HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 June 2012

AETOXISCLEROL TAMPONNE 0.5% (10 mg/2 ml) IV
B/5 x 2 ml vials (CIP code: 347 752-4)

AETOXISCLEROL TAMPONNE 2% (40 mg/2 ml) IV
B/5 x 2 ml vials (CIP code: 347 754-7)

AETOXISCLEROL TAMPONNE 3% (60 mg/2 ml) IV
B/5 x 2 ml vials (CIP code: 347 753-0)

Applicant: KREUSSLER PHARMA

Lauromacrogol 400 (macrogol 9 lauryl ether or polidocanol)
ATC code: C05BB02 (ANTIVARICOSE THERAPY/SCLEROSING AGENTS FOR LOCAL INJECTION)

List II
Date of Marketing Authorisation: 24/07/1996 (national procedure)
Approved for hospital use (24/02/1999)

Reasons for request:

- Re-assessment of Actual Benefit on the transparency Committee's own initiative in accordance with article R 163-21 of the Social Security Code.
- Changes to Summary of Product Characteristics.

Medical, Economic and Public Health Assessment Division

1. CONTEXT OF EVALUATION

The Transparency Committee is re-evaluating the Actual Benefit (AB) of sclerosing agents for varicose veins of the lower limbs on its own initiative. This re-assessment follows the results of the National Pharmacovigilance Survey (2008-2010)[1] which demonstrated a risk of ischaemic complications at a distant site from the site of injection of a venous sclerosing agent.
The proprietary medicinal products concerned are those currently included on the list of medicines approved for hospital use and/or on the list of medicines reimbursed by National Insurance: AETOXISCLEROL and TROMBOVAR.
As the administration of these two drugs in foam form is currently an off-label use, this assessment only concerns the liquid forms. This assessment also does not concern the proprietary drug SCLEREMO, which is not included on the list of medicines approved for hospital use nor on the list of medicines reimbursed by National Insurance (the pharmaceutical company has not applied for reimbursement).

2. CHARACTERISTICS OF THE MEDICINAL PRODUCT

2.1. Active ingredient

Lauromacrogol 400 (macrogol 9 lauryl ether or polidocanol)

2.2. Indications

AETOXISCLEROL TAMPONNE 0.5%:
“Sclerotherapy of varicosities and varicose veins of the foot and perimalleolar region.”
AETOXISCLEROL TAMPONNE 2%:
“Sclerotherapy of medium-sized varicose veins.”
AETOXISCLEROL TAMPONNE 3%:
“Sclerotherapy of medium-sized and large varicose veins.”

2.3. Dosage

“For intravenous (IV) injection only.
It is advisable to start each treatment session with the administration of a minimal test dose.
1 to 4 ml of injectable solution per treatment session (½ to 2 ampoules).
Ensure that the needle is correctly positioned in the varicose veins.

Contraindications
- Known allergy to lauromacrogol 400 or one of its excipients
- Patients with prolonged immobility
- Recent thromboembolic episode
- Progressive cancer
- Known symptomatic patent foramen ovale
- Erysipelas and lymphangitis in the area to be treated

1 AFSSAPS. “Enquête sur les sclérosants veineux et le risque d’accidents ischémiques” [Enquiry into venous sclerosing agents and the risk of ischaemic accidents]. National Pharmacovigilance Commission, report of meeting of 25 May 2010. http://www.afssaps.fr/var/afssaps_site/storage/original/application/aa07caf63db776ac463eb68290f9676b.pdf

Special warnings
Any injection outside a vein may trigger severe necrosis.
Intra-arterial injections are particularly serious and may necessitate amputation.
As it is possible for the product or cell debris to be carried to the heart, the presence of PFO may favour the occurrence of arterial accidents. As such, investigations for patent foramen ovale are recommended before sclerotherapy in patients with a history of cerebrovascular accident, pulmonary hypertension or migraine with aura.
The injections must be carried out exclusively by an experienced physician. Ultrasound guidance is recommended.
Sclerotherapy is not recommended in patients with:
- a history of thromboembolic disease;
- increased risk of thromboembolic disease;
- known hereditary thrombophilia.

If sclerotherapy is required, preventative anticoagulant treatment may be initiated.

Precautions for use
In patients with a known but asymptomatic patent foramen ovale, smaller volumes should be used and any closed-glottis effort (Valsalva manoeuvre) should be avoid in the minutes following the injection .
In patients with migraine, smaller volumes should be used.
Concomitant use with beta-blockers has the risk of reducing cardiovascular compensation reactions in the event of anaphylactic shock.
For a few minutes after the injection, look out for signs suggestive of hypersensitivity (redness of the skin and conjunctiva, pruritus, cough, etc.) and neurological signs (scotomas, amaurosis, migraine with aura, paraesthesia, focal deficit).
This drug contains small quantities of ethanol (alcohol), less than 100 mg per ampoule.”

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification

C : Cardiovascular system
C05 : Vasoprotectives
C05B : Antivaricose therapy
C05BB : Sclerosing agents for local injection
C05BB02 : Polidocanol

3.2. Medicines

There are other sclerosing agents reimbursed by National Insurance:
TROMBOVAR 1% and 3% indicated for "Sclerotherapy of varicose veins, oesophageal varices, sebaceous cysts, lipomas and mucoid cysts."

3.3. Other health technologies

There are other techniques for occluding varicose veins (radiofrequency ablation, endovenous laser treatment, saphenous vein clipping), excision techniques (crossectomy and stripping, phlebectomy) and conservative techniques (ambulatory haemodynamic treatment of venous insufficiency, external valvuloplasty).

It should be noted that for some 15 years, techniques for converting the sclerosing agent into a foam have been developed, in order to reduce miscibility in the blood flow and to increase the contact time. However, the Marketing Authorisation for sclerosing agents only provides for their injection in liquid form. Administration of a foam form is therefore currently an off-label use.

4. REMINDER OF THE COMMITTEE'S OPINIONS

Opinion of 2 July 1997

"Transparency Committee conclusions
Improvement in actual benefit (IAB)
VEINOSCLEROL 0.5%, VEINOSCLEROL 2% and VEINOSCLEROL 3% do not offer an improvement in actual benefit in relation to the reference treatment drugs in the same therapeutic category.
Transparency Committee recommendations
The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services."

Opinion of 6 January 1999

The proprietary medicinal products VEINOSCLEROL 0.5%, 2% and 3% will be marketed under the name AETOXISCLEROL TAMPONNE 0.5%, 2% and 3%.

5. USAGE DATA

AETOXISCLEROL

The sales data provided by the pharmaceutical company show that 1,680,375 ampoules of AETOXISCLEROL were sold in 2011, distributed as follows:

Dosage	Boxes of 5 ampoules
AETOXISCLEROL 0.5%	194,715
AETOXISCLEROL 2%	98,325
AETOXISCLEROL 3%	43,035

As the dosages in the Marketing Authorisation provide for the injection of 1 to 4 ml of solution per treatment, i.e. ½ to 2 ampoules per treatment session, the number of sclerotherapy sessions performed with AETOXISCLEROL in 2011 can be estimated to be between 840,188 and 3,360,750.

As stated previously (paragraph 3.3), two varicose veins sclerotherapy practices coexist. The older approach uses a sclerosing agent in liquid form, which is the only presentation with Marketing Authorisation. Over the past 15 years or so, another practice has been developed: the extemporaneous conversion of the liquid form into a foam. This is achieved by mixing the liquid sclerosing agent with a gas (ambient air or CO_2). The foam form is not standardised and a number of variants have been described. As the preparation obtained is very unstable, it is created by a health professional immediately before injection. It should be noted that whatever the form of sclerosing agent used (foam or liquid), the drug is reimbursed by National Insurance, even though one of these two forms constitutes an off-label use.

6. ANALYSIS OF AVAILABLE DATA

Data allowing assessment of the efficacy of sclerotherapy using liquid sclerosing agents for varicose veins of the lower limbs have been sought since 2002, and come from literature reviews and a meta-analysis.
However, these publications do not distinguish clearly between the different sclerosing agents or their dosage, nor sometimes their form (liquid or foam). Clinical trials conducted with polidocanol in liquid form have also been included.
The assessment of AETOXISCLEROL's safety is based primarily on the National Pharmacovigilance Survey and changes to the SPC which result from data from the literature.
The pharmaceutical company has also supplied a periodic safety update report (PSUR) covering the period from 1 April 2008 to 31 March 2011.

6.1. Efficacy of sclerotherapy

Literature reviews and a meta-analysis compared sclerotherapy to surgery, to placebo or to other sclerosing agents in the treatment of varicose veins and telangiectasias, primarily in terms of recurrence of varicose veins, improvement in symptoms (such as pain and discomfort) and improvement in aesthetic appearance.

Sclerotherapy versus surgery in the treatment of varicose veins
In the meta-analysis by Murad[2] (2011), one of the analyses compared surgery versus liquid sclerotherapy. No difference was observed between these two techniques in terms of varicose veins recurrence (RR: 0.56; 95% CI: 0.29-1.06) (10 clinical trials). However, after exclusion of three trials with a follow-up period less than or equal to 2 years, a reduction in the number of recurrent varicose veins was observed with surgery in comparison to sclerotherapy (RR: 0.45; 95% CI: 0.22-0.93). The authors nonetheless noted the weak methodology of the trials included (poorly described randomisation, primarily open-label trials, short duration of follow-up).

A Cochrane[3] review aiming to compare sclerotherapy with surgery has also been published (2009). Nine randomised controlled clinical trials were included. The endpoints and classification systems of these trials were very heterogeneous, with the result that no meta-analysis could be performed. The authors conclude that the quality of evidence from these trials does not allow either of the two techniques to be recommended over the other.

Assessment of different sclerosing agents in the treatment of varicose veins
A Cochrane[4] review aiming to evaluate the efficacy (improvement of symptoms and of aesthetic appearance, recurrence rate) and safety of sclerotherapy in the symptomatic and aesthetic treatment of varicose veins has been published (2006). Seventeen randomised trials were included. Three studies comparing sodium tetradecyl sulfate to other sclerosing agents did not show any difference in terms of efficacy and tolerance. The authors conclude that there are no robust data from randomised trials that can influence the choice of sclerosing agent, nor the form used (liquid or foam).

2 Murad M.H. *et al.* A systematic review and meta-analysis of the treatments of varicose veins. J Vasc Surg. 2011 May; 53 (5 Suppl): 49S-65S.
3 Rigby KA. *et al*. Surgery versus sclerotherapy for the treatment of varicose veins. *Cochrane Database of Systematic Reviews* 2009, Issue 1 (initially published 2004).
4 Tisi PV, Beverley C, Rees A. Injection sclerotherapy for varicose veins. *Cochrane Database of Systematic Reviews* 2011, Issue 5 (initially published 2006).

Comparisons between different sclerosing agents and versus placebo in the treatment of telangiectasias

A Cochrane review[5] aiming to evaluate the efficacy in terms of aesthetic improvement and safety of sclerosing agents in the treatment of telangiectasias of the lower limbs was also published (2011). This review included 10 randomised trials (484 patients) comparing sclerosing agents (including polidocanol and sodium tetradecyl sulfate) to placebo, to no treatment or to another sclerosing agent (or combination of sclerosing agents). The data did not allow a meta-analysis to be performed. No difference was observed in terms of efficacy between sclerosing agents, but only superiority (particularly for polidocanol and sodium tetradecyl sulfate) versus placebo. Similarly, no difference was observed in terms of patient satisfaction for one sclerosing agent over the others. The authors state that the quality of evidence in this field is weak, and that the methodological quality of these trials was weak overall. They conclude that to date, there is not sufficient proof to recommend the use of one sclerosing agent rather than another in the treatment of telangiectasias of the lower limbs.

Comparison evaluating health technologies in the treatment of varicose veins, reticular veins and telangiectasias

An assessment of health technologies has also been conducted by the Alberta Heritage Foundation for Medical Research (2004),[6] which concludes, on the basis of data from the literature (randomised clinical trials, systematic reviews, guidelines and consensus documents), from expert opinions and from clinical practice:

- that sclerotherapy seems to be a preferential treatment in the management of reticular veins and telangiectasias (in terms of pain relief and/or relief of discomfort, and short-term improvement in aesthetic appearance). Polidocanol and sodium tetradecyl sulfate are relatively well tolerated. The authors emphasise, however, that there is no standardised protocol for use;
- in clinical practice, sclerotherapy seems to be limited to small veins, post-surgical treatment of the remaining veins and cases of recurrence.

In conclusion, the authors emphasise that there is no solid evidence allowing sclerotherapy to be recommended or not recommended in the symptomatic treatment of varicose veins, whatever their size.

6.2. Efficacy of polidocanol used in liquid form: data from clinical trials

The literature reviews and the meta-analysis (Murad) cited above do not allow any distinction between the different sclerosing agents or their doses, or sometimes between their forms (liquid or foam). Clinical trials conducted with polidocanol used in liquid form were also sought and the randomised controlled trials are presented in the table below.

The main clinical trials (randomised controlled trials in more than 30 patients) showed:

- elimination of reflux of the great saphenous vein (with incontinence) at 3 weeks in 35% to 40% of patients treated with a single injection of 2 to 2.5 ml of liquid polidocanol 3%;
- elimination of reflux of the great saphenous vein (with incontinence) at 3 months in 27% of patients treated with 4 ml of liquid polidocanol 3% (mean number of sessions per patient: 1.6);
- complete sclerosis of reticular veins at 3 months in 54% of patients treated with 0.5 ml polidocanol (1% to 2.5%).

However, the clinical trials are generally of weak methodological quality with follow-up periods that are too short to evaluate long-term efficacy, and numbers of patients that are sometimes too low.

5 Schwartz L, Maxwell H. Sclerotherapy for lower limb telangiectasias. *Cochrane Database of Systematic Reviews* 2011, Issue 12.

6.Corabian P, Harstall C. Sclerotherapy for leg varicose veins. Alberta Heritage Foundation for Medical Research, May 2004.

Table 1: Efficacy of polidocanol used in liquid form: data from randomised clinical trials

Methods	Indication	Treatments	Endpoint	Results
Rabe E. et al. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. EJVS 2008 Feb.35; 238-45				
Open-label randomised controlled trial Multicentre trial comparing efficacy of polidocanol foam versus liquid	Incontinence of the great saphenous vein (diameter less than 12 mm) CEAP: C_2-C_5, Ep, As, Pr	- 4 ml polidocanol 3% liquid 5 ml foam (7.4 ml sterile air + 1.6 ml polidocanol 3%) - Class II support stockings for at least 8 hours/day for 14 days	Primary: Elimination of reflux (<0.5 sec) measured 3 cm from the saphenofemoral junction by Duplex ultrasound 3 months after the last injection. Secondary: Occlusion of the great saphenous vein 3 cm and 25 cm from the saphenofemoral junction evaluated by Duplex ultrasound; Validated patient questionnaire on quality of life before treatment and 3 months after the last injection (Chronic Venous Insufficiency Questionnaire); Evaluation of treatment by the patient on a 5-point scale.	N=106 with primary varicose veins due to incontinence of the great saphenous vein (liquid N=52, foam N=54). The mean number of treatment sessions per patient was 1.3 for the foam and 1.6 for the liquid form. Elimination of reflux in 69% of patients treated with the foam versus 27% of patients treated with the liquid form (p<0.0001). The number of patients with occlusion of the great saphenous vein at 3 cm and 25 cm was higher in the groups treated with the foam versus the liquid form (p ≤0.0001). Patient satisfaction was higher in the group treated with foam (p=0.0008). Substantial differences in response rate were observed between centres. No serious adverse effect was observed.
Hamel-Desnos C. et al. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. Dermatol Surg. 2003 Dec; 29: 1170-5				
Multicentre randomised trial comparing efficacy of polidocanol foam versus liquid	Incontinence of the great saphenous vein (diameter 4-8 mm)	- Polidocanol 3% foam (ratio 1:5) (2.5 ml of foam contains 0.5 ml polidocanol) - Polidocanol 3% liquid 1 single injection of 2 ml (for a diameter of 4-6 mm) or 2.5 ml (for a diameter of 6-8 mm).	Primary: Elimination of reflux evaluated by Duplex ultrasound. Secondary: Length of occlusion, recanalisation and incidence of adverse effects.	N=88 (foam N=45, liquid N=43) Elimination of reflux of the great saphenous vein was observed in 84% of patients treated with the foam versus 40% treated with the liquid form (p<0.01) at 3 weeks. The occlusion was longer (no statistical calculation) in patients treated with the foam (28 cm on average versus 15 cm with the liquid form). At 6 months and 1 year, 6 recanalisations were observed in the group treated with the liquid form versus 2 with the foam (no statistical calculations). Inflammatory skin reactions (3 for the liquid form and 2 for the foam) and 1 haematoma (foam form) were observed.

<table>
<tr><th colspan="5">Ouvry P. et al. Efficacy of polidocanol foam versus liquid in sclerotherapy of the great saphenous vein: a multicentre randomised controlled trial with a 2-year follow-up. EJVS 2008 Sep; 36: 366-70</th></tr>
<tr><td>Multicentre randomised controlled trial comparing efficacy of polidocanol foam versus liquid</td><td>Incontinence of the great saphenous vein (diameter 4-8 mm)
CEAP: C_2-C_6</td><td>- 1 single injection of 2 to 2.5 ml polidocanol 3% liquid, or
- polidocanol 3% foam</td><td>Primary:
Elimination of reflux of the great saphenous vein evaluated by Duplex ultrasound.
Evaluation performed 3 weeks after treatment then every 6 months for 2 years.
Secondary:
Length of occlusion of the saphenous vein measured by ultrasound.</td><td>N=95 (liquid: N=48; foam: N=47)
Complete elimination of reflux of the great saphenous vein at 3 weeks in 17/48 (35%) of patients treated with the liquid form and 40/47 (85%) of patients treated with the foam (p<0.001).
The mean length of occlusion was greater in the group treated with the foam (26 cm vs. 9 cm, p<0.0001).
5 patients were lost to follow-up at 2 years (all belonging to the group of patients treated with the foam) and included in the final analysis as treatment failures (success rate i.e. absence of recanalisation at 2 years: 53% for the foam versus 12% for the liquid form).</td></tr>
<tr><th colspan="5">Alòs J. et al. Efficacy and safety of sclerotherapy using polidocanol foam: a controlled clinical trial. EJVS 2006 Jan; 31: 101-7</th></tr>
<tr><td>Multicentre, randomised, double-blind crossover study with 1 year of follow-up comparing efficacy of polidocanol foam versus liquid</td><td>Symptomatic primary reticular veins (>2 mm in diameter) or post-operative varicose veins (not involving the sapheno-femoral junction).</td><td>-Treatment with polidocanol foam and liquid forms in each patient, on similar varicose veins.
- Then compression for 48 hours (25-35 mmHg).
Concentrations and volumes used:
<table><tr><th>Diameter</th><th>Liquid</th><th>Foam</th></tr><tr><td>1-2 mm</td><td>1%</td><td>0.5%</td></tr><tr><td>2.1-3 mm</td><td>1.25%</td><td>0.65%</td></tr><tr><td>3.1-4 mm</td><td>1.5%</td><td>0.75%</td></tr><tr><td>4.1-5 mm</td><td>2%</td><td>1%</td></tr><tr><td>5.1-6mm</td><td>2.5%</td><td>1.25%</td></tr><tr><td>Volume /injection</td><td>0.5 ml</td><td>2 ml</td></tr><tr><td>Polido-canol quantity/ injection</td><td>0.5 ml</td><td>0.5 ml</td></tr></table></td><td>Primary:
Evaluation by Duplex ultrasound (diameter and length of sclerosed vein) on D15, D30 and D90.
Secondary:
Clinical evaluation (pain, inflammation, pigmentation) on D15, D30, D90 and D365.
Evaluation of patient satisfaction on a visual analogue scale.</td><td>N=75 (liquid: N=75; foam: N=75).
4 withdrawals from the trial at D90 and 12 at D365.
At D90: complete sclerosis in 94% of patients treated with the foam versus 54% for the liquid form (p<0.001) with a greater length of sclerosis in patients treated with the foam (10.1 cm versus 7.2; p<0.001).
Pain (D15 and D30, p<0.001) and pigmentation (D15 to D365, p<0.0001) was more frequent with the foam.
No statistically significant difference between the groups regarding patient satisfaction on D365.</td></tr>
</table>

<table>
<tr><td colspan="5">Rao J. et al. Double-blind prospective comparative trial between foamed and liquid polidocanol and sodium tetradecyl sulfate in the treatment of varicose and telangiectatic leg veins. Dermatol Surg 2005; 31: 631-5</td></tr>
<tr><td>Randomised, controlled, double-blind trial evaluating efficacy of polidocanol and sodium tetradecyl sulfate in liquid and foam forms</td><td>Varicose veins and telangi-ectasias of the lower limbs without incontinence of the sapheno-femoral and sapheno-popliteal junction</td><td>Patients randomised to receive polidocanol treatment in the veins of the right or left leg and sodium tetradecyl sulfate treatment in the veins of the other leg.
Dosage determined according to vein size:
<1 mm diameter: 0.25% STS liquid or 0.5% POL liquid
1-3 mm: 0.5% STS liquid or 1% POL foam
3-6 mm: 0.5% STS foam or 1% POL foam</td><td>Primary:
Evaluation from numbered photos of vein condition before treatment and 12 weeks after treatment using a 5-point scale ranging from 1 (aggravation) to 5 (complete eradication)</td><td>N=20
Results at 12 weeks:
<table>
<tr><td>Vein diameter</td><td colspan="2"><1 mm</td><td colspan="2">1-3 mm</td><td colspan="2">3-6 mm</td></tr>
<tr><td>Treat-ment</td><td>STS 0.25% liquid (N=19 veins)</td><td>POL 0.5% liquid (N=18 veins)</td><td>STS 0.5% liquid (N=15 veins)</td><td>POL 1% foam (N=14 veins)</td><td>STS 0.5% foam (N=10 veins)</td><td>POL 1% foam (N=10 veins)</td></tr>
<tr><td>Mean score</td><td>4.25</td><td>4.5</td><td>4.5</td><td>4.25</td><td>3.75</td><td>3.25</td></tr>
</table>
1: aggravation, 2: no change, 3: minimal eradication, 4: moderate eradication, 5: complete eradication
The adverse effects observed were expected, according to the authors, involving primarily ecchymosis and hyperpigmentation.</td></tr>
<tr><td colspan="5">Kahle B. et al. Efficacy of sclerotherapy in varicose veins - A prospective, blinded, placebo-controlled study. Dermatol Surg. 2004 May; 30: 723-8</td></tr>
<tr><td>Controlled, randomised, double-blind trial evaluating efficacy of liquid polidocanol versus placebo</td><td>Varicose veins (diameter 3-6 mm)
CEAP: C_{2}-$_{4}$, Ep, Asp, Pr without incontinence of the sapheno-femoral and sapheno-popliteal junction</td><td>Polidocanol liquid 2% (3-4 mm veins) and 3% (5-6 mm veins)
Placebo
Then adhesive compression bandage for 2-3 days, followed by support stockings (class II) for 1 week.</td><td>Primary:
Venous occlusion and haemodynamic improvement measured by Duplex ultrasound at weeks 1, 4 and 12.</td><td>N=25 (polidocanol N=14, placebo N=11)
Complete occlusion in 76.8% of patients treated with polidocanol (p<0.0001) 4 and 12 weeks after treatment, versus 0% in the placebo group.
Venous/arterial flow volume ratio decreased from 1.45 ± 0.66 to 1.06 ± 0.2 (p=0.05) at 12 weeks.</td></tr>
</table>

<table>
<tr><th colspan="5">Goldman MP. Treatment of varicose and telangiectatic leg veins: double-blind prospective comparative trial between aethoxyskerol and sotradecol. Dermatol Surg. 2002 Jan; 28(1): 52-5</th></tr>
<tr>
<td>Double-blind randomised trial evaluating efficacy of liquid polidocanol versus sodium tetradecyl sulfate</td>
<td>Varicose veins and telangi-ectasias of the lower limbs without incontinence of the sapheno-femoral and sapheno-popliteal junctions</td>
<td>- Polidocanol liquid (0.5%, 1%, 3%)
- Sodium tetradecyl sulfate liquid (0.25%, 0.5%, 1.5%)
Dosage determined according to vein size</td>
<td>Primary:
Evaluation from numbered photos of vein condition before treatment and 1, 4 and 16 weeks after treatment using a 5-point scale ranging from 1 (aggravation) to 5 (complete eradication)</td>
<td>N=129
No statistically significant difference in the primary endpoint was observed between the two treatments.

<table>
<tr><td>Diameter</td><td colspan="2"><1 mm</td><td colspan="2">1-3 mm</td><td colspan="2">3-6 mm</td><td colspan="2">Total</td></tr>
<tr><td>Treatment</td><td>STS 0.25% (N=32)</td><td>POL 0.5% (N=26)</td><td>STS 0.5% (N=28)</td><td>POL 1.0% (N=27)</td><td>STS 1.5% (N=27)</td><td>POL 3% (N=27)</td><td>STS (N=69)</td><td>POL (N=60)</td></tr>
<tr><td>Mean score</td><td>4.4 ± 0.6</td><td>4.6 ± 0.4</td><td>4.6 ± 0.8</td><td>4.4 ± 0.6</td><td>4.5 ± 0.4</td><td>4.7 ± 0.4</td><td>4.5 ± 0.7</td><td>4.5 ± 0.5</td></tr>
<tr><td>p</td><td colspan="2">p=0.055</td><td colspan="2">p=0.832</td><td colspan="2">p=0.581</td><td colspan="2">p=0.117</td></tr>
</table>
1 : aggravation, 2: no change, 3: minimal eradication, 4: moderate eradication, 5: complete eradication

The main adverse events were ecchymosis (STS: 70%, POL: 58%), hyperpigmentation (STS: 64%, POL: 53%), venous thrombosis (STS: 46%, POL: 42%), local urticaria (STS: 36%, POL: 23%) and skin necrosis (STS: 6.6%, POL: 0%).</td>
</tr>
</table>

6.3. Adverse effects

6.3.1 National Pharmacovigilance Survey into venous sclerosing agents and ischaemic adverse effects (2008-2010)

Introduction: This enquiry follows the signalling of one case of cardiorespiratory arrest and one case of transitory ischaemic accident occurring a few minutes after injection of AETOXISCLEROL in foam form.
It covers ischaemic adverse effects from venous sclerosing agents (AETOXISCLEROL, TROMBOVAR and SCLEREMO).
The aim was to identify any signal from use of the foam form in comparison to the liquid form.

Method: An analysis of the adverse effects reported in France (from the national pharmacovigilance databases and pharmaceutical company data), of the literature and of clinical trials was performed.

Results:
Spontaneous notifications revealed a risk of venous thrombosis, pulmonary embolism, migraine with aura, myocardial infarction, and transitory ischaemic accident or even cerebrovascular accident (CVA) common to all sclerosing agents. The cases notified spontaneously did not allow a profile to be established differentiating foam form from liquid form for each proprietary medicinal product.
The number of cases from spontaneous notification and from the literature is presented in Table 2.
The literature review found four published cases of CVA[7], including one where the foam form was implicated, with evidence of particles in the carotid artery on ultrasound. Two other publications report the occurrence of transitory ischaemic accident (TIA) following sclerotherapy. In addition, in a study[8] including 33 patients, the presence of intracardiac microemboli was demonstrated within 15 to 45 minutes of sclerotherapy in all patients. These results were confirmed by another study[9] in 45 patients, showing the presence of cerebral microemboli on cerebral ultrasound whereas MRI was normal. The incidences of adverse effects found in the literature allowed CVAs and TIAs to be described as rare, migraines and related disorders as common, neurological disorders of any kind (confusion, vertigo, seizures, etc.) as common, cardiac disorders as rare (except for tightness of the chest, which is very common), deep vein thrombosis and pulmonary embolism as uncommon to common, and skin necrosis as rare to common. The literature is focused on evaluation of the foam form, does not answer the question of dose-dependence and does not allow an individual profile to be established for each proprietary medicinal product.

7 Forlee MV. Stroke after varicose vein foam injection sclerotherapy. J Vas Surg 2006.
8 Ceulen and Vernooy. Microembolism during foam sclerotherapy of varicose veins. NEJM, 2008.
9 Rush JE, Wright DDI. More on microembolism and foam sclerotherapy. NEJM 2008. 359; 6:656-7.

Table 2: Number of cases from spontaneous notification and the literature – National Pharmacovigilance Survey into venous sclerosing agents and ischaemic adverse effects

		POL				STS				Glycerol Chrome alum	
		Solution		Foam		Solution		Foam			
		Notif.	Lit.	Notif.	Lit.	Notif.	Lit.	Notif.	Lit.	Notif.	Lit.
Neurological disorders	TIA, CVA	1	3	0	3	1	0	0	3	1	0
	Migraine, visual disorders	11	0	7	8	4	0	0	0	4	1
	Other	10	1	2	0	3	0	0	1	4	0
Cardiac disorders		6	0	3	1	1	1	0	2	0	1
Thromboembolic AEs	PE	1	3	0	1	2	1	0	0	0	0
	DVT	2	1	1	1	2	0	0	0	0	0
	Peripheral arterial thrombosis	2	0	0	0	1	6	0	0	2	0
Vasculitis		3	0	0	0	1	0	0	0	2	0

POL: Polidocanol
STS: Sodium tetradecyl sulfate
Notif.: Spontaneous notification (no. of cases)
Lit.: Literature (no. of cases)

Where the information was available, the time to onset of neurological and cardiac disorders was a few minutes after the injection.
Table 3 presents the number of adverse effects notified and the corresponding rates (number of cases per litre sold) per medicine. Almost 3.5 times more adverse effects were reported with AETOXISCLEROL but this medicine is sold more (4 times more in recent years) than TROMBOVAR (which has been out of stock since October 2009).

Table 3: Rates of notification of AEs (number of cases per litre sold) – National Pharmacovigilance Survey into venous sclerosing agents and ischaemic adverse effects

Brand name	**AETOXISCLEROL®**	**TROMBOVAR®**	**SCLEREMO®**
INN	Lauromacrogol 400	Sodium tetradecyl sulfate	Glycerol and chrome alum
Number of ischaemic AEs with the liquid	39	15	13
Number of ischaemic AEs with the foam	13	01	N/A
Total number of ischaemic AEs	52	15	13
Rate of notifications per litre sold	$63x10^{-5}$	$36x10^{-5}$	$56x10^{-5}$

Conclusion: The signal from spontaneous reporting is relatively weak but real. However, a strong signal is found in the literature. Furthermore, the chronology of onset is very suggestive. Thus, the risk of ischaemic complications at a distant site from the injection site, observed whatever the dosage form administered, can be considered as a class effect that remains relatively rare. It is still difficult to differentiate safety profiles between the foam and liquid forms. A number of mechanisms have been suggested that imply sclerosing agents have a causal role (vasospasm, migration of the product or of cell debris into the pulmonary circulation via the right heart, or via a patent foramen ovale [connecting the two atria in 20% to 35% of adults]). Finally, the literature and notifications do not demonstrate a dose-dependent effect. However, most authors describe their concern to administer the lowest doses possible in order to limit the effects.
Following this enquiry, suggestions have been made: to standardise SPCs, conduct additional research (i. to determine the nature of the circulating particles as well as their effects on haemostasis, ii. on larger numbers of patients in order to determine the incidence

and dose-dependent relationship of adverse effects, and iii. to establish the usefulness of physical means of preventing adverse effects) and, for physicians involved in the evaluation, recommendations for these future clinical studies.

Changes were made to the SPC in March 2011, following the pharmacovigilance enquiry, and are cited in Appendix 1. These primarily concern sections 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 4.8 “Adverse effects”. The contraindications added were as follows:

- Patients with prolonged immobility
- Recent thromboembolic episode
- Progressive cancer
- Known symptomatic patent foramen ovale
- Erysipelas and lymphangitis in the area to be treated

6.3.2 PSUR

The pharmaceutical company provided safety data covering the period from 1 April 2008 to 31 March 2011. As more than 5,600,000 ampoules had been sold, the number of patients exposed was estimated by the company to be between 2,800,000 and 11,300,000. In total, 58 serious adverse effects were reported, primarily nervous system complaints (n=14) and general or injection-site effects (n=13).

6.3.3 Data from the literature

A study[10] conducted over 8 weeks (+ 1 month follow-up), including 12,173 sessions of sclerotherapy (taking all sclerosing agents together) using the liquid form (5,434 sessions), foam form (6,395 sessions) or both forms (344 sessions) has been published. The incidence of adverse events observed was 0.1% for the liquid form and 0.3% for the foam form, with reversible visual impairments predominating (0.07% for the liquid form and 0.25% for the foam). One case of femoral venous thrombosis was observed after administration of the foam form.

From this trial, a longer-term follow-up[11] was conducted in 1,605 patients who had received at least one injection of polidocanol (72% of patients followed up at 12 months, and 59% at 24 months). Of the 6,284 sessions where polidocanol was injected, 1,986 used the liquid form and 4,298 the foam. The incidence of adverse events was 0.25% with the liquid form (1 cramp, 2 inflammatory reactions, 1 hyperpigmentation and 1 visual impairment) and 1.1% with the foam (primarily 13 visual impairments, 8 cases of muscular venous thrombosis and 7 headaches). One case of deep vein thrombosis was observed after use of the foam form. The majority of events occurred within 4 weeks (75%) or immediately after injection (51%).

6.4. Conclusion

The published data as a whole evaluate elimination of reflux, improvement of symptoms (such as pain and discomfort) and aesthetic improvement in the short term, but do not allow the evaluation of impact on incidence of and time to recurrence, progression to chronic complications such as trophic changes (including ulceration), or progression to acute complications such as superficial venous thrombosis (which could progress to peripheral deep vein thrombosis or pulmonary embolism) and varicose haemorrhage.

In view of all these data, the level of evidence for the efficacy of AETOXISCLEROL is low. Its effect size and clinical relevance cannot be assessed with precision.

The level of evidence of the data available does not allow the use of one treatment to be recommended over another, whatever the size of vein.

No difference in efficacy has been clearly demonstrated between the different sclerosing products.

10 Guex JJ. et al. Immediate and midterm complications of sclerotherapy: report of a prospective multicenter registry of 12,173 sclerotherapy sessions. Dermatol Surg. 2005; 31:123-8; discussion 128.

11 Guex JJ.et al. The French polidocanol study on long-term side effects: a survey covering 3,357 patient years. Dermatol Surg 2010 Jun; 36: 993-1003.

Sclerosing agents carry a risk of ischaemic adverse effects, whatever the form used (foam or liquid), which is considered to be a relatively rare class effect (National Pharmacovigilance Survey, AFSSAPS).

7. TRANSPARENCY COMMITTEE CONCLUSIONS

7.1. Actual benefit

Varicose veins are the most common physical sign of chronic venous insufficiency. They are usually primary, and more rarely secondary to an abnormality of the deep venous circulation (post-thrombotic syndrome). Occurring in the lower limbs, they may be asymptomatic and only cause aesthetic damage, or be accompanied by symptoms such as a sensation of heaviness, swelling, cramps and restless legs. This is a chronic disease that can progress to worsening symptoms and, more rarely, trophic changes (of which the main complication is ulceration), superficial venous thrombosis and/or varicose haemorrhage. Varicose veins do not pose any direct threat to life, but may be indirectly life-threatening via their complications. In the absence of treatment, superficial venous thrombosis on varicose veins extends to the saphenofemoral junction in 3.4% of cases and is associated with deep vein thrombosis or pulmonary embolism in 1.3% of cases. [12]

These medicinal products are intended as curative therapy.

The efficacy/adverse effects ratio is moderate.

These medicinal products are first-line or second-line therapies.

There are numerous treatment alternatives.

The actual benefit of AETOXISCLEROL is **moderate**.

7.2. Therapeutic use

The international CEAP (clinical, etiologic, anatomic, pathophysiologic) classification can specify the clinical stage of varicose vein disease and orient therapeutic management. It consists of the following stages:
C0: no visible or palpable sign
C1: telangiectasias and reticular veins
C2: “true” varicose veins
C3: oedema
C4: trophic changes such as panniculitis, white atrophy and lipodermatosclerosis
C5: healed venous ulcer
C6: open venous ulcer

In its 2004 report, ANAES concluded that sclerotherapy and surgery are recommended in the treatment of grade C varicose veins.[13] However, surgery and sclerotherapy do not necessarily correspond to the same indications. In addition, the working group suggested a strategy for the management of varicose veins of the lower limbs (Table 4).

12 Decousus H et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med 2010; 363:1222-1232.
13 ANAES. Traitement des varices des membres inférieurs [Treatments for varicose veins of the lower limbs]. June 2004.

Table 4: Suggestion by the working group for the choice of techniques in the management of varicose veins of the lower limbs (ANAES 2004)

CEAP classification	Reflux	Technique suggested**	Other techniques possible	Current limitations of techniques
AS2 (above-knee great saphenous vein) C2 to C6	Ostial and truncal reflux	Crossectomy and stripping (with branch phlebectomy)	- Echosclerotherapy - Radiofrequency ablation - Laser treatment	- Diameter greater than 10-12 mm*** - Diameter greater than 12 mm - Significant sinuosity of the varicose vein
	Truncal reflux without ostial reflux	Echosclerotherapy	- Stripping without crossectomy (with branch phlebectomy) - Radiofrequency ablation - Laser treatment	- Diameter greater than 12 mm - Significant sinuosity of the varicose vein
AS3 (below-knee great saphenous vein) C2 to C6	Truncal reflux	Echosclerotherapy	- Sclerotherapy - Phlebectomy	
AS4 (small saphenous vein) C2 to C6	Ostial and truncal reflux	Crossectomy and stripping (with branch phlebectomy)	- Echosclerotherapy - Laser treatment	- Diameter greater than 10-12 mm*** - Significant sinuosity of the varicose vein
	Truncal reflux without ostial reflux	Echosclerotherapy	- Stripping without crossectomy (with branch phlebectomy) - Laser treatment	- Significant sinuosity of the varicose vein
AS5 and saphenous branches C2 to C6	Isolated reflux of other saphenous and non-saphenous branches	Sclerotherapy	- Phlebectomy - Echosclerotherapy	
Specific case: anterior accessory great saphenous vein of the thigh C2 to C6	Ostial and truncal reflux of the anterior accessory great saphenous vein of the thigh, without great saphenous reflux	Phlebectomy of the anterior saphenous vein with ligature at the junction, with no other phlebectomy or crossectomy, associated with conservation of the saphenous trunk	- Echosclerotherapy - Sclerotherapy	
AP 17	Reflux in perforating veins of the thigh	Ligature by open surgery + phlebectomy	Echosclerotherapy	
AP 18 (C3, C5)	Reflux in perforating veins of the thigh	Ligature by open surgery + phlebectomy	Echosclerotherapy	
AP 18 (C4, C6)	Reflux in perforating veins of the thigh	Endoscopic surgery on subfascial perforating veins	Echosclerotherapy	Perforating vein in the ulcer

* The table only includes techniques that destroy the varicose veins; the working group could not give an opinion on conservative techniques, given the lack of literature.
** The techniques suggested have been defined by the working groups as the techniques that should be chosen as comparators in a controlled clinical trial for the indication considered. This choice has been based on the historical reference treatment or, for recently individualised indications, on the most appropriate criterion of adaptation for the pathophysiological target.
*** Corresponds to the limit most often found in clinical trials of sclerotherapy.

The German Phlebology Society considers sclerotherapy (without differentiating the liquid form from the foam form) to be a method of choice in the treatment of small varicose veins (reticular veins, telangiectasias).[14]

The Society for Vascular Surgery and the American Venous Forum[15] recommend liquid or foam sclerotherapy in the treatment of tributary veins, in the same capacity as phlebectomy (grade 1B).

On the whole, the place of sclerosing agents used in liquid form and of AETOXISCLEROL in the treatment strategy for varicose veins of the lower limbs has not been clearly established.
According to expert opinion, AETOXISCLEROL has a place in the treatment strategy for some varicose veins of the lower limbs, as first-line or second-line therapy depending on the

14 Rabe E. et al. Guidelines for sclerotherapy of varicose veins (ICD 10: I83.0, I83.1, I83.2, and I83.9). Dermatol Surg. 2004; 30: 687-93; discussion 693.
15 Gloviczki P. et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011; 53 (5 Suppl): 2S-48S.

CEAP classification (symptomatic C1 to C6) and the different concentrations of the product for adapting to the size of varicose vein. The main limitation remains, however, varicose veins with a diameter greater than 8-10 mm and/or an ostial reflux. It should be noted that the aim of treatment of telangiectasias and reticular veins is primarily aesthetic.
On the other hand, AETOXISCLEROL has a place in the treatment of tributary veins as supplementary therapy following traditional or endovenous surgery, or where there are contraindications to surgery.

7.3. Target population

An estimate of the number of patients who received a sclerotherapy procedure in 2011 in France was undertaken from the general sample of beneficiaries (*échantillon généraliste des bénéficiaires* – EGB).
The following CCAM procedures were used: session of sclerosis of a vein of the lower extremity, by transcutaneous intravenous injection with ultrasound guidance (ENJN001) and session of sclerosis of a varicose veins of the lower extremity, by transcutaneous intravenous injection without guidance (EJNF002).
If these EGB data are extrapolated to the French population,[16] the number of people who have had at least one sclerotherapy procedure in private establishments and surgeries in 2011 is estimated to be **312,336 (95% CI 300,909 to 323,764)**.
This estimate does not take into account sclerotherapy procedures performed as outpatient treatment in public hospitals.

7.4. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services.

[16] The EGB is a representative sample of patients with French national insurance. It contains anonymous information about the demographic characteristics of beneficiaries, services reimbursed and long-term health conditions since 2003. EGB data are extrapolated to the French population by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01/01/2011 (n = 594,370) in relation to the French population on 01/01/2011 (n = 65,001,181). The extrapolation coefficient obtained was 1/109.36.

Appendix 1: SPC comparison table (July 1996 / January 2011)
AETOXISCLEROL Tamponné 0.50%, 2% and 3%

	SPC July 1996	SPC January 2011
4.2 Posology	1 to 4 ml of injectable solution per treatment session (½ to 2 ampoules). Ensure that the needle is correctly positioned in the varicose veins.	*For intravenous (IV) injection only.* *It is advisable to start each treatment session with the administration of a minimal test dose.* 1 to 4 ml of injectable solution per treatment session (½ to 2 ampoules). Ensure that the needle is correctly positioned in the varicose veins.
4.3 Contraindications	• Intra-arterial injection • Known allergy to lauromacrogol 400	Known allergy to lauromacrogol 400 *or one of its excipients* *· Patients with prolonged immobility* *· Recent episode of thromboembolism* *· Progressive cancer* *· Known symptomatic patent foramen ovale* *· Erysipelas and lymphangitis in the area to be treated*
4.4 Special warnings and precautions for use	Warnings: The injections must be carried out by an experienced physician. Any injection outside a vein may trigger severe necrosis. Precautions for use: In cases of intolerance to alcohol or treatment with drugs triggering an Antabuse-like reaction	*Special* warnings: Any injection outside a vein may trigger severe necrosis. *Intra-arterial injections are particularly serious and may necessitate amputation.* *As it is possible for the product or cell debris to be carried to the heart, the presence of PFO may favour the occurrence of arterial accidents. As such, investigations for patent foramen ovale are recommended before sclerotherapy in patients with a history of cerebrovascular accident, pulmonary hypertension or migraine with aura.* The injections must be carried out *exclusively* by an experienced physician. *Ultrasound guidance is recommended.* *Sclerotherapy is not recommended in patients with:* *· a history of thromboembolic disease;* *· increased risk of thromboembolic disease;* *· known hereditary thrombophilia.* *If sclerotherapy is required, preventative anticoagulant treatment may be administered.* Precautions for use: *In patients with a known but asymptomatic patent foramen ovale, smaller volumesshould be used and expiration against a closed glottis (the Valsalva manoeuvre) should be avoided for several minutes following the injection.* *In patients with migraine, smaller volumes should be used.* *Concomitant use with beta-blockers has the risk of reducing cardiovascular compensation*

	to alcohol.	*reactions in the event of anaphylactic shock.* *Monitor the patient for signs suggestive of hypersensitivity (redness of the skin and conjunctiva, pruritus, cough, etc.) and neurological signs (scotomas, amaurosis, migraine with aura, paraesthesia, focal deficit) for several minutes after the injection.* *This drug contains small quantities of ethanol (alcohol), less than 100 mg per ampoule.*
4.8 **Adverse effects**	• Residual pigmentation in cases of sun exposure • Possible local skin intolerance reactions in cases of paravenous injection	*The adverse effects, observed with differing frequencies, are listed below by system-organ class.* *Immune system disorders: anaphylactic shock, angioedema, urticaria, asthma* *Nervous system disorders: headaches, migraine, paraesthesia, loss of consciousness, delirium, vertigo* *Eye disorders: phosphenes, scotomas, amaurosis* *Cardiac disorders: palpitations. Due to the arrhythmogenic properties of lauromacrogol, there is the possibility of cardiovascular collapse linked to the systemic passage of the product* *Vascular disorders:* *- neovascularisation, haematoma* *- superficial thrombophlebitis, phlebitis* *- deep vein thrombosis* *- pulmonary embolism* *- vasovagal syncope* *- vasculitis, leukocytoclastic vasculitis* *Respiratory, thoracic and mediastinal disorders: dyspnoea, tightness of the chest* *Gastrointestinal disorders: dysgeusia, nausea* *Skin and subcutaneous tissue disorders:* *Skin hyperpigmentation, ecchymosis* *Allergic dermatitis, contact urticaria, erythema* *Hypertrichosis (in the area treated)* *General disorders and accidents linked to the site of administration:* *Pain at the injection site (short term), thrombosis at the injection site (local intravaricose blood clots)* *Induration, oedema* *Local necrotic-type reactions, particularly of the skin and underlying tissue (and, in some rare cases, the nerves) have been observed in the treatment of leg varicose veins after accidental injection into the surrounding tissue (paravenous injection). The risk is increased at higher concentrations and with larger volumes injected.* *Fever, hot flashes* *Investigations: abnormal blood pressure* *Lesions and intoxication: nerve lesion*

5.1 Pharmacodynamic properties	VASCULAR PROTECTOR / VENOUS SCLEROSING AGENT FOR LOCAL INJECTION Powerful and painless sclerosing agent. It acts essentially of the endothelia of varicose veins. A sclerotic thrombus forms and remains limited to the area where the endothelium is altered.	*ANTIVARICOSE THERAPY* / ~~VENOUS~~ SCLEROSING AGENT FOR LOCAL INJECTION Injection leads to *local destruction of the endothelium, generally accompanied by vasospasm*, then to a thrombus.