic reaction had a past history of allergies (1995).

Deep vein thrombosis. Although very rare, DVT is a serious complication due to the risk of pulmonary embolism. It appears that DVT during treatment of varicose veins is mainly related to either improper treatment (e.g. volume of sclerosant too high, insufficient pre-treatment diagnosis) or to an underlying hypercoagulable state or accompanying risk factors for DVT (1993). In a well-designed study with 710 patients treated with either polidocanol foam (Varithena), surgery or conventional sclerotherapy (liquid or foam) eleven cases of DVT were observed at the beginning of the study (2006). After minimizing the application volume and stopping the foam column at 5 cm distal to the SFJ no further DVTs were detected. There is currently a contraindication in the proposed Aethoxysklerol SmPC for use in patients
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln.  
for inj.  

at high risk of thrombosis.

**Stroke and transient ischaemic attack.** A primary concern with the use of all foam sclerotherapy treatments (not just polidocanol-based) is the possibility of foam bubbles migrating from the injection site to other sites. In 2005 in a multicentre registry authors (2005) demonstrated the low complication rates of both liquid and foam sclerotherapy in a large patient population. Although rates were low, more complications such as visual disturbances were observed with the foam variant compared with the liquid form. Concerns have been raised over possible more serious CNS complications specifically from foam sclerotherapy treatment.

During foam sclerotherapy, bubbles can migrate from the site of application to the cardiac cavities (2008, 2008, 2009 and 2009). An existing patent foramen ovale (PFO) with right to left shunt might allow bubbles to enter the left circulatory system and possibly lead to microembolisms in combination with neurologic symptoms. The occurrence of such visual and neurologic adverse reactions in patients with a PFO and how to prevent these complications is a topic under discussion in the scientific community.

In 2009, a study evaluated patients with detectable gas emboli in the middle cerebral artery following foam sclerotherapy treatment with polidocanol (2009) for SSV and GSV incompetence. Out of 82 patients treated in this study, 61 patients had right-to-left shunt, and 57 had middle cerebral artery emboli detected during the procedure (92.9%). Despite these findings, no patients had MRI lesions, neurological or visual field disturbances or elevated cardiac markers. The author commented that, on the basis of this observation, the presence of bubbles in the circulation doesn’t always result in symptoms or ischaemic events, and these effects depend on various factors such as treatment parameters and the individual’s personal risk factors at the time of the procedure.

In 2012, an author reviewed published reports of sclerotherapy studies and commented that 13 serious neurological adverse reactions including TIA and stroke (not permanent) have been reported following either liquid and foam-based sclerotherapy (4 and 9 respectively) since 1994. The author discussed possible mechanisms for post sclerotherapy stroke, and hypothesised that the most likely cause is paradoxical embolism, which itself may be caused by the release of cell-derived by-products (e.g. endothelin-1), though this has not yet been proven clinically. The author further commented that right-to-left shunt and PFO was the most consistent risk factor, although the incidence of TIA associated with sclerotherapy is much lower than the existence rate of PFO in the general population (30% prevalence). Despite the lack of clear association, as a precaution a contraindication is currently proposed for the use of Aethoxysklerol foam in patients with known right-to-left shunt (Aethoxysklerol SmPC section 4.3).

The author also commented that patients with a past history of cryptogenic stroke or recurrent classic migraine (with aura) following sclerotherapy were at higher risk of neurological adverse reactions following future treatment. However, the incidence rate of TIA following sclerotherapy is still very low amongst patients with these pre-existing conditions. As a precaution, a warning regarding the use of foam in patients with previous history of visual or neurological symptoms following previous sclerotherapy treatment is included in the SmPC (Aethoxysklerol SmPC section 4.4).

In relation to stroke prevention the German consensus on foam sclerotherapy also recommends limiting the maximum dose of foam used per session to 10 mL (2004, 2008) to minimise thrombosis-related adverse reactions. This dose is currently proposed as the maximum Aethoxysklerol foam dosage in any one session, irrespective of patient’s body weight and polidocanol concentration.

The 2008 German consensus on foam sclerotherapy (2008) recommended several measures to reduce the adverse reactions associated with foam sclerotherapy, based on the experience of a number of practitioners regularly conducting foam sclerotherapy treatment. This is further supported by subsequent consensus and guidance documents previously discussed. Ultrasound guidance is advised to assess the foam distribution following injection, and in the proposed SmPC duplex ultrasound guidance for the treatment of non-visible veins is recommended.

Immediate compression of the leg, leg movement or Valsalva manoeuvre could potentially cause fresh foam to migrate to where no treatment is needed (2008). Hence the proposed SmPC advises that there should be no compression for 5-10 minutes on the treated area following foam sclerotherapy (compared with immediate compression following liquid treatment), and that the treated leg should be
immobilised for 2-5 minutes with no muscle activation. One author suggested leg elevation as a possible solution for minimising bubble migration, and the SmPC also recommends placing the leg horizontally or elevated at approximately 30° - 45° above the horizontal for injection.

Visual disturbances and migraine. Another reaction, visual disturbances are more common after foam sclerotherapy compared with liquid sclerotherapy, with around 1.5% incidence rate for the former, and also demonstrated through clinical observation and MRI that these were caused by migraine with aura, and not TIA (2010).

Tissue necrosis. Case reports describing also complications that are rare but severe comprise the adverse reactions after intra-arterial injection. Although extremely rare, inadvertent intra-arterial injections of Aethoxysklerol possibly constitute the worst complication in sclerotherapy treatment since it induces massive tissue damage with all its consequences. For the most severe outcome, an amputation following gangrene in the forefoot that occurred in the area of the inner malleolus immediately after inadvertent intra-arterial injection of the sclerosant, was reported (1976). One has to emphasise that the probability rate of amputations is lower in sclerotherapy when compared with surgical interventions (1991).

Other significant adverse events
Hypermigration constitutes one of the most common adverse event of sclerotherapy with any sclerosing agent, not only with Aethoxysklerol (1987).

Further information
Subsequent to submission of the dossier, the Applicant submitted information about a new safety signal related to reports of ‘stress cardiomyopathy’ (Takotsubo cardiomyopathy) associated with the use of polidocanol (and other agents) during sclerotherapy:

7 cases reported of diagnosed or suspected cases of Tako Tsubo cardiomyopathy" (TTC) or "stress cardiomyopathy following sclerotherapy with lauromacrogol 400. In general, based on the submitted information, no specific pattern is evident, in terms of medical history of the patients or other parameters and characteristics that might help identify patients at higher risk or help suggest preventive measures. Most cases concerned middle-aged/older women but this probably reflects the likely target patient group, expected to undergo sclerotherapy for varicose veins. There is no clear relationship to dose, concentration used or site of injection. In some cases possible confounding/contributing factors cannot be excluded; yet in most reports a relationship to Aethoxysklerol sclerotherapy seems probable. The events appear to be very rare, but the fact that despite the very long history of lauromacrogol 400 in sclerotherapy of varicose veins the first case was reported only in 2006, raises questions about underreporting, and patients/‘physicians’ awareness.

Stress cardiomyopathy is already stated as an undesirable effect in the SPC/PIL of Aethoxysklerol in the following European countries: Austria, Germany, Hungary, Netherlands, Poland, Portugal, and Spain. In all these European countries the addition of stress cardiomyopathy was approved following a full assessed Type II. Stress cardiomyopathy has been sufficiently addressed in the product information (SPC/PIL) for the proposed products.

Safety in special groups and conditions
A safety issue of importance is the management of thrombophilic patients. Previous studies (2005, 2009) suggested that in the three most common forms of thrombophilia sclerotherapy can be performed safely in combination with thromboprophylaxis. Thromboembolic prophylaxis during foam sclerotherapy of trunk varicose veins is also advised in patients not suffering from coagulopathies (2009). However, this is still a matter of debate. Others do not recommend thromboprophylaxis in patients not having any risk factors for thrombosis (2008). In a study, patients with a history of DVT and/or pulmonal embolism (including patients with the post-thrombotic syndrome) could be effectively treated with polidocanol without reports of DVTs, symptomatic pulmonary embolism, or neurological deficit (2013). Currently as a precaution, in the Aethoxysklerol SmPC there is a contraindication for the use of Aethoxysklerol in patients with thromboembolic disease or a high risk of thrombosis.

Renal and liver effects
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. PL 20685/0042, 0039-0040, 0043 and 0041

No published information is available on the effects of polidocanol on liver or renal function. However, non-clinical data suggests some effects on kidney and liver.

Drug interactions
Lauromacrogol 400 is a local anaesthetic. When combined with other anaesthetics, there is a well-established risk of an additive effect of these anaesthetics on the cardiovascular system.

Use in pregnancy and lactation
Pregnant women were excluded in 20 of 32 published studies mentioning exclusion criteria. There are no adequate published data regarding the use of Aethoxysklerol in pregnant women. Studies in animals showed reproductive toxicity, although no teratogenic potential. Therefore, it is currently proposed that Aethoxysklerol must not be used during pregnancy unless clearly necessary. Regarding breastfeeding, investigations on the possible excretion of polidocanol in the breast milk have not been performed/published in humans. Again, it is proposed that if sclerotherapy is necessary during breastfeeding, it is advisable to suspend breast-feeding for 2-3 days.

Safety information from post-marketing data
Further safety information from post-marketing data is derived from the pharmacovigilance system of Kreussler & Co. GmbH. During the period from January 2004 (when Kreussler & Co. GmbH started collecting safety data for submission of PSURs to regulatory authorities) through to November 2015 approximately 31.4 million patients (or 2.6 million patients per year) have been treated with Aethoxysklerol in the treatment of leg varices (estimation based on sales of 60.6 million ampoules for the treatment of leg varices worldwide).

During this period Kreussler & Co. GmbH received a total of 940 individual case safety reports (ICSRs) from spontaneous reporting, including competent authorities and literature. Those included 340 reports received through the Japanese Early Post-Marketing Phase Vigilance Program during the first 3 years after marketing authorisation.

This accounts for a rate of one adverse reaction per approx. 50,500 treated patients. Out of the 940 ICSRs received, 57 were classified as serious and unlisted (unknown), 82 as serious and known and 801 as non-serious. The most often reported reactions were: localized venous disorders (thrombophlebitis/phlebitis/venous thrombosis limb), pigmentation disorders (hyperpigmentation/discolouration), and skin reactions (urticaria/pruritus/blister/rash/erythema/dermatitis). None of the unknown reactions have been reported in such a number or with such a convincing evidence of causality that their implementation into the product company core safety information was considered as necessary.

Choice of maximal dose in relation to safety
The SmPCs currently proposes a maximum daily dose for the use of Aethoxysklerol liquid in sclerotherapy of no greater than 2 mg/kg of body weight per day. When applied as foam a maximum daily dose of 10 mL foam per session is recommended which is in line with the current sclerotherapy (2012 and 2014) and NICE guidelines (National Institute for Health and Care Excellence, 2013a and 2013b).

It is true that the maximum proposed dosages recommended in the guidelines are based on results collated from preclinical trials and have not been thoroughly tested in a controlled clinical trial setting. However, the mentioned maximum liquid Aethoxysklerol dose has been applied for the treatment for more than 50 years and proved to be a safe threshold as indicated by the safety profile which is described in the dossier. Furthermore, the maximum dose of 2 mg/kg bodyweight per day is today well established within the clinical practice and through the literature (2012).

Since the development of foam formulations in the mid-1990s the maximum dose has been adapted with increasing clinical experience from 6 to 8 mL per session and day (first European consensus meeting on foam sclerotherapy (2004) to the maximum dose recommended today (10 mL). As documented in numerous publications this threshold proved to a safe dosage margin.
IV.6 Risk Management Plan
The applicant has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aethoxysklerol.

A summary of safety concerns is listed in the table below:

Table 12: Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Deep vein thrombosis</td>
<td>1. Medication errors leading to severe necrosis and possible amputation (from intra-arterial injection, extraveneous injection or injected volume, concentration or pressure being too high)</td>
</tr>
<tr>
<td>2. Pulmonary embolism</td>
<td>2. Administration in the facial area resulting in potential permanent loss of sight</td>
</tr>
</tbody>
</table>

Missing information
1. Use in pregnancy and lactation
2. Use in children

Routine pharmacovigilance and risk minimisation measures are proposed. This is acceptable.

IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted, from a clinical point of view.

V. USER CONSULTATION
A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Etoxisclerol, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml. The bridging report is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable.

Aethoxysklerol in its liquid form has been used for sclerotherapy of varicose veins for many decades; although its use as foam is more recent it can still be considered “well-established” (for more than 10 years) in the EU, according to the requirements of Article 10a. In addition, the submitted bibliographic evidence support its efficacy and safety across most types of varicose veins. Aethoxysklerol is also expected to be used by specialists who are aware of the limitations and risks of sclerotherapy, and the importance of the proper use of such a product.

On the basis of the data and justifications provided, the benefit risk balance is considered positive for Aethoxysklerol in the proposed indications.

The grant of Marketing Authorisations is recommended.
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj. PL 20685/0042, 0039-0040, 0043 and 0041

In accordance with Directive 2010/84/EU, the current version of the SmPCs and package leaflets is available on the MHRA website. The current labelling text is presented below.

Aethoxysklerol 2.5 mg/ml solution for injection, PL 20685/0042
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj.

Aethoxysklerol 5 mg/ml solution for injection, PL 20685/0039

Active substance:
- 5 mg/ml lauromacrogol 400.
- Each 2 ml ampoule contains 10 mg lauromacrogol 400.

Excipients:
- ethanol 06%, potassium dihydrogen phosphate, disodium phosphate dihydrate, water for injections.
- See leaflet for further information.

Keep out of the sight and reach of children.

After first opening the ampoule should be used immediately.

PL.20685/0039 (5 mg/ml)

PL 20685/0042, 0039-0040, 0043 and 0041
Aethoxysklerol 10 mg/ml solution for injection, PL 20685/0040

10 mg/ml solution for injection

Active substance: 10 mg/ml lauromacrogol 400. Each 2 ml ampoule contains 20 mg lauromacrogol 400.

Excipients: ethanol 96%, potassium dihydrogen phosphate, disodium phosphate dihydrate, water for injection. See leaflet for further information.

Keep out of the sight and reach of children.

After first opening the ampoule should be used immediately.

PL20685/0040 (10 mg/ml)
Aethoxysklerol 20 mg/ml solution for injection, PL 20685/0043
Aethoxysklerol 2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml and 30 mg/ml soln. for inj.

Aethoxysklerol 30 mg/ml solution for injection, PL 20685/0041

Active substance:
30 mg/ml lauromacrogol 400. Each 2 ml ampoule contains 60 mg lauromacrogol 400.

Excipients:
ethanol 99%, potassium dihydrogen phosphate, disodium phosphate dihydrate, water for injections.

See leaflet for further information.

Keep out of the sight and reach of children.

After first opening the ampoule should be used immediately.

PL20665/0041 (30 mg/ml)

PL 20685/0042, 0039-0040, 0043 and 0041

Aethoxysklerol® 30 mg/ml solution for injection

Lauromacrogol 400

5 ampoules of 2 ml

Lot: 7G27101
EXP: 07.2020
Aethoxysklerol 2.5 mg/ml solution for injection
Aethoxysklerol 5 mg/ml solution for injection
Aethoxysklerol 10 mg/ml solution for injection
Aethoxysklerol 20 mg/ml solution for injection
Aethoxysklerol 30 mg/ml solution for injection

(Lauromacrogol 400)

UK Licence No: PL 20685/0042, 0039-0040, 0043 and 0041

STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

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