kreussler PHARMA

AETHOXYSKLEROL 0,25-3 %

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:

Aethoxy-sklerol	0.25 %	0.5 %	1 %	2 %	3 %
Lauro-macrogol 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 gradations of indications are applicable :

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

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

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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

Aethoxysklerol / Examples of indication	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 1.0 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.

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 saphenofemoral junction. If ultrasound monitoring reveals a foam bolus in the deep vein system, muscle activation, such as, e.g. 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

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 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.

Sclerotherapy of varices

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

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 via the Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

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 recanalization 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 % (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-.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, behavior 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.