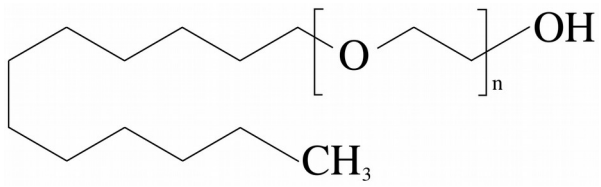
PRODUCT INFORMATION

AETHOXYSKLEROL ® (LAURETH-9)

NAME OF THE MEDICINE

Laureth-9 (polidocanol): Chemical name: Polyethylene glycol monododecyl ether (WHO).

Molecular formula: $C_{12}H_{25}(OCH_2CH_2)_nOH$ where the mean of n is approximately 9.



CAS 9002-92-0 Mean MW ≅ 600

Laureth-9 is a mixture of monolauryl ethers of macrogols containing an average of 9 oxyethylene groups in the polyoxyethylene chain, it contains a lipophilic and a hydrophilic part. This molecular structure leads to the characteristic physio-chemical property of the sub- stance, the surface activity.

DESCRIPTION

Aethoxysklerol is a sterile solution of laureth-9 available in four strengths 0.5%, 1%, 2%, 3% buffered to pH 6.5 – 8.0. Excipients in Aethoxysklerol are ethanol, sodium phosphate-dibasic dihydrate, potassium phosphate monobasic and water for injections.

PHARMACOLOGY

The action of laureth-9 in this technique is considered to be that of irritation to the intima of the vein wall (disruption of the vascular endothelium causing a thrombus formation that occludes the blood vessel reducing it to a fibrotic cord). Subsequent application of a compression bandage or stocking to the leg compresses the vein walls so that the vein is permanently occluded by the development of fibrosis in the wall of the compressed vein. Toxicological effects of laureth-9 occurred at relatively low dose levels in experimental animals, with rabbits being the most sensitive species examined. Dose related decreases in cardiac contractility, heart rate, blood pressure, and PQ interval were observed in rats treated with laureth-9 at ≥ 0.25 mg/kg IV. However, in the animal studies, the drug was administered intrave-nously without compression of the vein, as is the case for the clinical use of laureth-9. Other effects, such as emesis, hypersalivation and spasm were also observed in animals, and tended to occur during and soon after laureth-9 administration.

CLINICAL TRIALS

The pivotal trial in the USA consisted of two substudies in 324 patients comparing Aethoxysklerol and sodium tetradecyl sulfate (STS) in the treatment of varicose veins of the lower extremities. The primary efficacy variable for both studies was *Disappearance of Varicosities* which was determined by a panel of three vascular surgeons who were blinded to the treatment conditions and rated on a scale of 1 to 5. The secondary efficacy variables were *Overall Clinical Improvement* (deter mined by the same panel) on an eleven point scale and *Patient Satisfaction* determined by patients on a four point scale. No difference was detected with regard to primary endpoint, disappearance score, for any of the three vein size strata in either sub study.

Table 1: Disappearance scores (Ohio Sub study)

Vein size	STS	Aethoxysklerol	LSM Diff*	P-value
≤1 mm	4.30 (n=21)	3.96 (n=25)	+0.34	0.104
≥ 1-3 mm	4.00 (n=23)	4.28 (n=23)	-0.28	0.191
≥ 3-6 mm	4.27 (n=25)	4.51 (n=25)	-0.25	0.219

* difference of least-squares means (– score flavors Aethoxysklerol over STS) from ANOVA model

Table 2: Disppearance scors (MICA Sub study)

Vein size	STS	Aethoxysklerol	LSM Diff*	P-value
≤1 mm	4.20 (n=32)	4.51 (n=26)	-0.31	0.055
≥ 1-3 mm	4.29 (n=28)	4.31 (n=27)	-0.04	0.832
≥ 3-6 mm	4.48 (n=27)	4.56 (n=27)	-0.09	0.581

* difference of least-squares means (– score flavors Aethoxysklerol over STS) from ANOVA model

Overall clinical improvement was greater in Aethoxysklerol treated patients than in STS patients with the between treatment difference being statistically significant in the MICA sub study (p=0.020) and not statistically significant in the Ohio sub study (p=0.051). There were no statistically significant differences in either sub study in patient satisfaction score after controlling for vein size.

INDICATIONS
The solutions are indicated for the treatment of varicose veins (up to6 mm diameter) of the lower limbs by compression sclerotherapy.

CONTRAINDICATIONS
Sclerotherapy of varices of the lower limbs is contraindicated in:

- know allergy to laureth-9 or any of the excipients
- bed-ridden patients, and patients unable to walk
- arterial disease such as severe artherosclerotic peripheral vascular disease
- patients with thromboembolic disorders and patients with high risk of thrombosis (those with multiple risk factors such as taking oral contraceptive tablets, hormone replacement therapy, adiposis, smoking, longer periods of immobilisation)
- Other contraindications include acute superficial thrombophlebitis; significant valvular or deep vein incompetence; huge superficial veins with wide open communications to deeper veins; acute cellulitis; phlebitis migrans; allergic conditions; acute infections; varicosities caused by abdominal and pelvic tumours unless the tumour has been removed; uncontrolled systemic disease such as diabetes, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases

Depending on severity, sclerotherapy may be contraindicated in:

- known hypercoagulability
- spider veins: arterial occlusive disease (Fontaine stage II)
- leg oedema (if it cannot be influenced by compression)
- symptoms of diabetic micro-angiopathy
- neuropathy
- inflammatory skin reactions in the injection area
- acute severe cardiac diseases (endocarditis, myocarditis). Note that heart failure, if stabilised by previous treatment, is not a contraindication to sclerotherapy. The same applies to arterial hypertension if it has been adequately managed by previous treatment
- febrile states
- advanced age with impaired mobility or very poor general condition

PRECAUTIONS
Effects on Fertility No effect on fertility was observed when male and female rats were treated intermittently with laureth-9 at IV doses up to 10 mg/kg (once a week exposure in rats was about 80% of the maximum human dose in terms of surface area) prior to mating. Aethoxysklerol should only be administered by physicians experienced in injection sclerotherapy. Thorough assessment for valvular competence and deep vein patency should be undertaken prior to injection. Careful needle placement and slow injection technique of the minimum effective dose are essential. Aethoxysklerol must never be injected intra-arterially because this can cause severe necrosis that may necessitate amputation. A vascular surgeon must be called in immediately if any such incidents occur.
In order to avoid undue adverse reactions when performing sclerotherapy in the ankle area, only a small quantity of a low concentration of Aethoxysklerol should be used. The risk of inadvertent intra-arterial injection in the foot and ankle region should also be taken into consideration. Laureth-9 (polidocanol) is a local anaesthetic. When combined with other anaesthetics, there may be a risk of intensifying desired or undesired effects of

anaesthetics on the cardiovascular system (e.g. proarrhythmic effect). All Aethoxysklerol preparations contain 5% (v/v) ethanol (to be considered in cases of patients with former alcoholism).

Anaphylaxis
Although the incidence of anaphylactic reactions is very rare when Aethoxysklerol is injected into veins, the physician carrying out the procedure should be equipped for anaphylactic emergencies should they occur. The injection should be stopped immediately and standard emergency procedure should be followed including the administration of oxygen, adrenaline and intravenous steroids. Airway management including intubation should not be delayed if upper airway obstruction is progressive.

Allergy
Prior to treatment, a history of allergy should be taken for all patients, in particular allergic reactions to previous administration of Aethoxysklerol.

Effects on Fertility
No effect on fertility was observed when male and female rats were treated intermittently with laureth-9 at IV doses up to 10 mg/kg (once a week exposure in rats was about 80% of the maximum human dose in terms of surface area) prior to mating.

Use in Pregnancy (Category B3)
Studies in rats have shown that laureth-9 and/or its metabo lites cross the placenta and distribute to the foetus. Administration of laureth-9 by IV injection at doses ≥ 2.5 mg/kg to pregnant rabbits once daily from gestation day 6 to 14–18 was associated with increased resorptions, foetal malforma tions (mainly of the limbs and head) and foetal death. The no-effect dose for embryofoetal toxicity and malformations was 1.25 mg/kg IV (about 20% of the maximum proposed human dose of 2 mg/kg IV, based on body surface area). No evidence for a teratogenic effect of laureth-9 was noted in rats at doses up to 4mg/kg/day IV treated daily from gestation days 7–17 (about 80% of the maximum human dose based on body surface area). However, this dose of laureth-9 caused an increase in the number of runts in rats. Treatment of rats with laureth-9 at IV doses ≥ 2.5 mg/kg (about 20% of the maximum dose based on body surface area) from late gestation and during the lactation period was associated with an increased number of stillbirths and abortions. A no-effect dose for these effects was not established. There are no adequate and well-controlled studies in pregnant women. Therefore, laureth-9 should not be used in pregnant women.

Use in Lactation
It is not known whether laureth-9 is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Aethoxysklerol is administered to a nursing woman. Laureth-9 and/or its metabolites were found in the milk of lactating rats for at least 48hr after a single IV dose of [14 C]-laureth-9. Administration of laureth-9 at IV doses up to 10 mg/kg (about 80% of the maximum human dose based on body surface area) to lactating rats had no effect on offspring development.

Paediatric Use
There are no data and therefore Aethoxysklerol is not recommended for use in children.

Genotoxicity
In short-term studies investigating the genotoxic potential of laureth-9, no evidence of mutagenicity was noted; however, a concentration-dependent increase in the incidence of chromosomal abnormalities (polyploid cells) was observed in cultured Chinese hamster fibroblasts, suggesting a possible genotoxic effect of the drug.

Carcinogenicity
The carcinogenic potential of laureth-9 has not been adequately assessed in long-term animal studies.

INTERACTIONS WITH OTHER MEDICINES
There are no data on drug interactions with laureth-9.

ADVERSE EFFECTS
Pivotal Clinical Trial Aethoxysklerol and sodium tetradecyl sulfate injection caused reactions that were expected based upon the known pharmacological properties of the drugs and/or the mode of application of the drug (needle injection). Immediate local reactions (pain on injection, inflammation, swelling and local allergic reactions) and delayed local reactions (hyperpigmentation, vein thrombosis, ecchymosis and neovascularisation) were all related to the injected agent and to the known effects on vascular endo thelium. In

both groups the most common repeated adverse events were hyperpigmentation, vein thrombosis, ecchymosis and pain on injection. All adverse events (independent of the number of treatments per patient)

	OHIO sub study		**MICA sub study**	
	STS	**Aethoxysklerol**	**STS**	**Aethoxysklerol**
N	75	75	91	81
Any	89%	88%	100%	98%
Hyper pigmentation	72%	65%	64%	53%
Skin necrosis	4.0%	2.7%	5.5%	0.0%
Rash	-	-	8.8%	11%
Vein thrombosis*	59%	61%	46%	42%
Neovascularisation	5.3%	9.3%	11%	7.2%
Ecchymosis	63%	49%	70%	58%
Pain	31%	45%	41%	43%
Local allergy	4.0%	6.7%	36%	23%
Inflammation	4.0%	0.0%	59%	41%
Swelling	-	-	40%	19%
Oedema	-	-	2.2%	0.0%
Taste disturbance	0.0%	2.7%	1.1%	0.0%
Visual field defect	-	-	1.1%	0.0%
Paraesthesia	0.0%	1.3%	2.2%	3.6%
Dizziness	-	-	2.2%	0.0%

* It should be noted that while vein thrombosis is reported as an adverse event, it is often part of the pharmacological mechanism of action of laureth-9 and is expected with sclerotherapy.

Post Marketing
Spontaneous reporting world-wide of adverse reactions associated with the use of Aethoxysklerol. The following adverse reactions have been observed with the frequencies seen below:
Very common (≥ 1/10); common (≥ 1/100 - < 1/10); uncommon (≥ 1/1,000 - < 1/100); rare (≥ 1/10,000 - < 1/1,000); very rare (< 1/10,000 or not known).

Immune system disorders
Very rare: anaphylactic shock, angioedema, urticaria generalised, asthma
Nervous system disorders
Very rare: cerebrovascular accident, headache, migraine, paraesthesia (local), loss of consciousness, confusional state, dizziness
Eye disorders
Very rare: visual disturbance
Cardiac disorders
Very rare: cardiac arrest, palpitations
Vascular disorders
Common: neovascularisation, haematoma
Uncommon: thrombophlebitis superficial, phlebitis
Rare: deep vein thrombosis (unknown aetiology, possibly due to the underlying disease)
Very rare: pulmonary embolism, syncope vasovagal, circulatory collapse, vasculitis
Respiratory, thoracic and mediastinal disorders
Very rare: dyspnoea, chest discomfort, cough
Gastrointestinal disorders
Very rare: dysgeusia, nausea
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, connective tissue and bone 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

DOSAGE AND ADMINISTRATION
Dosage and selection of the Aethoxysklerol concentration depends on the size of the varices to be sclerosed. Sclerotherapy is followed by compression bandaging of the limb. Extensive varicosis should always be treated in several sessions. When first treating a patient prone to hypersensitivity reactions, no more than one injection should be given. Depending on the outcome and size of the area to be sclerosed, several injections may be given at subsequent treatment sessions, provided that the maximum dosage 2 mg/kg body weight per day is not exceeded.

Method of administration
- Aethoxysklerol is to be injected into the lumen of the affected vein.
- Aethoxysklerol is for single patient use only.
- Only inject into a leg placed horizontally or elevated 30-45° above the horizontal.

The most appropriate syringe and needle size for each vein size should be used. After puncture of the vein, the injection should usually take place with the patient in a horizontal position. Intravenous placement of the needle should be assured. Especially for smaller veins, directing the needle tangentially will assist in the intravenous positioning. The injection of Aethoxysklerol should be done slowly, avoiding administration into the surrounding tissue.
Sclerotherapy of reticular varices, spider veins, central veins of spider veins, small varices
One or two repeat treatments may be necessary, depending on the extent of the varices and on the treatment success.
Sclerotherapy of medium-sized varices
Several repeat treatments at intervals of 1–2 weeks may be necessary, depending on the severity and extent of the varices and on the success of the previous treatments.

Subsequent Care
The success of compression sclerotherapy depends on the thorough and careful follow-up compression treatment.
Once the injection sites have been covered, a firm compression bandage or elastic stocking should be applied. The patient should walk, preferably under observation, for at least 30 minutes.
Sclerotherapy of reticular varices, spider veins, central veins of spider veins, small varices
The bandage should usually be worn for 2–3 days after sclerotherapy of spider veins, otherwise for 3–7 days.
Sclerotherapy of medium-sized varices
The bandage should usually be worn for 4-6 weeks.

Dosage
A guide to the most appropriate dose of Aethoxysklerol is given in the following table.

Indication	Volume / Injection	Concentration
Spider veins	0.1 – 0.2 mL	0.5%
Central veins of spider veins	0.1 – 0.2 mL	1%
Reticular/small varices	0.1 – 0.3 mL	1%
Medium size varices	0.5 – 1 mL	2 – 3%

OVERDOSAGE
Overdose (caused by injection of an excessive amount of Aethoxysklerol for the vein size being injected) may result in local necrosis, especially if extravasation occurred. No serious sequelae were observed in patients who received Aethoxysklerol doses in excess of the recommended maximum dose of 2 mg/kg body weight per day. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS
Aethoxysklerol 0.5% contains 10 mg laureth-9 in 2 mL ampoule.
Pack of 5 ampoules
Aethoxysklerol 1% contains 20 mg laureth-9 in 2 mL ampoule.
Pack of 5 ampoules
Aethoxysklerol 2% contains 40 mg laureth-9 in 2 mL ampoule.
Pack of 5 ampoules
Aethoxysklerol 3% contains 60 mg laureth-9 in 2 mL ampoule.
Pack of 5 ampoules

The solutions should be stored below 25°C and used before the expiry date on the container.

NAME AND ADDRESS OF THE SPONSOR
Getz Healthcare Pty Ltd.
5 Orion Road
Lane Cove, NSW, 2066
Sydney, Australia

POISON SCHEDULE OF THE MEDICINE
Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG
05/07/2001

DATE OF MOST RECENT AMENDMENT
30/01/2012