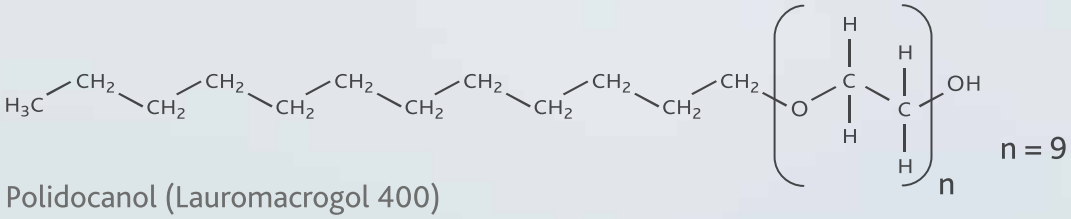
[Basic Facts about Polidocanol]

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®

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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?

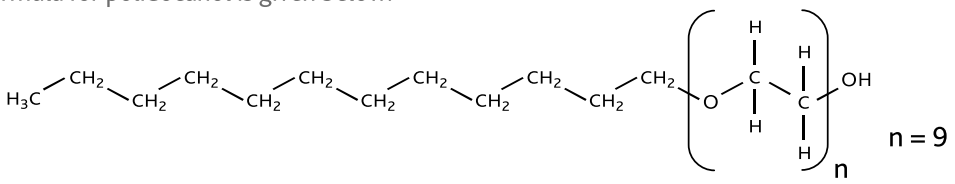
A modern sclerosant, the active substance polidocanol belongs to the class of non-ionic detergents. It is only possible to prepare a stable microfoam for sclerotherapy using detergent-type sclerosing agents. Microfoam is essential for the treatment of varicose veins, since foam sclerotherapy with polidocanol 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

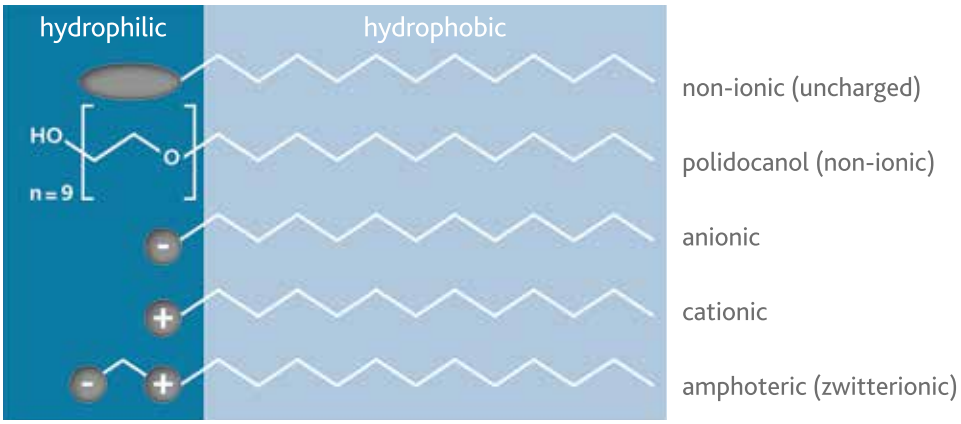
Depending on the manufacturer, polidocanol may have different molecule chain length distribution patterns and therefore different physical properties. Depending on the temperature, pure polidocanol is a white, ointment-like or waxy mass or a colourless to slightly yellowish, clear liquid. The melting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

3. Mechanism of Action of Polidocanol

Detergent action

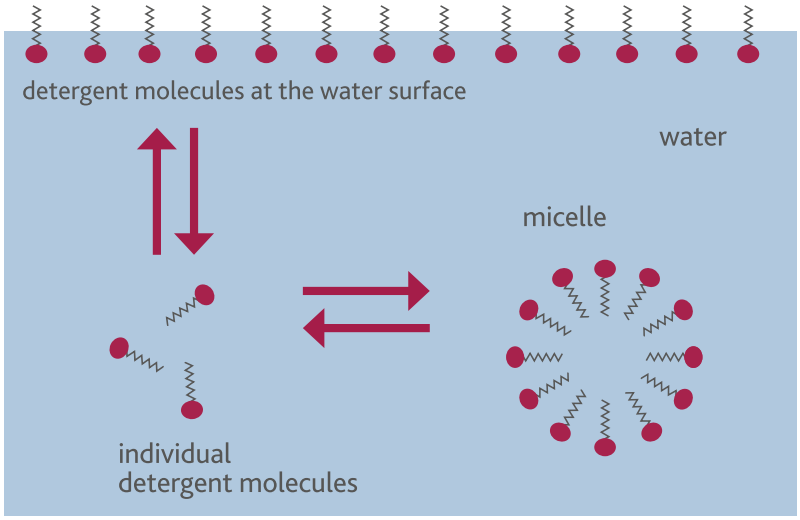
In the German language detergents are understood to be synthetic interface-active or surface-active substances. Together with soaps that are manufactured from vegetable and animal fats, they come under the large group of surfactants, which means all substances with "cleaning properties" in solutions.
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.

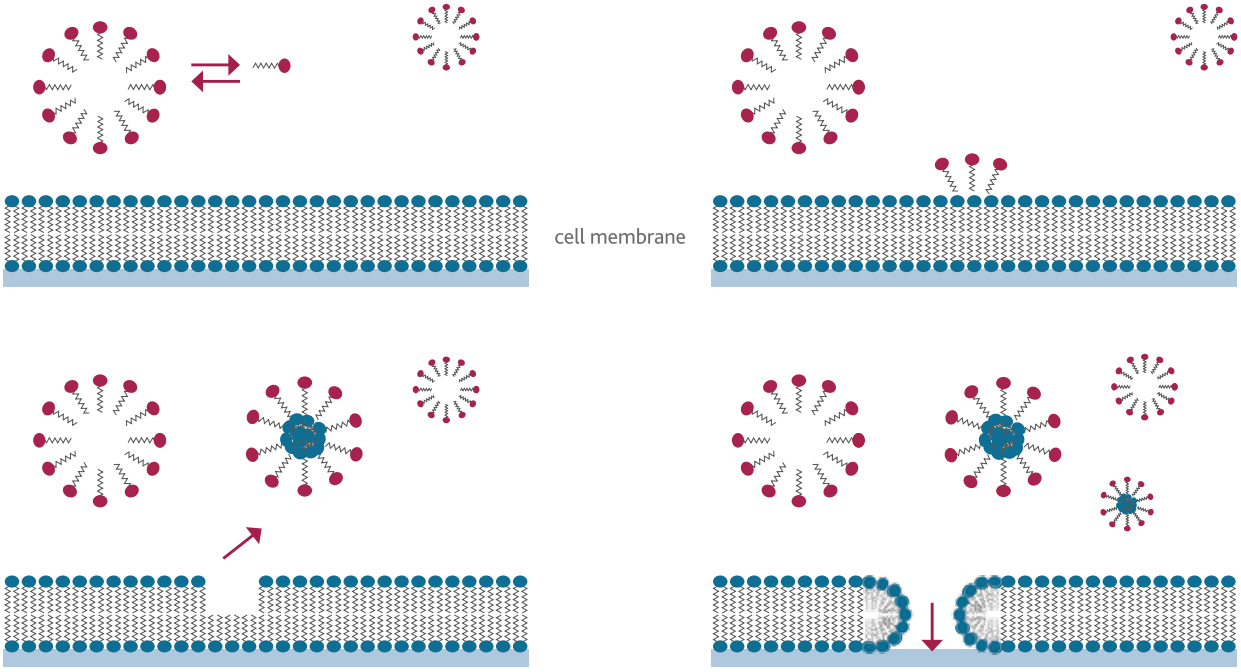
When detergents such as polidocanol are added to water they form a thin layer at the surface of the water and, as a result, the surface tension of the water is reduced. The molecules arrange themselves at the interface in a quite specific way. The hydrophilic ends point towards the water and the hydrophobic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

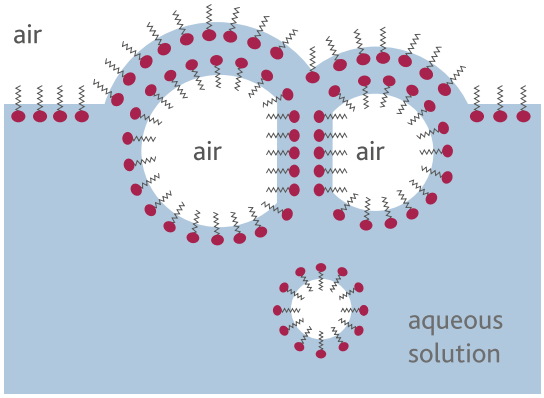
Although it does not have the typical structure of a local anaesthetic at first glance, polidocanol also has a local anaesthetic effect.

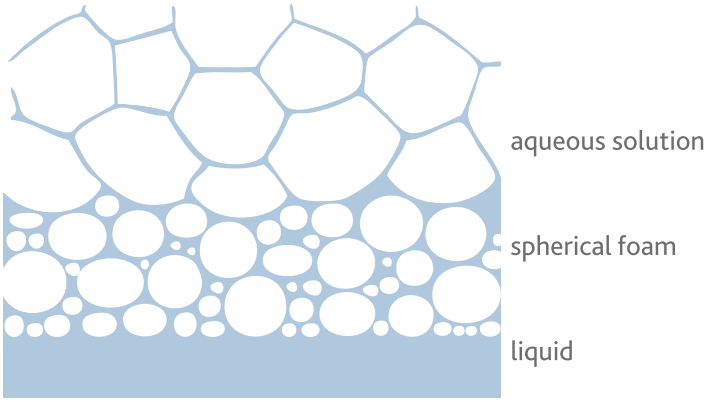
Like all local anaesthetics, polidocanol reduces the membrane permeability for Na^+ ions and, in higher concentrations, also for K^+ ions and therefore locally and reversibly suppresses the excitability of the pain-mediating receptors and the conduction capacity of the sensory nerve fibres. In higher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