[Beautiful healthy legs]

Aethoxysklerol®

Sclerotherapy is considered to be the method of first choice for the treatment of small calibre varicose veins.*

Sklerosierungsmittel
Sclerosing agent
Agent sclérosant
Sostanza sclerosante
Medio esclerosante

* Translated from
German Association of the Scientific Medical Societies (AWMF) - Standing Guidelines Commission.
"Sklerosierungsbehandlung der Varikose". Date 31.12.2018. Available at: https://www.awmf.org/leitlinien/detail/ll/037-015.html

kreussler PHARMA

Aethoxysklerol® worldwide No1 of sclerosing agents

Kreussler Pharma

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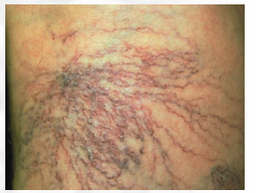
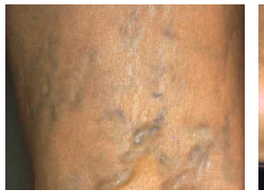
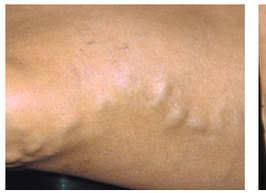
Aethoxysklerol®



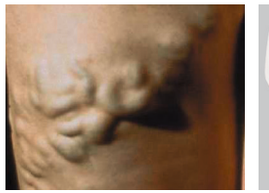
Besenreiservarizen
Spider veins
Télangiectasies
Teleangectasia
Telangiectásias



Retikuläre und kleine Varizen
Reticular and small varices
Veines réticulaires et petites
Varici reticolares e piccolo calibro
Varices reticulares y varices pequeñas



Mittelgroße Varizen
Medium-sized varices
Varices moyennes
Varici di medio calibro
Varices medianas



Große Varizen
Large varices
Varices tronculaires
Varici di grosso calibro
Varices grandes

Hämorrhoiden
Haemorrhoids
Hémorroïdes
Emorroidi
Hemorroides

	maximum number of ampoules to reach the maximum dose of 2 mg polidocanol per kg bodyweight in a patient weighing								
		50 kg	60 kg	75 kg	90 kg				
2.5 mg/ml Polidocanol[1]		20	24	30	36	Aethoxysklerol 0.25 %			
5 mg/ml Polidocanol[1]		10	12	15	18	Aethoxysklerol 0.5%			
10 mg/ml Polidocanol[1]		5	6	7.5	9	Aethoxysklerol 1%[2]	Aethoxysklerol 1%		
20 mg/ml Polidocanol[1]		2.5	3	3.5	4.5			Aethoxysklerol 2%	
30 mg/ml Polidocanol[1]		1.5	2	2.5	3			Aethoxysklerol 3%	Aethoxysklerol 3%	Aethoxysklerol 3%
Volume (ml) per injection						0.1 – 0.2 ml	0.1 – 0.3 ml	0.5 – 2.0 ml[3]	0.5 – 2.0 ml[3]	0.5 – 1.0 ml[4]

Aethoxysklerol® universell einsetzbar bei optimaler Wirkung und Verträglichkeit
Aethoxysklerol® universally applicable with an optimum of efficacy and tolerance
Aetoxisclerol® universellement applicable avec efficacité et tolérance optimales
Atossisclerol® utilizzo universale con un massimo di efficacia e toleranza
Etoxisclerol® aplicación universal con efecto y tolerancia óptima

Availability of different concentrations depends on national marketing authorisation.
Dosage according to the German SPC.

[1] Polidocanol, also known as Lauromacrogol 400, is produced by Kreussler and GMP-approved
[2] For spider veins, Aethoxysklerol 1% is administered only in central veins of spider veins
[3] In the first treatment session, only one injection of 0.5 – 1 ml should be given
[4] For sclerotherapy of haemorrhoidal disease, a total of 3 ml should not be exceeded during one treatment session; when treating an 11 o'clock haemorrhoid in men, the quantity injected must not exceed 0.5 ml

CONNECTOR + 0.2µm FILTER

For the production of a high quality foam

Kreussler Pharma
Chemische Fabrik Kreussler & Co. GmbH
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Tel.: +49 (0)611 9271-0 • Fax: +49 (0)611 9271-111
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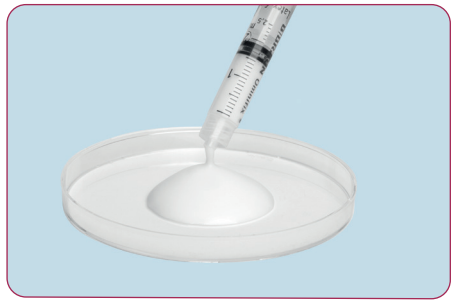
kreussler PHARMA

CONNECTOR + 0.2µm FILTER



The connector + 0.2µm filter is a single-use medical device made up of two components:

- A female/female luer lock connector
- An 0.2µm air filter for sterilization of room air

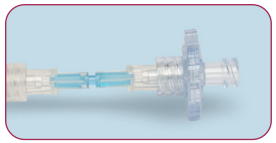
For preparation of the foam. For injection do not use needles with a diameter less than 25 G (0.5mm diameter), since it could reduce the quality of the foam.
To increase the foam quality in respect to the half-life time, use non-siliconized syringes for drawing up Aethoxysklerol. This will reduce the contact time of Aethoxysklerol with the silicon inside the syringes.

FEATURES

For production of a fine bubbled foam for sclerotherapy treatments of medium and larger varicose veins.

Please refer to the SmPC of Aethoxysklerol® 2% and 3% in your country.

Connector + 0.2µm **Filter**
Medical device of class IIa
CE 0459



PREPARATION

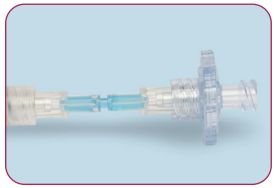
Take the connector + 0.2µm filter kit as well as two 2.5ml syringes (one of them should be non-siliconized) and a needle for drawing up the sclerosing agent.

PRODUCTION AND COLLECTION OF STERILE AIR

Take the siliconized syringe and attach the connector.
Attach the 0.2µm filter on the free end of the connector.
Check that all elements are firmly connected. Draw exactly 2.0ml of air into the syringe (in order to prepare 2.5ml of foam).

COLLECTING THE SCLEROSING AGENT

Attach the needle/cannula to the tip of the second syringe (non-siliconized), collect exactly 0.5ml of sclerosing agent. Remove carefully all residual air bubbles from the syringe.
Caution: If the quantity of the collected sclerosing agent and air differs from the recommended volumes, the physical properties of the foam will be changed.



FOAM PREPARATION

Disconnect the filter from the connector and immediately connect the syringe with the sclerosing agent. Hold the set in such a way that each syringe is in one hand and that the thumbs are on each syringe plunger. Pump the entire content from one syringe into the other 10 times without interruption and within approximately 10 seconds.

DISASSEMBLING

Transfer all foam into the siliconized syringe and disconnect it from the connector.

CONTROLLING THE QUALITY OF THE FOAM

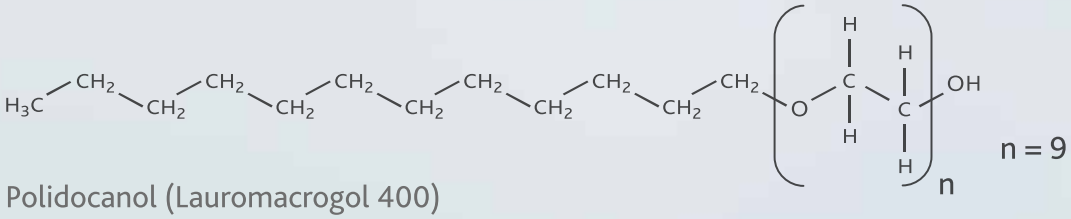
By expelling a small amount of foam the quality of the foam should be checked before injection. The foam must be compact, homogeneous and without bubbles visible to the naked eye (diameter < 0.3mm), comparable to “whipped cream”. In the case of any visible bubbles, the preparation must be repeated.

MAXIMUM TIME FROM THE PREPARATION TO THE INJECTION

The foam should be injected within 60 seconds after preparation has started. After 60 seconds, the residual foam must be discarded. Prepare fresh foam again if necessary.

[Basic Facts about Polidocanol]

INFORMATION BROCHURE FOR PHYSICIANS



Polidocanol (Lauromacrogol 400)

kreussler PHARMA

[Sclerotherapy of varicose veins]

For beautiful and healthy legs

Your partner for healthy legs
50 Years
Aethoxysklerol®

Table of Contents

1. The Sclerosing Agent Aethoxysklerol®

Sclerotherapy has been used successfully as a method of treatment for all types of varicose veins for many decades. Its area of application includes spider veins and reticular varicose veins, side branch and saphenous varicose veins, residual and recurrent varicose veins and venous ulcers. Sclerotherapy is also often used in combination with varicose vein surgery or thermal treatment methods because the two last-mentioned procedures cannot be used to treat all types of varicose veins.
In addition, sclerotherapy is the therapy of choice in many countries for treatment of first degree haemorrhoidal disease and is a long-established treatment option for acute bleeding oesophageal varices.

How long has Aethoxysklerol® existed?

The medicinal product containing the active substance polidocanol was approved in 1966 in Germany under the name Aethoxysklerol® and, due to its advantages, also spread quickly into neighbouring countries and, over the years, throughout the entire world. Aethoxysklerol® is now approved for the treatment of varicose veins in 30 countries, for the treatment of haemorrhoidal disease in 21 countries and is marketed in more than 50 countries.
Aethoxysklerol® contains the active substance polidocanol in different concentrations so that each indication can be treated with the optimum concentration. Aethoxysklerol® 0.25%, 0.5%, 1%, 2% and 3% are available in Germany, but not all five concentrations are available in all countries due to regulatory reasons.

How was the sclerosing action of polidocanol discovered?

Like many great inventions, Aethoxysklerol® did not originate primarily from targeted research, but as a result of chance and the ingenious idea of one individual. As far back as 1930, polidocanol was tested as a possible washing agent for textiles. In the process, the good local anaesthetic action of polidocanol was noticed. This property was only taken up again at the end of the 40s in research on new injection anaesthetics by BASF. However, further examination showed that intravascular administration of higher concentrations caused irritation of the vein wall and that polidocanol cannot be used in injection anaesthesia. The use of the side effect of "irritation and destruction of the vein wall" specifically as a desired main effect for sclerotherapy of varicose veins was a great achievement of the then medical-scientific director of Kreussler Pharma, Otto Henschel (1913-1999). Henschel tested the effect of polidocanol and optimised the sclerosing agent in the 60s using the methods that were available at that time.

2. The Active Substance Polidocanol

To which type of sclerosing agent does polidocanol belong?

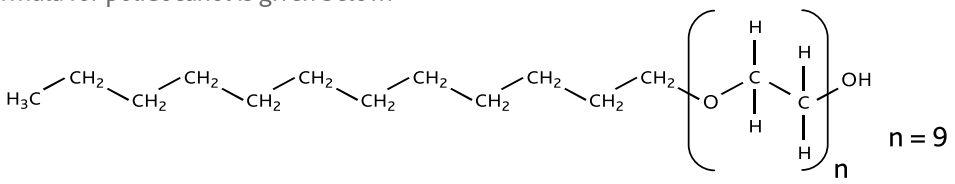
A modern sclerosant, the active substance polidocanol belongs to the class of non-ionic detergents. It is only possible to prepare a stable microfoam for sclerotherapy using detergent-type sclerosing agents. Microfoam is essential for the treatment of varicose veins, since foam sclerotherapy with polidocanol has become established worldwide as a treatment method for larger varicose veins (see page 8).

What is polidocanol and what is its structure?

Polidocanol consists of a fatty alcohol part containing 12 C atoms, called the dodecyl part, and a chain of several oxyethylene units (—O—CH_2—CH_2) that are connected via ether (—O—) bonds.
The molecular formula is $C_{30}H_{62}O_{10}$, the semi-structural formula is:

CH_3—$(CH_2)_{11}$—$(O—CH_2—CH_2)_n$—OH; n = 9
dodecyl part oxyethylene units

The structural formula for polidocanol is given below:



Here "n" stands for the number of oxyethylene units and can be between 1 and 24. Therefore, polidocanol is not a molecule with a single defined structure but a mixture of molecules with different chain lengths due to the different number of oxyethylene units. The average number of oxyethylene units and thus the average chain length is 9, which is expressed by n = 9.
It is crucial for the action of polidocanol that the oxyethylene unit chain is hydrophilic (has a strong affinity for water) and the dodecyl portion is hydrophobic (water-repellent) so that polidocanol is capable of forming micelles (see page 6).
Polidocanol is an active substance that does not occur in nature and is produced from the starting materials (1-)dodecanol and ethylene oxide. Dodecanol can be obtained from coconut oil or palm kernel oil and is therefore of plant origin.

Is polidocanol an alcohol?

From a chemical point of view polidocanol has an alcohol group (OH group) and belongs to the large group of alcohols. However, polidocanol has nothing to do with the term alcohol in general (linguistic) use or the chemical compound ethanol.

What other names is polidocanol known by?

Polidocanol has more than 100 different names. In the European Pharmacopoeia, polidocanol can be found under the name lauromacrogol 400 (International Nonproprietary Name = INN). Here the number 400 refers to the average molar mass of the oxyethylene units without the alcohol part.
A few common names are given below:

- Laureth-9
- Macrogol-9-lauryl ether
- Polyoxyethylene dodecyl ether
- Dodecyl polyglykol ether
- Hydroxy polyethoxy dodecane
- Pistocain
- Polyethylene glycol dodecyl ether
- Thesit®

We will be happy to send you a list of all names known to us upon request.

Properties

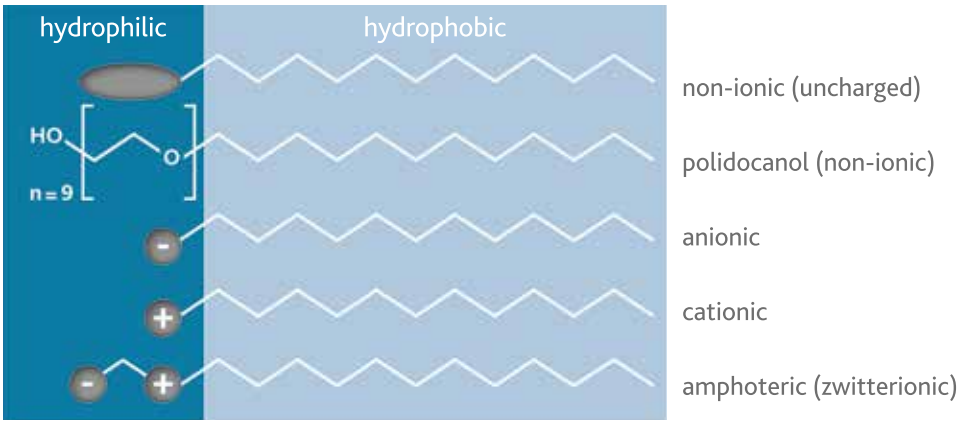
Depending on the manufacturer, polidocanol may have different molecule chain length distribution patterns and therefore different physical properties. Depending on the temperature, pure polidocanol is a white, ointment-like or waxy mass or a colourless to slightly yellowish, clear liquid. The melting point is approximately 24 °C.

3. Mechanism of Action of Polidocanol

Detergent action

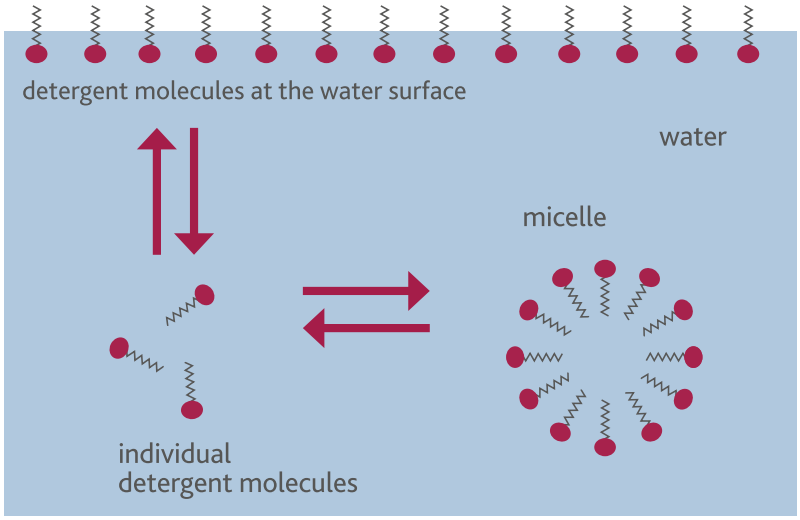
In the German language detergents are understood to be synthetic interface-active or surface-active substances. Together with soaps that are manufactured from vegetable and animal fats, they come under the large group of surfactants, which means all substances with "cleaning properties" in solutions.
In contrast, in the English language, the term detergent is usually taken to mean not only synthetic soaps but also soaps manufactured from vegetable and animal fats.
Interface-active means that these substances accumulate at the interface between two phases. Surface-active means that they accumulate on the surface of a liquid where it meets the gas phase. As a result they reduce the interfacial or surface tension.

Detergents may have a non-ionic, anionic, cationic or amphoteric (zwitterionic) structure:



As already mentioned, polidocanol belongs to the group of non-ionic detergents. The hydrophobic part consists of the 12 hydrocarbons in the fatty alcohol portion and the hydrophilic part consists of the oxyethylene units.

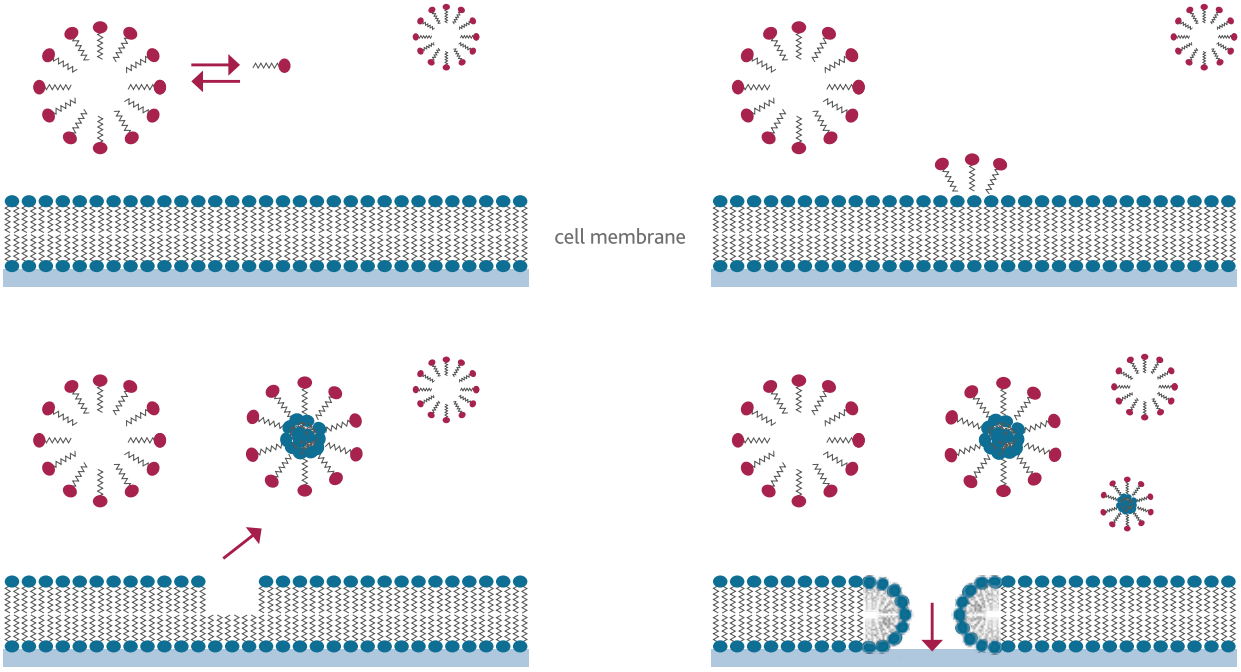
When detergents such as polidocanol are added to water they form a thin layer at the surface of the water and, as a result, the surface tension of the water is reduced. The molecules arrange themselves at the interface in a quite specific way. The hydrophilic ends point towards the water and the hydrophobic ends protrude towards the air.
The molecules are initially dissolved in solution as individual particles.



However, the solubility of the individual molecules is limited and above a certain concentration known as the critical micelle concentration, the polidocanol molecules arrange together into spherical aggregates called micelles. The molecules align themselves so that the hydrophobic ends collect inside the micelles and the hydrophilic ends face towards the water. The critical micelle concentration can be changed by adding buffers and salts.
The surface- and interface-active effect of polidocanol is a requirement for the sclerosing action.

Sclerosing action

The polidocanol molecules interact with the membrane consisting of a phospholipid bilayer that encases all cells. With the aid of the micelles, membrane proteins and lipids are dissolved out of the membrane and held in solution in the blood. As a result of this, "holes" are formed in the cell membrane and the membrane is gradually destroyed, causing the death of the affected cells. Thus, depending on the concentration, sclerosing agents can destroy all types of cells. Even with concentrations as low as that in Aethoxysklerol® 0.25% the critical micelle concentration is exceeded and micelles are present in solution as well as individual particles.



In phlebology, sclerotherapy is understood to be the systematic elimination of varicose veins by injection of a sclerosing agent into the affected veins. Polidocanol interacts with the endothelial cells of the vein walls where it also dissolves proteins and lipids from the cell membranes. This leads to the desired destruction of the endothelial cells of the varicose veins. At higher polidocanol concentrations both the inner and deeper layers of the vein wall are destroyed. The targeted damaging of the vein wall initially causes parietal localised thrombus formation. As a result of infiltration of fibroblasts the thrombosed vein is converted permanently to connective tissue and cannot be recanalised. This process is also called sclerosis. Ideally, the fibrous strand is broken down by the body over time. The functional result of sclerotherapy is thus equivalent to the surgical removal of a varicose vein.

In the case of haemorrhoidal disease sclerotherapy results in the destruction of tissue cells and a desired limited inflammatory reaction. In the longer term, tissue fibrosis also occurs here so that the haemorrhoidal tissue is fixed above the dentate line and a prolapse is prevented. In addition, sclerotherapy causes closure of the vessels supplying the haemorrhoidal nodes so that the reduced blood flow leads to shrinking of the haemorrhoidal tissue.

Washing action

Surfactants are the most important ingredient of washing agents and therefore polidocanol could also be used for washing. Oil, dust and other dirt particles are enclosed within the surfactant molecules ensuring that this dirt can be washed out of the dirty fabric. In the case of grease spots, for example, the hydrophobic parts of the surfactant molecules arrange around the fat drops, remove them from the textile fibre and enclose them in the aqueous solution so that the hydrophilic part is facing the water. Thus, "wrapped" by the surfactant molecules, the grease can be washed out with water.

Emulsifying action

Interface-active also means that the detergent reduces the interfacial tension between two phases (e.g. water and oil) and, as a consequence, promotes mixing of these two phases. The two phases can no longer be separated and are called an emulsion. For example, oil drops are "held in solution" in an aqueous solution by micelles. Depending on the use, interface-active substances such as polidocanol are therefore also called emulsifiers. This property of polidocanol is used particularly in cosmetics.

Local anaesthetic action

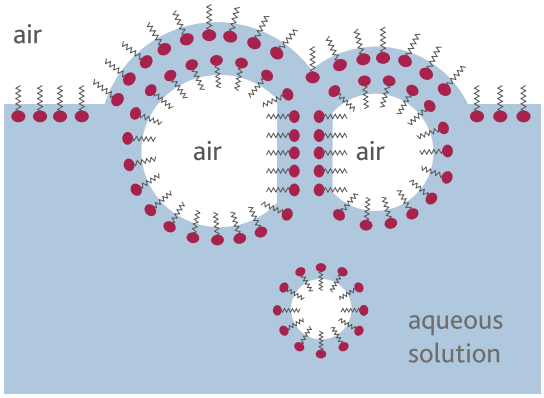
Although it does not have the typical structure of a local anaesthetic at first glance, polidocanol also has a local anaesthetic effect.

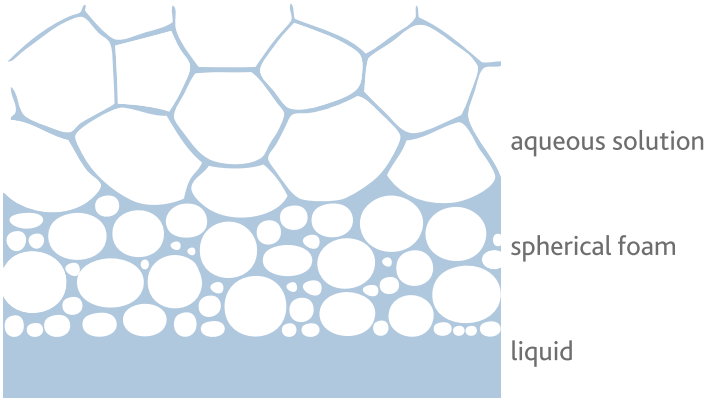
Like all local anaesthetics, polidocanol reduces the membrane permeability for Na^+ ions and, in higher concentrations, also for K^+ ions and therefore locally and reversibly suppresses the excitability of the pain-mediating receptors and the conduction capacity of the sensory nerve fibres. In higher concentrations local anaesthetics and therefore also polidocanol can even inhibit cardiac conduction.

Polidocanol acts as a topical, conduction and infiltration anaesthetic but, due to its cytotoxic action, is only used in topical anaesthesia in concentrations of 3-5%. It is used on the skin especially often because of its antipruritic effect.

"Foaming" action and polidocanol microfoam

From a physical viewpoint, foam is a dispersion (mixture of two different substances that cannot dissolve in one another or chemically react with each other) of gas in a detergent-containing solution. The reduction of the surface tension of the aqueous phase through accumulation of the detergent at the interface between water and air makes it possible to incorporate a gas such as air in such a solution by blowing it into the solution, foaming up or similar methods. The gas bubbles generated in this way are enclosed or separated by liquid walls and form the foam. Spherical bubbles are formed if there is sufficient space between the bubbles. If the bubbles are close enough, they form mutual, relatively flat contact surfaces (polyhedra). Therefore such a foam is also called a polyhedral foam.





The lifetime of such a foam is always limited. Due to gravity, the inter-lamellar liquid between the foam bubbles slowly flows downwards. As a result, the wall in the upper region becomes thinner and thinner until it ruptures.

The time by which half of the foam has returned to a liquid is called the half-life and is one of the characteristic parameters for the respective foam.

A viscous, stable and fine-bubbled sclerosing foam can be produced from liquid detergent-type sclerosing agents using air and a special injection system such as the EasyFoam® Kit. Polidocanol microfoam has a larger surface area than liquid sclerosing agents and thus can interact with more endothelial cells of the varicose veins. Other advantages of the microfoam are that it mixes more slowly with the blood and cannot be displaced by blood as quickly and that the foam provokes a strong spasm of the veins. All things considered, the contact time and reactivity at the endothelium is extended so that the polidocanol microfoam has an even stronger effect than the liquid on larger varicose veins.

Foam sclerotherapy has become established throughout the world for the treatment of larger varicose veins and the first clinical studies on foam sclerotherapy of haemorrhoids have already been published.

4. Polidocanol - a Widely Used Active Ingredient and Excipient

Polidocanol is often used as an active substance and excipient in pharmacy and cosmetics.
As a drug polidocanol is used in human medicine as a sclerosing agent and a topical anaesthetic. Particularly frequently, polidocanol is used in antipruritics, dental preparations, sunburn preparations, wound gels and in oil baths or bath additives. Drugs containing the active substance polidocanol that are known in Germany include Aethoxysklerol® and Recessan® ointment from Kreussler. In dermatological preparations for topical application, polidocanol is found in concentrations of 0.5 to 3% as a local anaesthetic additive.
In skincare products and cosmetics the substance is primarily used in concentrations of 1.5 to 4% as an emulsifier, cosurfactant and for stabilising the complete formulation. Polidocanol is particularly common in leave-on products such as skincare creams and skin lotions as well as in rinse-off products such as shampoos, hair conditioners or washing lotions.
Therefore, polidocanol can theoretically be applied by every person daily over a long period of time. Moreover, it is known that polidocanol can be absorbed by healthy human skin and is thus to be expected to be present in blood at the ng/ml level. This versatile use of polidocanol can cause sensitisation that can trigger an allergic reaction in very rare cases.

5. What is Special about Polidocanol in Aethoxysklerol®?

Aethoxysklerol® ampoules are the sole polidocanol-containing drugs approved in Germany and most other countries by the respective authorities for the sclerotherapy of varicose veins (0.25%, 0.5%, 1%, 2% and 3%) and haemorrhoidal disease (3%). The efficacy and safety of Aethoxysklerol® have been established in many clinical studies.
The quality standards for drug production have been raised considerably in recent years and the production of polidocanol by the pharmaceutical manufacturer Kreussler was one of the first GMP-compliant drug production processes in Germany and, internationally, the first US FDA-compliant polidocanol production process.
Each polidocanol concentration that is produced as a sclerosing solution requires a separate approval for pharmaceutical products by the respective authorities.
The patient should be told about the use of an unapproved drug (no-label) before each treatment and should confirm his/her consent in writing. In this case the treating physician is responsible for the medical correctness of the application as well as any adverse drug reactions.
The responsible authority checks each drug for efficacy and safety before approval, which is not the case for different mixtures and concentrations.
The quality criteria for the production of sclerosing solutions for injection are checked at regular intervals by the competent authorities for all Aethoxysklerol® products and therefore the quality of the polidocanol solution is ensured for Aethoxysklerol®. Sclerosing agents that are produced elsewhere and dilutions must also be of the quality required according to pharmaceutical science and the pharmacopoeia. In the case of a quality defect, the pharmaceutical company cannot be held liable since only approved drugs are subject to this liability.

When preparing sclerosing solutions the following points must be observed and/or checked:

- Polidocanol must be of active substance quality and GMP quality. On both a qualitative and quantitative basis, technical polidocanol can contain prohibited impurities. According to the pharmacopoeia, for example, only 1 ppm of ethylene oxide and not more than 10 ppm of dioxane may be detectable. Tests must be performed for these toxic and/or carcinogenic impurities.
- Polidocanol with an average oxyethylene chain length of 9-11 has the best sclerosing efficacy and should be used for the preparation.
- Polidocanol solution is overlaid with nitrogen during sterilisation, otherwise polidocanol is decomposed by oxygen and heating and harmful aldehydes including formaldehyde and acetaldehyde can increasingly be formed.
- Sterility testing must be performed in accordance with national specifications.
- A check must be made under appropriate visual conditions that the injection solution is clear and practically free of visible particles. Since 2005 it has also been necessary to use the Light Obscuration Particle Count Test or the Microscopic Particle Count Test to check for particles that are not visible to the eye.
- Bacterial endotoxin testing and pyrogen testing must be carried out.
- Appropriate analytical tests must be used to prove that the content of active substance complies exactly with the specification.
- Aethoxysklerol® does not contain any preservatives and therefore may only be dispensed in single-dose containers. Sclerosing solutions in larger containers for multiple withdrawals must demonstrably ensure appropriate preservation so that no contamination is possible. In practice withdrawal must always occur under aseptic conditions.
- Appropriate containers must be selected since interactions between container and polidocanol are to be expected. For example, simple rubber closures should not be used because polidocanol can react with rubber material even after a short time.

6. Practical Tips for Using Aethoxysklerol®

What to do after sclerotherapy in cases of undiagnosed pregnancy

From single reports and some older studies it is known that there have not been any problems or irregularities during pregnancy and birth in women who have received sclerotherapy while being unaware that they were pregnant. Also, results of animal studies have not shown any evidence of a teratogenic effect of polidocanol.
However, as a precautionary measure, physicians should not perform sclerotherapy on women with diagnosed pregnancy and if sclerotherapy has been started, it must not be continued until pregnancy and breast-feeding have ended. Varicose veins that come into being during pregnancy can regress spontaneously after birth when the hormonal situation and pressure return to normal. Therefore, sclerotherapy should be delayed for a few weeks after the birth.

Sclerotherapy during breast-feeding

Animal experiments lead one to assume that a certain amount of polidocanol could be excreted into breast milk. As no studies are available on possible excretion into human breast milk, as a precautionary measure, breast-feeding should be discontinued for 2-3 days after sclerotherapy.

How rapidly is polidocanol eliminated from the body?

In clinical studies the plasma half-life of unmetabolised polidocanol molecules was 0.94-1.27 hours and the terminal elimination half-life of ^{14}C-polidocanol and its labelled metabolites was 4.09 hours. It can therefore be assumed that polidocanol will be eliminated from the body within two days. In addition, accumulation after repeated application of polidocanol at the time intervals normally used in sclerotherapy can be ruled out.

Polidocanol in cases of alcohol dependency

Although polidocanol has an OH group, it has nothing to do with alcohol in the sense of ethanol. However, Aethoxysklerol® contains 5 vol. % ethanol, which must be taken into consideration in the event of previous alcohol dependency and could theoretically give rise to a relapse.

Can Aethoxysklerol® be stored in the refrigerator or frozen?

Aethoxysklerol® is normally stored at room temperature. The product can, but does not have to be, stored in a refrigerator. Due to the low volume of the solution (2 ml), product refrigerated at 4-8 °C reaches room temperature within a few minutes, after which it can be injected. Injection of a solution that is too cold can be painful.
If ampoules have been inadvertently frozen, in principle they can be used after thawing. However, no studies are available on this topic. It should also be noted that the ampoule could have been damaged as a result of freezing.

How long can opened ampoules be used for?

Aethoxysklerol® is designated as a single-use product because it does not contain any preservative. The ethanol in the product (5 vol. %) acts as a solvent and is not a satisfactory preservative. Therefore repeated withdrawal carries the risk of contamination and an ampoule or vial that has already been opened should on no account be kept any longer.

How long may polidocanol be kept in syringes?

Aethoxysklerol® should always be drawn up freshly from the ampoule or vial (oesophageal varices) and should be used promptly. The filling of several syringes with Aethoxysklerol® in the morning for use in the course of the day is to be avoided because of possible interactions of polidocanol with the syringes. Polidocanol attacks plastics and can dissolve syringe components, e.g. silicone, so that the syringes can swell and stop moving smoothly. When foam is used, the dissolved-out silicone can shorten the half-life of the foam considerably.

Can Aethoxysklerol® be diluted?

In principle, the mixing (dilution) of a drug with another solution represents a pharmaceutical manufacturing step. Whether and the extent to which this is done in line with current quality and hygiene standards cannot generally be assessed by the manufacturer. The fact of the matter is that the pharmaceutical company ceases to be liable for the altered product. In other words: Any person who dilutes or alters the drug is formally and solely responsible and therefore liable for the new product.
If Aethoxysklerol® is diluted with physiological saline solution, the sterility, shelf life, critical micelle concentration and pH can change. Aethoxysklerol® contains buffer substances to maintain a constant specified pH. As a result of dilution, the constancy of the pH is no longer assured. This can affect the critical micelle concentration and therefore have an impact on the micelle concentration at the site of action. A greatly changed pH can also result in pain during injection.
No investigations and studies are available for the diluted products.

Bei Fragen wenden Sie sich bitte an:
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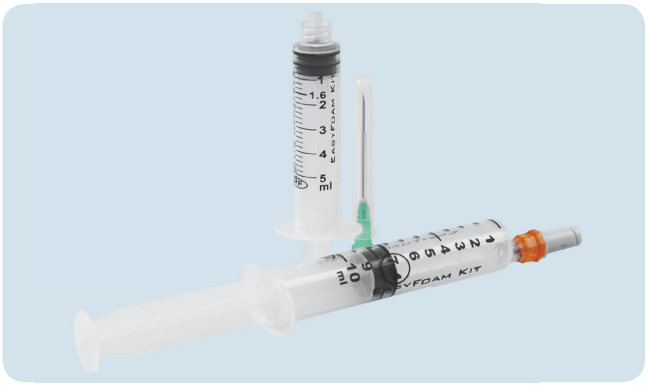
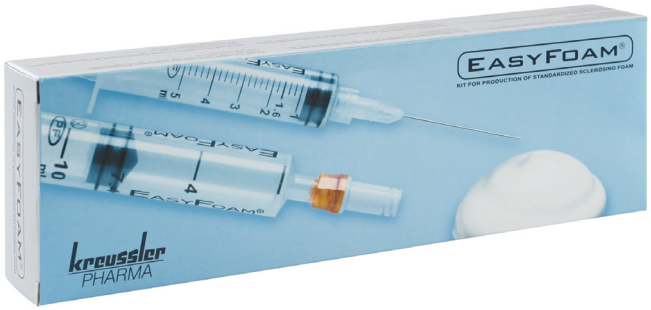
Tel.: +49 (0)611 9271-0
Fax: +49 (0)611 9271-111
E-Mail: info@kreussler.com





EasyFoam® Kit

Kurzanleitung zur Herstellung eines standardisierten Mikroschaums

Vertrieb
Chemische Fabrik Kreussler & Co. GmbH
Rheingaustr. 87 - 93
D-65203 Wiesbaden

kreussler PHARMA

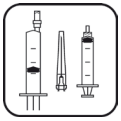
EasyFoam® Kit

Kurzanleitung

Bitte beachten Sie auch die vollständige EasyFoam® Kit Gebrauchsanweisung!

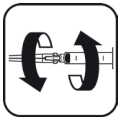
1. Vorbereitende Schritte

Überprüfen des EasyFoam® Kits:
- die sterile Sichtverpackung muss unbeschädigt sein
- das Haltbarkeitsdatum darf nicht überschritten sein



- das 3-teilige EasyFoam® Kit muss vollständig sein
  - ✓ 1 Einmalspritze (5 ml)
  - ✓ 1 Kanüle 40 x 0,8 mm, 21 G x 1 ½″

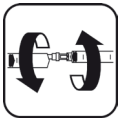
- ✓ 1 Einmalspritze (10 ml) fest verschraubt mit einem Zweiwege-Rückschlagventil und Konnektor, befüllt mit 7,4 ml Sterilluft



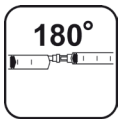
Verbinden Sie die Kanüle des Kits mit der 5 ml Spritze. Öffnen Sie anschließend eine Ampulle Sklerosierungsmittel und ziehen Sie exakt 1,6 ml luftblasenfrei in die 5 ml Spritze auf. Entfernen Sie anschließend die Kanüle.

Eine von 1,6 ml abweichende Menge an Sklerosierungsmittel kann zu einer Veränderung der physikalischen Eigenschaften des Schaums führen! Die Herstellung eines standardisierten Mikroschaums kann dann nicht gewährleistet werden.

2. Zusammenbau des EasyFoam® Kits

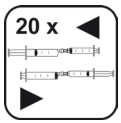


Halten Sie die 10 ml Spritze an dem Zweiwege-Rückschlagventil mit der einen Hand fest. Setzen Sie das EasyFoam® Kit zusammen, indem Sie unter mäßigem Druck bei gleichzeitiger Drehbewegung die 5 ml Spritze mit dem Zweiwege-Rückschlagventil der 10 ml Spritze verbinden.



Achten Sie darauf, dass Sie das Gewinde beim Zusammendrehen nicht überdrehen oder verkanten und dass die beiden Spritzen eine Linie bilden.

3. Schaumherstellung



Halten Sie das EasyFoam® Kit jetzt so, dass je eine Spritze in einer Hand und die Daumen jeweils auf den Spritzenstempeln liegen. Pumpen Sie den **gesamten Inhalt** des EasyFoam® Kits **innerhalb von ca. 10 Sekunden 20 mal** ohne Unterbrechung von einer Spritze in die andere. Halten Sie dabei den Stempel der 5 ml Spritze gut mit dem Daumen fest, da diese unter erhöhtem Druck steht!

Vor dem Auseinanderdrehen des EasyFoam® Kits muss der Stempel der 5 ml Spritze auf die Markierung „5 ml“ und der Stempel der 10 ml Spritze auf „4 ml“ gestellt werden. Andernfalls kann beim Auseinanderdrehen Schaum austreten. Mit der 5 ml Spritze kann injiziert werden.

Der Mikroschaum hat die erforderliche Qualität, wenn:
- keine mit dem bloßen Auge sichtbaren Gasbläschen enthalten sind und
- keine Flüssigkeit und/oder keine Luft ungemischt vorliegt.

4. Anwendung des Mikroschaums

Applizieren Sie den Sklerosierungsschaum innerhalb von 30 Sekunden nach der Herstellung, da sich sonst die physikalischen Eigenschaften des Schaums ändern und ggf. nachteiligen Einfluss auf die Therapie haben können.

Verwenden Sie zur Injektion keine Kanülen, die einen geringeren Durchmesser als 25G haben, da sonst der Schaum zerstört werden könnte.

[Beautiful healthy legs]

Aethoxysklerol®

"Sclerotherapy is considered to be the method of choice for the treatment of small-caliber varicose veins."*

Summary of Product Characteristics*

Foam Sclerotherapy with Aethoxysklerol®
Approved in Germany since 2009

* Translated from
Rabe E, Gerlach H, Breu FX, Guggenbichler S, Stücker M, Pannier F. Leitlinie: Sklerosierungsbehandlung der Varikose der deutschen Gesellschaft für Phlebologie. Phlebologie. 2012; 41: 206-213.

kreussler PHARMA

Aethoxysklerol® worldwide No1 of sclerosing agents

Kreussler Pharma

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*Translated from the German Summary of Product Characteristics.

www.kreussler-pharma.de

Summary of Product Characteristics

1 Name of the medicinal products

Aethoxysklerol® 0.25 %
Aethoxysklerol® 0.5 %
Aethoxysklerol® 1 %
Aethoxysklerol® 2 %
Aethoxysklerol® 3 %
Active substance: lauromacrogol 400 (polidocanol)

2 Qualitative and quantitative composition

Aethoxysklerol is a sclerosant based on lauromacrogol 400 and contains the following amounts of active substance:

Type and quantity of active substance
2 ml contain:

Aethoxysklerol	0.25 %	0.5 %	1 %	2 %	3 %
Lauromacrogol 400	5 mg	10 mg	20 mg	40 mg	60 mg

Excipients
For a full list of excipients, see section 6.1

3 Pharmaceutical form

Solution for intravenous injection (varices), solution for submucous injection (haemorrhoidal disease).

4 Clinical particulars

4.1 Indications

Different concentrations of Aethoxysklerol are required, depending on the size of the varices to be treated. For the treatment of haemorrhoidal disease, Aethoxysklerol 3 % is used. The following concentrations are available:

Mode of administration	**Aethoxysklerol-concentration**					
	0.25 %	0.5 %	1 %	2 %	3 %	
Spider veins	·	·				Liquid
						Foam
Central veins of spider veins	·	·	·			Liquid
						Foam
Reticular varices			·			Liquid
						Foam
Small varices			·			Liquid
			·			Foam
Medium-sized varices				·	·	Liquid
				·	·	Foam
Large varices					·	Liquid
					·	Foam
Haemorrhoidal disease (1st and 2nd degree)					·	Liquid
						Foam

If several concentrations are stated for treatment, the diameter of the vein and the patient's individual situation should be considered. In case of doubt the lower concentration should be chosen.

For endoscopic sclerotherapy of acute bleeding from oesophageal varices:

Cf. SPC Aethoxysklerol 1 % F.

4.2 Posology and method of administration

Dosage with single and daily doses
Generally, the dose of 2 mg lauromacrogol 400 per kg body weight per day should not be exceeded.
For a patient weighing 70 kg, a total of up to 140 mg lauromacrogol 400 can be injected (exception: cf. dosage for haemorrhoidal disease).
140 mg lauromacrogol 400 are contained in:

Aethoxysklerol 0.25 %	56 ml solution for injection
Aethoxysklerol 0.5 %	28 ml solution for injection
Aethoxysklerol 1 %	14 ml solution for injection
Aethoxysklerol 2 %	7 ml solution for injection
Aethoxysklerol 3 %	4.6 ml solution for injection

Aethoxysklerol may be used for foam sclerotherapy (see section 5.1, pharmacological properties).
For preparation of a standardised, homogeneous, fine-bubbled, viscous foam, please consult the instructions of the individual systems.

When applying as sclerosing foam, the total dose of 10 ml foam per session and day - irrespective of the patient's body weight - should not be exceeded.

Extensive varicosis should always be treated in several sessions.

When treating a patient with varices and predisposition to hypersensitivity reactions for the first time, no more than one injection should be administered. Depending on the response, several injections may be administered in subsequent treatment sessions, provided that the maximum dosage is not exceeded.

Sclerotherapy of spider veins
Depending on the size of the area to be treated, 0.1-0.2 ml Aethoxysklerol 0.25 % or 0.5 % are injected intravascularly.

Sclerotherapy of central veins of spider veins
Depending on the size of the area to be treated, 0.1-0.2 ml Aethoxysklerol 0.25 % -1 % are injected intravascularly.

Sclerotherapy of reticular varices
Depending on the size of the varix to be treated, 0.1-0.3 ml Aethoxysklerol 1 % are injected intravascularly.

Sclerotherapy of small varices
Depending on the size of the varix to be treated, 0.1-0.3 ml liquid Aethoxysklerol 1 % are injected intravascularly.

When using Aethoxysklerol 1 % foam, e.g. for the treatment of collateral varices, up to 4 ml (max. 6 ml) are injected per puncture. When treating perforating veins up to 2 ml (max. 4 ml) are injected per puncture. The total daily dose must not be exceeded.

Sclerotherapy of medium-sized varices
Depending on the diameter of the varices to be treated, Aethoxysklerol 2 % or 3 % is used in fluid form. In the first treatment, only one injection of 0.5-1 ml Aethoxysklerol 2 % or 3 % should be administered. Depending on the outcome and the length of the segment to be treated, several injections with up to 2 ml per injection may be administered in subsequent treatment sessions, provided that the maximum dose is not exceeded.

When using Aethoxysklerol 2 % foam, e.g. for the treatment of perforating veins, up to 2 ml foam are injected per puncture, and up to 4 ml per puncture for the treatment of the great saphenous vein and the small saphenous vein (6 ml max. for the great saphenous vein). The total daily dose must not be exceeded.

When using Aethoxysklerol 3 % foam, e.g. for the treatment of the great and small saphenous veins, up to 4 ml (6 ml max. for the great saphenous vein) are injected per puncture. The total daily dose must not be exceeded.

Sclerotherapy of large varices
In the first treatment, only one injection of 1 ml of liquid Aethoxysklerol 3 % should be administered. Depending on the outcome and the length of the segment to be treated, several injections (2-3) with up to 2 ml per injection may be administered in subsequent treatment sessions, provided that the maximum dose is not exceeded.

When using Aethoxysklerol 3 % foam, e.g. for the treatment of the great and small saphenous vein, up to 4 ml (6 ml max. for the great saphenous vein) are injected per puncture. The total daily dose must not be exceeded.

Concentrations of sclerosing foam depending on indications

Examples of indication	**Aethoxysklerol**		
	1 %	2 %	3 %
Great saphenous vein		·	·
Small saphenous vein		·	·
Collateral varices	·		
Perforating veins	·	·	

Note: The concentrations listed refer to liquid Aethoxysklerol for the preparation of sclerosing foam.

Sclerotherapy of haemorrhoidal disease
During one treatment session, a total of 3 ml Aethoxysklerol 3 % should not be exceeded. Depending on the findings, a maximum of 1 ml per haemorrhoid is administered as a strictly submucous injection. When treating an 11 o'clock haemorrhoid in men, the quantity injected must not exceed 0.5 ml.

Method and duration of administration
Sclerotherapy of spider veins
Sclerotherapy of central veins of spider veins
Sclerotherapy of reticular varices
Sclerotherapy of small varices

Injections should only be carried out in a leg placed horizontally or elevated approx. 30-45° above the horizontal. All injections must be given intravenously, including those into spider veins.

Highlighted in colour: passages for foam sclerotherapy. Unmarked passages refer to liquid alone or both liquid and foam.

Very fine needles (e.g. insulin needles) and smooth-moving syringes are used. The puncture is carried out tangentially and the injection given slowly with the needle in intravenous position.
When using sclerosing foam, the needle should not be smaller than 25G.

Sclerotherapy of medium-sized and large varices
Irrespective of the mode of venepuncture (in a standing patient with the cannula only or in a sitting patient with a syringe ready for injection) injections should only be carried out only in a leg placed horizontally or elevated 30-45° above the horizontal.

Injections must be strictly intravenous!

When performing foam sclerotherapy, direct puncture and injection into non-visible truncal veins, perforating veins and varices in the inguinal region or popliteal fossa should be guided by ultrasound (preferably with duplex). When treating other non-visible varices, guidance of the puncture and injection by ultrasound is recommended.

Notes:
Depending on the degree and extent of the varices, several repeat treatments may be required.
Thrombi, which occasionally develop, are removed by stab incision and thrombus expression.

Compression treatment after injection of liquid Aethoxysklerol
Once the injection site has been covered, a tight compression bandage or elastic stocking must be applied. After that, the patient should walk for 30 minutes, preferably within reach of the practice.

Compression treatment after injection of Aethoxysklerol sclerosing foam
After covering of the injection site, the patient's leg is immobilised for 2-5 minutes. Valsalva's manoeuvre and muscle activation should be avoided in the patient; immediate compression in the injection area should be refrained from as well. Compression is applied after approximately 10 minutes when treating the great and small saphenous vein and after approximately 5 minutes when treating collateral varices, recurrent varices or perforating veins.

Duration of compression
The compression should be applied for 2-3 days after sclerotherapy of spider veins, otherwise for 5-7 days.
Compression should be applied for 3-5 weeks after sclerotherapy of medium-sized and large varicose veins. For extensive varicosis, compression treatment with short-traction bandages for several months is recommended.
To make sure the bandage does not slip, especially on the thigh and conical limbs, a foam bandage support under the actual compression bandage is recommended.
The success of sclerotherapy relies on thorough and careful follow-up compression treatment.

Sclerotherapy of haemorrhoidal disease
The injection must be strictly submucous and given directly into the haemorrhoid or above (cranial to) it into the surrounding tissue of the feeding vessels.
Special care should be taken in the region of the internal anal sphincter muscle due to the risk of damage and subsequent incontinence problems. When treating an 11 o'clock haemorrhoid in men, the quantity injected must not exceed 0.5 ml Aethoxysklerol 3 % because of the proximity to the urethra and the prostate.
Depending on the degree of haemorrhoidal disease, several repeat treatments may be required.

4.3 Contraindications
Sclerotherapy of varices
Sclerotherapy of varices is absolutely contraindicated in:
· known allergy to lauromacrogol 400 or any of the other ingredients of Aethoxysklerol
· acute severe systemic diseases (especially if untreated)
· immobility
· severe arterial occlusive disease (Fontaine stage III and IV)
· thromboembolic diseases
· high risk of thrombosis (e.g. known hereditary thrombophilia or patients with multiple risk factors such as use of hormonal contraceptives or hormone replacement therapy, obesity, smoking and extended periods of immobility).
Moreover, the following absolute contraindication applies to foam sclerotherapy:
· known symptomatic patent foramen ovale.

Depending on severity, sclerotherapy of varices may be relatively contraindicated in:
· febrile states
· bronchial asthma or known strong predisposition to allergies
· very poor general health
· arterial occlusive disease (Fontaine stage II) when treating spider veins
· leg oedema (if it cannot be influenced by compression)
· inflammatory skin disease in the area of treatment
· symptoms of microangiopathy or neuropathy
· reduced mobility.

Moreover, the following relative contraindications apply to foam sclerotherapy:
· known asymptomatic patent foramen ovale
· visual, psychic or neurological symptoms after previous foam sclerotherapy.

Sclerotherapy of haemorrhoidal disease
Sclerotherapy of haemorrhoidal disease is absolutely contraindicated in:
· known allergy to lauromacrogol 400 or any of the other ingredients of Aethoxysklerol
· acute severe systemic disease (especially if untreated)
· acute inflammations in the anal region.

Depending on severity, sclerotherapy of haemorrhoidal disease may be relatively contraindicated in:
· febrile states
· bronchial asthma or known strong predisposition to allergies
· very poor general health
· chronic inflammatory bowel disease (e.g. Crohn's disease)
· known hypercoagulability.

4.4 Special warnings and precautions for use
All Aethoxysklerol products contain 5 % (v/v) alcohol. This must be taken into account in patients with previous alcoholism.
Aethoxysklerol products contain potassium, but less than 1 mmol (39 mg) potassium per ampoule.
Aethoxysklerol products contain sodium, but less than 1 mmol (23 mg) sodium per ampoule.

Sclerotherapy of varices
Sclerosants must never be injected intra-arterially because this can cause severe necroses which may necessitate amputation. A vascular surgeon must be called in immediately if any such incidents occur (see section 4.9)!
An indication in the facial area must be strictly evaluated for all sclerosants because intravascular injection can lead to pressure reversal in the arteries and hence to irreversible visual disturbances (blindness).
In certain body regions such as in the foot or malleolar region, the risk of inadvertent intra-arterial injection may be increased. Therefore, only small amounts should be used in low concentrations with particular care during treatment.
The recommended mean volume of sclerosing foam per session is 2 to 8 ml; the maximum volume of sclerosing foam per session (for one or more injections) is 10 ml.
When treating truncal veins, the foam injection is given at a minimum distance of 8 to 10 cm to the sapheno-femoral junction. If ultrasound monitoring reveals a foam bolus in the deep vein system, muscle activation, such as dorsal flexion of the ankle joint, should be performed by the patient.

Sclerotherapy of haemorrhoidal disease
When treating haemorrhoidal disease, care must be taken not to damage the internal anal sphincter muscle in order to avoid incontinence problems.
When treating an 11 o'clock haemorrhoid in men, the quantity injected must not exceed 0.5 ml Aethoxysklerol 3 % because of the proximity to other structures (urethra and prostate).

4.5 Interaction with other medicinal products and other forms of interaction
Lauromacrogol 400 is a local anaesthetic. When combined with other anaesthetics, there is a risk of an additive effect of these anaesthetics on the cardiovascular system.

4.6 Pregnancy and breast-feeding

Pregnancy
There are no adequate data from the use of Aethoxysklerol in pregnant women. Studies in animals showed reproductive toxicity, but no teratogenic potential (see 5.3 Preclinical Safety Data).
Therefore, Aethoxysklerol must not be used during pregnancy unless clearly necessary.

Breast-feeding
Investigations on the possible excretion of lauromacrogol 400 in the breast milk have not been performed in humans. If sclerotherapy is necessary during breast-feeding, it is advisable to suspend breast-feeding for 2-3 days.

4.7 Effects on ability to drive and use machines
No negative effects on the ability to drive and use machines are known for Aethoxysklerol.

4.8 Adverse drug reactions
Sclerotherapy of varices
The adverse reactions listed below have been reported in association with the worldwide use of lauromacrogol 400. In some cases, these reactions were troublesome, but only temporary in most cases. As these were often

Highlighted in colour: passages for foam sclerotherapy. Unmarked passages refer to liquid alone or both liquid and foam.

spontaneous reports, with no reference to a defined patient group and without any control group, it is not possible to calculate frequencies exactly or establish a definite causal relationship to drug exposure in each case. However, a sound estimate on the basis of the long-term experience is possible.

Local adverse reactions (e.g. necroses), especially of the skin and of the underlying tissue (and, in rare cases, of the nerves) were observed when treating varicose veins in the leg after inadvertent injection into the surrounding tissue (paravascular injection). The risk increases with increasing Aethoxysklerol concentrations and volumes.

In addition, the following adverse reactions were observed with the frequencies seen below (information given according to MedDRA (Medical Dictionary for Regulatory Activities)): *Very common (≥10 %); common (≥1 % - < 10 %); uncommon (≥ 0.1 % - < 1 %); rare (≥ 0.01 % - < 0.1 %); very rare, including isolated cases (< 0.01 %).*

Immune system disorders
Very rare: anaphylactic shock, angioedema, urticaria (generalised), asthma (asthmatic attack)

Nervous system disorders
Very rare: cerebrovascular accident, headache, migraine (with 'rare' frequency when using sclerosing foam), paraesthesia (local), loss of consciousness, confusional state, dizziness, aphasia, ataxia, hemiparesis, hypoaesthesia oral

Eye disorders
Very rare: visual impairment (visual disturbance) ('rare' when using sclerosing foam)

Cardiac disorders
Very rare: cardiac arrest, stress cardiomyopathy, palpitations, heart rate abnormal

Vascular disorders
Common: neovascularisation, haematoma
Uncommon: thrombophlebitis superficial, phlebitis
Rare: deep vein thrombosis (possibly due to the underlying disease)
Very rare: pulmonary embolism, syncope vasovagal, circulatory collapse, vasculitis

Respiratory, thoracic and mediastinal disorders
Very rare: dyspnea, chest discomfort (sensation of pressure in the chest), cough

Gastrointestinal disorders
Very rare: dysgeusia, nausea, vomiting

Skin and subcutaneous tissue disorders
Common: skin hyperpigmentation, ecchymosis
Uncommon: dermatitis allergic, urticaria contact, skin reaction, erythema
Very rare: hypertrichosis (in the area of sclerotherapy)

Musculoskeletal and connective tissue disorders
Rare: pain in extremity

General disorders and administration site conditions
Common: injection site pain (short-term), injection site thrombosis (local intravaricose blood clots)
Uncommon: necrosis, induration, swelling
Very rare: pyrexia, hot flush, asthenia, malaise

Investigations
Very rare: blood pressure abnormal

Injury, poisoning and procedural complications
Uncommon: nerve injury

Sclerotherapy of haemorrhoidal disease
When treating haemorrhoids, local adverse reactions such as burning, pain, discomfort, and pressure sensation were observed during and after injection, especially in the 11 o'clock position in men (prostate region). These reactions are of a temporary nature and may last 2-3 days in rare cases. Sclerotherapy of haemorrhoidal disease is painless if the proper technique is used since there are no sensitive nerve fibres in the region of injection.

In addition, the following adverse reactions were observed with the frequencies seen below (information given according to MedDRA (Medical Dictionary for Regulatory Activities)):
Very common (≥10 %); common (≥1 % - < 10 %); uncommon (≥ 0.1 % - < 1 %); rare (≥ 0.01 % - < 0.1 %); very rare, including isolated cases (< 0.01 %).

Immune system disorders
Very rare: anaphylactic shock, angioedema, urticaria (generalised), asthma (asthmatic attack)

Nervous system disorders
Very rare: loss of consciousness, confusional state, dizziness

Cardiac disorders
Very rare: palpitations

Vascular disorders
Very rare: syncope vasovagal, circulatory collapse

Gastrointestinal disorders
Uncommon: proctitis, anal pruritus
Very rare: nausea

Skin and subcutaneous tissue disorders
Uncommon: dermatitis allergic, urticaria contact, skin reaction

Reproductive system and breast disorders
Very rare: erectile dysfunction

General disorders and administration site conditions
Common: burning sensation mucosal, injection site pain, discomfort, sensation of pressure
Uncommon: induration
Rare: necrosis (local, rarely with extension into the surrounding tissue), injection site haemorrhage, injection site thrombosis (intrahaemorrhoidal)
Very rare: pyrexia

Investigations
Very rare: blood pressure abnormal

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the competent authorities in the respective countries.

4.9 Overdose
Emergency measures and antidotes

Anaphylactic reactions
Anaphylactic reactions are rare, but potentially life-threatening situations.
The attending doctor should be prepared for emergency measures and have a suitable emergency kit available.

Treatment of local intoxication after improper administration when treating leg varices
a) Intra-arterial injection
1. Leave cannula in place; if already removed, relocate the puncture site
2. Inject 5-10 ml of a local anaesthetic, without the addition of adrenaline
3. Inject 10,000 IU heparin
4. Pack the ischaemic leg in wadding and lower
5. Hospitalise the patient as a precaution (vascular surgery)

b) Paravenous injection
Depending on the quantity and concentration of Aethoxysklerol injected paravenously, inject 5 to 10 ml of physiological saline, if possible combined with hyaluronidase at the application site. If the patient is in severe pain, a local anaesthetic (without adrenaline) may be injected.

5 Pharmacological properties

5.1 Pharmacodynamic properties
ATC-Code: C05BB02
Lauromacrogol 400 has a concentration-dependent and volume-dependent damaging effect on the endothelium of blood vessels.
Application of a compression bandage following sclerotherapy of varices compresses the damaged vein walls so that excessive thrombus formation and recanalisation of the initially formed parietal thrombus are prevented. This gives rise to the desired transformation into fibrous tissue and hence sclerosis.
In addition, lauromacrogol 400 has a local anaesthetic effect and locally and reversibly suppresses the excitability of the terminal sensory organs (receptors) as well as the conduction capacity of the sensory nerve fibres.

Clinical studies
Sclerotherapy of varices
Extensive findings are available for Aethoxysklerol in the different concentrations, however, no long-term results from controlled clinical studies are known.

Aethoxysklerol 0.25 %
Placebo-controlled study
There is a result from a study which compared Aethoxysklerol 0.25 % with physiological saline as placebo in 22 and 23 patients, respectively. Photographs were taken from a leg area with spider veins before treatment and from the same area 4 weeks after a single sclerotherapy session. These photographs were sent to two independent phlebologists for assessment. The success of treatment was assessed with a VAS scale from 0-100 mm ("0" meant treatment failure, i.e. no disappearance of spider veins, and "100" meant that 100 % of the spider veins disappeared in the marked treatment area). Both experts estimated the efficacy of Aethoxysklerol 0.25 %

Highlighted in colour: passages for foam sclerotherapy. Unmarked passages refer to liquid alone or both liquid and foam.

(mean score of 31 and 30, respectively) - independently of each other - to be significantly better than that of the placebo (mean score of 15.3 and 16.3, respectively).
As secondary criteria, patient satisfaction and the equally blinded investigator's assessment of treatment success were determined (0 = no change/not satisfied, further treatment urgently required, 1 = slight improvement/less satisfied, further treatment recommended, 2 = marked improvement/satisfied, further treatment may be necessary, 3 = very good improvement/very satisfied, no further treatment required).
The investigator (mean for active substance 1.41, mean for placebo 0.22) and the patients (mean for active substance 2.09, mean for placebo 0.91) considered the treatment success to be markedly better after just one session. Both preparations were very well tolerated.

Aethoxysklerol 0.5 %
Comparison with sodium tetradecyl sulfate
For Aethoxysklerol 0.5 %, the results from two similar studies from the USA are available, in which Aethoxysklerol 0.5 % was compared with sodium tetradecyl sulfate in a total of 51 patients. No significant difference regarding the disappearance of small varices (< 1 mm) was seen between the two treatment groups. Aethoxysklerol 0.5 % yielded an efficacy score of 4.51 (standard deviation 0.47) in one study and 3.96 (standard deviation 0.83) in the other one 4 months after treatment
(1 = worse than before treatment, 2 = the same as before, 3 = a minority of varices disappeared, 4 = majority of varices disappeared, 5 = all varices disappeared).

Placebo-controlled study
In a placebo-controlled study, Aethoxysklerol 0.5 % (13 patients) showed significantly better results than the placebo group (14 patients) when treating small varices (diameter in the standing patient < 1 mm). The primary efficacy variable was the degree of disappearance of varices. It was distinguished between "worsened", "ineffective", "slightly effective", "effective" and "clearly effective".
The patient satisfaction, also determined by a 5-score scale ("not satisfied", "slightly unsatisfied", "neither satisfied nor unsatisfied", "generally satisfied", "satisfied"), showed a statistically significant superiority of Aethoxysklerol 0.5 % as well.

EASI study
In a multicentre, randomised, double-blind study (EASI study), a total of 338 patients were treated with Aethoxysklerol 0.5 % (spider veins (n = 94)), with Aethoxysklerol 1 % (reticular varices (n = 86)), with the sclerosing agent sodium tetradecyl sulfate 1 %, which is registered in the USA for both types of varices (n = 105), or with isotonic saline as placebo (used for both types of varices as well (n = 53)).
For the evaluation of the primary endpoint, digital images of the 10x10 cm^2 treatment area were taken according to a standardised procedure. The attending doctor and two blinded experienced medical specialists compared the digital images of the treatment area 12 weeks after the last of three possible treatment sessions with those taken immediately prior to treatment. Efficacy was assessed based on digital images with 1 = worse than before, 2 = same as before, 3 = moderate improvement, 4 = good improvement or 5 = complete success of treatment. Assessment of the efficacy of Aethoxysklerol was 4.52 ± 0.65. Placebo was significantly worse with 2.19 ± 0.41 ($p < 0.0001$). Assessment of sodium tetradecyl sulfate 1 % (4.47 ± 0.74) was similar to Aethoxysklerol. A success of treatment, defined as a score of 4 or 5, was achieved in 95 % of patients treated with Aethoxysklerol, in 92 % of patients treated with sodium tetradecyl sulfate 1 %, but only in 8 % of patients treated with placebo (difference to placebo ($p < 0.0001$)).
After 12 and 26 weeks, the patients assessed their degree of satisfaction (1 = very unsatisfied, 2 = unsatisfied, 3 = moderately satisfied, 4 = satisfied and 5 = very satisfied). A statistically significant greater number of patients ($p < 0.0001$; 88 %, 84 %) were satisfied or very satisfied with Aethoxysklerol compared with sodium tetradecyl sulfate 1 % (64 %, 63 %) or placebo (13 %, 11 %).
The incidence of local symptoms, e.g. irritation, hyperpigmentation and haematoma, was significantly higher in the patients treated with sodium tetradecyl sulfate 1 %. This may also account for the lower satisfaction of those patients.

Aethoxysklerol 1 %
Comparison with sodium tetradecyl sulfate
For Aethoxysklerol 1 %, the results from two similar studies from the USA are available, in which Aethoxysklerol 1 % was compared with sodium tetradecyl sulfate in a total of 50 patients. No significant difference regarding the disappearance of small varices (1-3 mm) was seen between the two treatment groups. Aethoxysklerol 1 % yielded an efficacy score of 4.31 (standard deviation 0.62) in one study and 4.28 (standard deviation 0.89) in the other study 4 months after treatment (1 = worse than before treatment, 2 = the same as before, 3 = a minority of varices disappeared, 4 = majority of varices disappeared, 5 = all varices disappeared).

Placebo-controlled study
In a placebo-controlled study (medium-sized varices, diameter in the standing patient 1-3 mm), same trial design as already described for Aethoxysklerol 0.5 %, Aethoxysklerol 1 % (15 patients) was significantly better (disappearance of varices as assessed by a 5-score scale) than placebo (11 patients). Aethoxysklerol 1 % was also significantly better in the patient assessment (5-score scale).

EASI study
Aethoxysklerol 1 % was investigated in a multicentre, randomised, double-blind study (EASI study) together with Aethoxysklerol 0.5 %. The summary of the study results can therefore be found in the section on Aethoxysklerol 0.5 %.

Aethoxysklerol 2 %
Placebo- and concentration-controlled study
Aethoxysklerol 2 % and 3 % were compared with physiological saline serving as placebo in a prospective clinical study in a total of 15 patients with collateral varices. Twelve weeks after sclerotherapy, the duplex sonography findings (detectable occlusion, internal echoes, absence of pathological retrograde blood flow) were significantly different from the placebo group. The VAFI (veno-arterial flow index) measured for the patients treated with Aethoxysklerol fell significantly from a baseline value of 1.49 to 1.06 while no significant reduction was seen in the placebo group. No stratification of the results according to lauromacrogol 400 concentrations was made. The majority of patients in the active treatment group (10 out of 15) received Aethoxysklerol 2 %.

Aethoxysklerol 3 %
Comparison with sodium tetradecyl sulfate
For Aethoxysklerol 3 %, the results from two similar studies from the USA are available, in which Aethoxysklerol 3 % was compared with sodium tetradecyl sulfate in a total of 52 patients. No significant difference in the disappearance of medium-sized to large varices (3 to 6 mm) was seen between the two treatment groups. Aethoxysklerol 3 % yielded an efficacy score of 4.56 (standard deviation 0.45) in one study and 4.51 (standard deviation 0.46) in the other 4 months after treatment (1 = worse than before treatment, 2 = the same as before, 3 = a minority of varices disappeared, 4 = majority of varices disappeared, 5 = all varices disappeared).

Placebo-controlled study
In a placebo-controlled study, Aethoxysklerol 3 % (14 patients) showed significantly better results than the placebo group (11 patients) when treating large varices (diameter in the standing patient ≥ 3 mm). The primary efficacy endpoint was the degree of disappearance of varices as assessed by a 5-score scale ("worsened", "ineffective", "slightly effective", "effective" and "clearly effective"). Patient satisfaction, also determined by a 5-score scale, ("not satisfied", "slightly unsatisfied", "neither satisfied nor unsatisfied", "generally satisfied", "satisfied") showed a statistically significant superiority of Aethoxysklerol 3 % as well.

Comparison with sclerosing foam
In a multicentre, randomised study (ESAF study), 106 patients with incompetent great saphenous veins were treated either with Aethoxysklerol foam (prepared from Aethoxysklerol 3 % using the foam kit (EasyFoam®)) or with liquid Aethoxysklerol 3 %. The primary endpoint was the elimination of reflux (< 0.5 sec), as measured by duplex ultrasonography 3 cm below the sapheno-femoral junction 3 months after the last injection.
After injection of standardised Aethoxysklerol foam, the treatment objective was achieved in a significantly greater number of patients (69 %) than in the control group (27 %). The secondary endpoints of occlusion of the vein, reflux time, refill time and patient satisfaction improved to a significantly better extent with Aethoxysklerol foam as well. The mean number of treatment days required for successful treatment was 1.3 in the Aethoxysklerol foam group and was lower than in the control group. The number of side effects was low and no differences were observed between the two groups.

In another clinical study (total of 95 patients) from France standardised Aethoxysklerol sclerosing foam (DSS), prepared from Aethoxysklerol 3 %, was compared with liquid Aethoxysklerol 3 %. After 3 weeks, treatment was successful (elimination of reflux) in 85 % of patients treated with Aethoxysklerol foam in a single injection (the regimen provided for in the study protocol). After classical treatment with liquid Aethoxysklerol, this value was 35 %. Two years after the last injection, the patients were requested for a follow-up visit. Five patients did not come for that follow-up visit. These were formally defined as treatment errors. Thus, the total success rate (sclerosing foam) was reduced to 53 % after two years, after a single application of 2.5 ml Aethoxysklerol foam.

Dosage data, studies with various polidocanol concentrations
Aethoxysklerol 0.25 %, 0.5 %, 1 %, 2 % and 3 % were investigated in concentration-controlled studies for

efficacy (summary assessment of disappearance of varices, macroscopic assessment and patient assessment) in various types of varices according to a 5-score scale. It was distinguished between "worsened", "ineffective", "slightly effective", "effective" and "clearly effective".

Small varices
Comparison of Aethoxysklerol 0.5 % (18 patients) and 1 % (18 patients):
No statistically significant differences.
Comparison of Aethoxysklerol 0.25 % (18 patients) and 0.5 % (19 patients): Statistically significant superiority of Aethoxysklerol 0.5 %.

Medium-sized varices
Comparison of Aethoxysklerol 0.5 % (26 patients) and 1 % (28 patients):
Statistically significant superiority of Aethoxysklerol 1 %.
Comparison of Aethoxysklerol 1 % (23 patients) and 2 % (24 patients): No statistically significant differences.

Large varices
Comparison of Aethoxysklerol 2 % (30 patients) and 3 % (26 patients):
Statistically significant superiority of Aethoxysklerol 3 %.

Sclerotherapy of haemorrhoidal disease
The results from a study are available, in which the efficacy and tolerability of Aethoxysklerol 3 % (112 patients) were compared with those of 5 % phenol in oil (108 patients) in the treatment of 1st and 2nd degree haemorrhoidal disease. After 2 sessions, a total of 97 % of the patients had been treated successfully. The differences in the symptoms before and after treatment were statistically significant ($p < 0.001$) in both groups. There was no significant difference between the Aethoxysklerol group and the phenol in oil group.
However, in this study Aethoxysklerol showed fewer adverse drug reactions than phenol in oil: After injection, temporary pain was found significantly more frequently in the phenol in oil group than in the Aethoxysklerol group (24 patients in the phenol in oil group, 11 patients in the Aethoxysklerol group, $p < 0.01$). Necroses and ulcers were only seen in the phenol in oil group (4 necroses, 8 ulcers).

5.2 Pharmacokinetic properties
Six healthy subjects received an injection of 37 mg ^{14}C-lauromacrogol 400 as a strongly diluted solution into the great saphenous vein. The concentration-time course of lauromacrogol 400 in plasma was biphasic - with a terminal elimination half-life of lauromacrogol 400 and its labelled metabolites of 4.09 h. The AUC_{∞} was 3.16 µg x h/ml and the total clearance 11.68 l/h. 89 % of the administered dose were eliminated from the blood within the first 12 hours.
In another study, the plasma concentrations of parent lauromacrogol 400 molecules were determined in 6 patients with varices (diameter > 3 mm) after treatment with Aethoxysklerol 3 %. The plasma half-life was 0.94 - 1.27 h and the AUC_{∞} 6.19 - 10.90 µg x h/ml. The mean total clearance was 12.4 l/h and the distribution volume 17.9 l.

5.3 Preclinical safety data
In animal experiments, Aethoxysklerol has a relatively low acute toxicity. Safety pharmacological studies showed negative chronotropic, inotropic and dromotropic effects, with a blood pressure drop. Additional proarrhythmic effects were seen when other local anaesthetics were given concomitantly. After repeated administration of Aethoxysklerol, some animals of all species investigated showed histological alterations in the intestine, adrenal gland and liver, and rabbits additionally in the kidneys.
Lauromacrogol 400 caused haematuria in all species investigated. At doses of 4 mg/kg body weight/day and higher, male rats showed an increase in liver weight after daily application on 7 consecutive days and an increase in ALAT (GPT) and ASAT (GOT) activity at doses of 14 mg/kg/day and higher.

Mutagenicity
Lauromacrogol 400 was tested extensively *in vitro* and *in vivo*. All tests were negative, except one *in vitro* test where lauromacrogol 400 induced polyploids in mammalian cells. However, if the medicinal product is used according to the instructions, no relevant clinical genotoxic potential is expected.

Reproduction toxicity
The daily intravenous administration of lauromacrogol 400 over several weeks or during organogenesis had no influence on male or female fertility or early embryo development in rats and did not induce teratogenic effects in rats or rabbits; however, embryotoxic and foetotoxic effects (increased embryo/foetal mortality, reduced foetal weights) were seen in the maternal toxic dose range. When administration was restricted to intervals of 4 consecutive days during organogenesis, neither maternal toxic nor embryotoxic/foetotoxic effects occurred (rabbits). Peri- and postnatal development, behaviour and reproduction were not impaired in rats whose mothers received intravenous lauromacrogol 400 every other day during late gestation and in the lactation period. Lauromacrogol 400 crosses the placental barrier in rats.

6 Pharmaceutical particulars

6.1 Excipients
Ethanol 96 %, potassium dihydrogen phosphate, disodium phosphate dihydrate (Ph. Eur.), water for injections.

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
All Aethoxysklerol products are available as solution for injection in packs of 5 ampoules (glass of hydrolytic class 1) of 2 ml each.

6.6 Instructions for use
The ampoule is intended for single use. Any residual amount must be discarded.
Please consult the instructions of the individual systems when preparing standardised sclerosing foam.

7 Marketing authorisation holder

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8 Marketing authorisation numbers

Name of the medicinal product	Reg. No.
Aethoxysklerol 0.25 %	6248007.00.00
Aethoxysklerol 0.25 %	3003385.01.00
Aethoxysklerol 0.5 %	6248007.01.00
Aethoxysklerol 1 %	6248007.02.00
Aethoxysklerol 1 %	3003385.00.00
Aethoxysklerol 2 %	6248007.03.00
Aethoxysklerol 3 %	6248007.04.00

9 Date of first authorisation/ renewal of the authorisation

The authorisations of all medicinal products were last renewed in November and December 2004 (20.11.2004, 23.11.2004, 13.12.2004).

10 Date of revision of the text

November 2017

11 Classification for supply

Medicinal product subject to medical prescription.

Highlighted in colour: passages for foam sclerotherapy. Unmarked passages refer to liquid alone or both liquid and foam.