Examination of the dossier for the proprietary medicinal products included for a period of 5 years, renewable by tacit agreement, from 31.12.2008

**TROMBOVAR 1% IV**
B/10 x 2 ml ampoules (CIP code: 310 867-2)

**TROMBOVAR 3% IV**
B/10 x 2 ml ampoules (CIP code: 310 868-9)

Applicant: KREUSSLER PHARMA

sodium tetradecyl sulfate
ATC code: C05BB04 (ANTIVARICOSE THERAPY/SCLEROSING AGENTS FOR LOCAL INJECTION)

List II
Date of Marketing Authorisation: 10.06.1987 (national procedure)
Approval for hospital use (12.01.1982)/reimbursement by National Insurance (30%)

**Reasons for request:**
- Re-evaluation of the actual benefit following an initiative by the transparency Committee as provided for by Article R 163-21 of the Social Security Code.
- Renewal of inclusion on the list of proprietary medicinal products refundable by National Health Insurance.
- Changes to the Summary of Product Characteristics.
1. CONTEXT OF THE EVALUATION

The Transparency Committee took the initiative to reassess the actual benefit (AB) of sclerosing agents for the treatment of varicose veins of the lower limbs. This initiative was taken following the results of the national pharmacovigilance survey (2008-2010)\textsuperscript{1} which revealed a risk of ischaemic complications at a distance from the point of injection of a venous sclerosing agent.

The medicinal products concerned are those currently included on the list approved for use by hospitals and/or on the list of medicinal products refundable by National Insurance: AETOXISCLEROL and TROMBOVAR.

Since the use of these two medicinal products in foam form is at present an off-label practice, this evaluation concerns only the liquid forms. This evaluation also does not cover the medicinal product SCLEREMO, which is not on the list of medicines approved for use by hospitals or on the list of medicines refundable by National Insurance (since the company has not applied for reimbursement).

At the same time, the company was reminded of its duty to apply to the Committee for renewal of the inclusion of its medicines on the list of medicines refundable by National Insurance.

2. CHARACTERISTICS OF THE MEDICINAL PRODUCT

2.1. Active ingredient

Sodium tetradecyl sulfate

2.2. Indication

“Sclerosis of varicose veins, oesophageal varices, sebaceous cysts, lipomas and mucoid cysts.”

2.3. Dosage

“Strictly for intravenous administration.

It is desirable to start each injection session by administering a minimal test dose. The 1% solution is more commonly used than the 3% solution; The use of TROMBOVAR 3% must be restricted to the sclerosis of large varicose veins and varicose veins resistant to treatment with the 1% solution.

The usual dosage is 0.5 to 2 ml of injectable solution per session at points 6 to 12 cm apart, without exceeding, particularly for TROMBOVAR 3%, a total dose of 10 ml per session. Injections must be repeated every week or every two weeks, increasing the injection sites and progressively increasing the total dose per session.

\textsuperscript{1} AFSSAPS. “Survey on venous sclerosing agents and the risk of ischaemic accidents”, National Pharmacovigilance Committee, minutes of the meeting of 25 May 2010. http://www.afssaps.fr/var/afssaps_site/storage/original/application/aa07caf63db776ac463eb68290f9676b.pdf
**Contraindications**
- Known allergy to sodium tetradecyl sulfate or any of the excipients
- Patients suffering prolonged immobilisation
- A recent thromboembolic episode
- Progressing cancer
- Known symptomatic patent foramen ovale
- Erysipelas and lymphangitis in the area to be treated
- Children younger than 3 years.

**Special warnings**
Any injection outside a vein can cause serious necrosis.
Intra-arterial injection is particularly serious and may lead to a need for amputation.
Since there is a possibility of the product or cellular debris passing into the right heart, the presence of PFO may promote the occurrence of arterial accidents. Consequently, a check for patent foramen ovale is recommended before sclerotherapy in patients with a history of stroke, PAH or migraine with aura.
Injections must be given only by an experienced doctor. Ultrasound guidance is recommended.
Sclerotherapy is not recommended in patients with:
- a history of thromboembolic disease,
- an increased risk of thromboembolic disease,
- known hereditary thrombophilia.
If sclerotherapy is required, preventive anticoagulant treatment may be initiated.

**Precautions for use**
In patients with known but asymptomatic patent foramen ovale, smaller volumes should be used and any closed-glottis effort (Valsalva manoeuvre) should be avoided in the minutes following the injection.
In migraine patients, smaller volumes should be used.
Combination with beta-blockers is likely to reduce compensatory cardiovascular reactions in the event of anaphylactic shock.
For a few minutes after the injection, look out for signs suggestive of hypersensitivity (cutaneous and conjunctival redness, pruritus, cough, etc.) and neurological signs (scotoma, amaurosis, migraine with aura, paraesthesia, focal deficit).”
3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification

C : Cardiovascular system
C05 : Vasoprotectives
C05B : Antivariocose therapy
C05BB : Sclerosing agents for local injection
C05BB04 : Sodium tetradecyl sulfate

3.2. Medicinal products

These are other sclerosing agents reimbursable by health insurance:
AETOXISCLEROL TAMPONNE 0.5% (lauromacrogol 400), indicated in “sclerosis of varicose veins and varices of the foot and the perimalleolar region.”
AETOXISCLEROL TAMPONNE 2% (lauromacrogol 400), indicated in “sclerosis in medium-diameter varicose veins.”
AETOXISCLEROL TAMPONNE 3% (lauromacrogol 400), indicated in “sclerosis in medium- and large-diameter varicose veins.”

3.3. Other health technologies

These are other techniques for the obliteration of varicose veins (radiofrequency ablation, endovenous laser, endosaphenous clipping), excision techniques (crossectomy and stripping, phlebectomy) and conservative techniques (haemodynamic treatment of venous insufficiency on an outpatient basis (CHIVA), external valvuloplasty).

It should be noted that for about fifteen years there have been techniques for converting a sclerosing agent into a foam so as to reduce miscibility with the blood flow and to increase the contact time. However, the Marketing Authorisation for sclerosing agents makes provision only for their injection in liquid form. Use in the form of foam is therefore currently an off-label practice.
4. REMINDER OF THE COMMITTEE’S OPINIONS

Opinion of 24 November 1999

“Usual serious nature of the condition treated:
The condition treated with this proprietary medicinal product is not life-threatening, nor does it cause serious complications, or any disability, or a marked deterioration in quality of life.

Efficacy/safety of use of the medicinal product:
This proprietary medicinal product is a curative therapy.
The efficacy of this medicinal product in this indication is substantial.

Therapeutic use:
This proprietary medicinal product is an adjuvant medication.
There are medicinal and non-medicinal treatment alternatives to this proprietary medicinal product.

Public health benefit:
Not applicable.

Transparency Committee conclusions:
Level of actual benefit of this medicinal product: moderate.”

5. USAGE DATA

TROMBOVAR
Since TROMBOVAR has been out of stock since October 2009, no ampoules were sold in 2011.

As stated earlier (section 3.3), there are two methods of sclerosing varicose veins. The older one is sclerosis in liquid form; this is the only presentation with Marketing Authorisation. Another practice emerged about 15 years ago: extemporaneous conversion of the liquid form into a foam form. This is achieved by mixing the liquid sclerosing agent with a gas (ambient air or $CO_2$). The foam form has not been standardized and many variants have been described. Since the resultant preparation is extremely unstable, it is carried out by a healthcare professional immediately before injection. It should be noted that whatever the form of sclerosing agent used (foam or liquid), the cost is refundable by health insurance even if one of the two forms is used off-label.
6. ANALYSIS OF AVAILABLE DATA

A search for data since 2002 was carried out to evaluate the efficacy of the sclerotherapy of lower-limb varicose veins using liquid sclerosing agents; the data are taken from literature reviews and a meta-analysis. However, these publications do not make a clear distinction between the different sclerosing agents, their dosage or sometimes even the form used (liquid or foam). A search was also carried out for clinical studies carried out using sodium tetradecyl sulfate in liquid form. The evaluation of the tolerance of TROMBOVAR is based mainly on the national pharmacovigilance survey and the resultant changes to the SPC. The company also supplied tolerance data covering the period from 1 January 2002 to 30 October 2008 (PSUR and line listings).

6.1. Efficacy of sclerotherapy

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

Sclerotherapy versus surgery in the treatment of varicose veins

In the meta-analysis by Murad (2011), one of the analyses consisted in comparing surgery with liquid sclerotherapy. No difference was observed between these two techniques in terms of the recurrence of varicose veins (RR: 0.56; 95% CI: [0.29-1.06]) (10 clinical studies). However, after the exclusion of three studies with follow-up of less than or equal to 2 years, a reduction in the number of recurrences of varicose veins was observed with surgery as compared with sclerotherapy (RR: 0.45; 95% CI: 0.22-0.93). The authors note, however, the methodological weakness of the studies included (randomisation poorly described, most studies open, short follow-up period).

A Cochrane review with the aim of comparing sclerotherapy with surgery was also published (2009). Nine randomised controlled clinical studies were included. The endpoints and classification systems of these clinical studies were very heterogeneous and did not enable a meta-analysis to be performed. The authors conclude that the level of evidence of the studies does not allow one of the techniques to be recommended in preference to the other.

Evaluation of the different sclerosing agents in the treatment of varicose veins

A Cochrane review with the aim of evaluating the efficacy (improvement in symptoms and in aesthetic appearance, recurrence rate) and tolerance of sclerotherapy in the symptomatic and aesthetic treatment of varicose veins was published (2006). Seventeen randomised studies were included. Three studies comparing sodium tetradecyl sulfate with other sclerosing agents did not show any difference in terms of efficacy and tolerance. The authors conclude that there are no data from robust randomised studies which could influence the choice of sclerosing agent or its formulation (liquid/foam).

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

A Cochrane review\(^5\) with the aim of evaluating efficacy in terms of the aesthetic improvement and the tolerance of sclerosing agents in the treatment of lower-limb telangiectasia was also published (2011). It included 10 randomised studies (484 patients) comparing sclerosing agents (including polidocanol and sodium tetradecyl sulfate) with placebo, no treatment and another sclerosing agent (or a combination of sclerosing agents). The data did not allow a meta-analysis to be made. No difference in terms of efficacy was observed between sclerosing agents, merely superiority (particularly of polidocanol and sodium tetradecyl sulfate) versus placebo. Similarly, no difference was observed in terms of patient satisfaction with one of the agents as compared with the others. The authors mention that the level of evidence in this area is weak, and that the methodological quality of the studies is on the whole poor. The authors conclude that at present there is insufficient evidence to recommend the use of one sclerosing agent rather than another in the treatment of lower-limb telangiectasia.

Evaluation report on health technologies in the treatment of varicose veins, reticular veins and telangiectasia

In addition, there is a health technology evaluation made by the Alberta Heritage Foundation for Medical research (2004)\(^6\), which concluded, on the basis of data from the literature (randomised clinical studies, systematic reviews, guidelines and consensus documents), expert opinions and clinical practice:

- that sclerotherapy seems to be the treatment of choice in the management of reticular veins and telangiectasia (in terms of the relief of pain and/or discomfort, and the short-term improvement in aesthetic appearance). Polidocanol and sodium tetradecyl sulfate are relatively well tolerated. However, the authors stress that there is no standard protocol for their use.
- in clinical practice, treatment with sclerotherapy seems to be limited to small-diameter veins, the post-surgery treatment of remaining varicose veins or cases of recurrence.

In conclusion, the authors stress that there is no sound evidence for recommending or advising against sclerotherapy in the symptomatic treatment of varicose veins, whatever their diameter.


6.2. Efficacy of sodium tetradecyl sulfate used in liquid form: data from clinical studies

The literature reviews and the meta-analysis presented earlier do not allow any clear distinction to be made between the different sclerosing agents, their dosage, or sometimes even their form of use (liquid or foam). Thus, a search was carried out for clinical studies carried out with sodium tetradecyl sulfate used in liquid form, and the main ones are presented below.

**Demagny study**

This is a randomised, single-centre study. The aim was to compare with efficacy of sodium tetradecyl sulfate (1.5% to 3%) in its liquid form versus the foam in the echo-guided sclerosing treatment of the arches of the great (GSV) and small saphenous veins (SSV). In this study, 254 patients were included and 400 leaky saphenous veins were treated (300 GSV and 100 SSV less than 9 mm in diameter) and followed up for up to 6 months. The veins were sclerosed on D0, 50% with the liquid form and 50% with the foam form. The volumes and concentrations used were as follows:

- For the GSV:
  - liquid form: 2 ml at 3%
  - foam form: 0.5 ml at 3% + 0.2 ml of air to obtain 2 ml of foam at 3%

- For the SSV:
  - liquid form: 2 ml at 1.5% or 3% for the second session
  - foam form: 0.5 ml at 1.5% or 3% + 0.2 ml of air to obtain 2 ml of foam at 1.5 or 3% or 3%.

The primary efficacy endpoint was the absence of reflux, assessed by means of colour echo-Doppler on D30, D60 and D180. If this reflux was still present on D30, a second sclerosis session was given with double the concentration of STS (SSV) or two new injections at different sites (GSV).

The results on D180 showed:

- For the GSV: a success rate of 67% with the foam form versus 47% with the liquid form
- For the SSV: a success rate of 84% with the foam form versus 64% with the liquid form

As regards tolerance, 1 case of a cutaneous allergic reaction (palms of the hands) with the liquid form and 5 cases of transient amaurosis with the foam form were observed.

**EASI study**

This is a randomised double-blind, multicentre study the aim of which was to evaluate the efficacy and tolerance of polidocanol versus sodium tetradecyl sulfate and placebo (isotonic saline) in the sclerotherapy of telangiectasia and reticular veins (C1) using a standardised digital imaging system.

The primary efficacy endpoint was the improvement in the veins (disappearance) 12 weeks after the last injection (polidocanol versus placebo). This improvement was measured as follows: digital photos of the treated areas were taken on inclusion, then immediately before the first injection and 12 and 26 weeks after the last injection. The images from weeks 12 and 26 were then compared with those recorded before the first treatment. The change was evaluated by the investigator and two independent evaluators using a graduated 5-point scale going from 1 (worsening) to 5 (complete cure). The patient’s satisfaction was also evaluated in weeks 12 and 26 using a verbal scale going from 1 (very dissatisfied) to 5 (very satisfied).

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The maximum dose of the liquid sclerosing agent was 4.8 ml for telangiectasia and 2.4 ml for reticular veins. Two additional injections were possible, 3 and 6 weeks after the first one.

A total of 316 patients were randomised to receive: polidocanol 0.5% (for the treatment of telangiectasia, n = 82) or 1% (treatment of reticular veins n = 76), 1% sodium tetradecyl sulfate (treatment of telangiectasia n = 51 and reticular veins n = 54) or placebo (n = 53). A statistically significant difference was observed in favour of polidocanol versus placebo for the primary efficacy endpoint (p<0.0001).

Table 1: Mean values for the improvement in veins in weeks 12 and 26

<table>
<thead>
<tr>
<th></th>
<th>Polidocanol</th>
<th>Sodium tetradecyl sulfate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>4.52 ± 0.65*</td>
<td>4.47 ± 0.74*</td>
<td>2.19 ± 0.68</td>
</tr>
<tr>
<td>Week 26</td>
<td>4.54 ± 0.67*</td>
<td>4.77 ± 0.77*</td>
<td>2.21 ± 0.72</td>
</tr>
</tbody>
</table>

Scale graded 1 to 5: 1) deterioration 2) no change 3) slight improvement 4) good improvement 5) complete recovery

*p<0.0001 versus placebo

Patients were on the whole more satisfied with treatment with polidocanol in weeks 12 and 26 (84%, 88%) than with sodium tetradecyl sulfate (64%, 63%; p < 0.0001) or placebo (14%, 11%; p < 0.0001). Polidocanol was well tolerated apart from the expected local reactions at the injection site. Adverse effects were more common with sodium tetradecyl sulfate than with polidocanol (p < 0.001) with, in particular: pigmentation disorder (STS: 74.3% versus POL: 41.1% and placebo: 3.8%), necrosis (STS: 14.3% versus POL: 0.6%, placebo: 0%), ulcer (STS: 7.6% versus 0% in the other two groups), neovascularisation (STS: 20.0% versus POL: 8.9%, placebo: 3.8%), scars (STS: 12.4% versus POL: 0.6% and placebo: 0%).

Goldman study

This is a randomised, double-blind clinical study the aim of which was to assess the efficacy and tolerance of polidocanol and sodium tetradecyl sulfate (in liquid form) in the treatment of lower-limb varicose veins and telangiectasia. A total of 129 patients without incontinence of the sapheno-femoral and sapheno-popliteal junctions were randomised to receive treatment with polidocanol or sodium tetradecyl sulfate. The dose to be administered was determined from the diameter/calibre of the veins. The primary efficacy endpoint was the evaluation of the condition of the veins using a 5-point scale going from 1 (deterioration) to 5 (total disappearance) which was used to determine a mean score. This evaluation was made on the basis of digital photos taken before treatment and 1, 4 and 16 weeks after by an independent group of three doctors.

Table 2: Results for the primary efficacy endpoint

<table>
<thead>
<tr>
<th>Diameter of the veins</th>
<th>Treatment</th>
<th>STS 0.25% (n=32)</th>
<th>POL 0.5% (n=26)</th>
<th>STS 0.5% (n=29)</th>
<th>POL 1.0% (n=27)</th>
<th>STS 1.5% (n=27)</th>
<th>POL 3% (n=27)</th>
<th>STS (n=69)</th>
<th>POL (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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></td>
<td>p</td>
<td>p = 0.055</td>
<td>p = 0.832</td>
<td>p = 0.581</td>
<td>p = 0.117</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 : deterioration, 2: no change, 3: minimal disappearance, 4: moderate disappearance, 5: complete disappearance

No difference in the primary efficacy endpoint was observed between the two treatments, whatever the diameter of the veins.

Adverse effects are mainly ecchymosis (STS: 70%, POL: 58%), hyperpigmentation (STS: 64%, POL: 53%), vein thrombosis (STS: 46%, POL: 42%), contact urticaria (STS: 36%, POL: 23%), cutaneous necrosis (STS: 6.6%, POL: 0%).

Rao study

This is a randomised, double-blind clinical study the aim of which was to assess the efficacy and safety of polidocanol and sodium tetradecyl sulfate in liquid and foam forms in the treatment of lower-limb varicose veins and telangiectasia.

A total of 20 patients without incontinence of the sapheno-femoral and sapheno-popliteal junction were randomised to receive, in the veins of the left or right leg, treatment with polidocanol (POL) and, in the veins of the other leg, treatment with sodium tetradecyl sulfate (STS).

The dose to be administered was determined from the diameter of the veins:
- < 1 mm in diameter: 0.25% liquid STS (n = 19 veins) or 0.5% liquid POL (n = 18 veins),
- 1-3 mm: 0.5% liquid STS (n = 15 veins) or 1% foam POL (n = 14 veins),
- 3-6 mm: 0.5% foam STS (n = 10 veins) or 1% foam POL (n = 10 veins).

The primary efficacy endpoint was the evaluation of the condition of the veins using a 5-point scale going from 1 (deterioration) to 5 (total disappearance) which was used to determine a mean score. This evaluation was made on the basis of digital photos taken before treatment and 12 weeks after by an independent group of four doctors.

No statistical calculation was made.

Table 3: Results for the primary efficacy endpoint at 12 weeks

<table>
<thead>
<tr>
<th>Diameter of the veins</th>
<th>Treatment</th>
<th>STS 0.25% liquid (n=19)</th>
<th>POL 0.5% liquid (n=18)</th>
<th>STS 0.5% liquid (n=15)</th>
<th>POL 1% foam (n=14)</th>
<th>STS 0.5% foam (n=10)</th>
<th>POL 1% foam (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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>
</tbody>
</table>

1 : deterioration, 2: no change, 3: minimal disappearance, 4: moderate disappearance, 5: complete disappearance

The adverse effects observed were expected, according to the authors, and were mostly ecchymosis and hyperpigmentation.

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6.3. Adverse effects

6.3.1 National pharmacovigilance survey of venous sclerosing agents and ischaemic adverse effects (2008-2010)

Introduction: This survey follows the report of a case of cardiorespiratory arrest and a case of a transient ischaemic accident which occurred a few minutes after the injection of AETOXISCLEROL in foam form. It covers the ischaemic adverse effects of venous sclerosing agents (AETOXISCLEROL, TROMBOVAR and SCLEREMO). The aim was to identify any signal with use of the foam form by comparison with the liquid form.

Method: An analysis of the adverse effects reported in France (taken from the national pharmacovigilance database and the company’s data), the literature and clinical studies was carried out.

Results: Spontaneous reports show a risk of venous thrombosis, pulmonary embolism, migraine with aura, myocardial infarction, transient ischaemic accident or even stroke common to all sclerosing agents. Spontaneously reported cases cannot be used to produce a differential profile of the foam forms as compared with the liquid forms for each medicinal product. The number of cases from spontaneous reporting and the literature is presented in Table 4. A review of the literature found four published cases of stroke\(^\text{11}\) including one implicating the foam form with echographic evidence of particles in the carotid artery. Two other publications report the occurrence of a transient ischaemic accident (TIA) following sclerotherapy. In addition, in one study\(^\text{12}\) of 33 patients, evidence was found of the presence of intracardiac foam microemboli within 15 to 45 minutes after sclerotherapy in all patients. These results were confirmed by another study\(^\text{13}\) of 45 patients showing the presence of cerebral micro-emboli revealed by cranial Doppler examination whereas the MRI was normal. The frequencies of adverse effects found in the literature are sufficient to class stroke and TIAs as rare, migraine and related disorders as common, neurological disorders of any kind (confusion, vertigo, epilepsy, etc.) as common, cardiac disorders as rare (except for feelings of chest tightness which were very common), deep vein thrombosis and pulmonary embolism as uncommon to common, cutaneous necrosis as rare to common. The literature concentrates on the evaluation of the foam form, does not answer the question of dose-dependence and also cannot be used to prepare an individual profile for each proprietary medicinal product.

\(^{12}\) Ceulen and Vernooy, Microembolism during foam sclerotherapy of varicose veins. NEJM, 2008.
Table 4: Number of cases from spontaneous reporting and the literature – National pharmacovigilance survey of venous sclerosing agents and ischaemic adverse effects

<table>
<thead>
<tr>
<th>Neurological disorders</th>
<th>Solution</th>
<th>Foam</th>
<th>Solution</th>
<th>Foam</th>
<th>Glycerin</th>
<th>Chrome alum</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA, stroke</td>
<td>POL</td>
<td>STS</td>
<td>POL</td>
<td>STS</td>
<td>POL</td>
<td>STS</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Migraine, visual disorders</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolic AEs</td>
<td>Peripheral arterial thrombosis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

POL: Polidocanol
STS: Sodium tetradecyl sulfate
Rep.: Spontaneous reporting (number of cases)
Lit: Literature (number of cases)

Where information was available, the time to the occurrence of neurological and cardiac disorders was a few minutes after the injection.

Table 5 presents the number of adverse effects reported and the corresponding rates (number of cases per litre sold) per proprietary medicinal product. Almost 3.5 times more adverse effects were reported with AETOXISCLEROL but this proprietary medicinal product is more widely sold (4 times more in the last few years) than TROMBOVAR (which has been out of stock since October 2009).

Table 5: Rate of AE reporting (number of cases per litre sold) – National pharmacovigilance survey of venous sclerosing agents and ischaemic adverse effects

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Aetoxisclerol®</th>
<th>Trombovar®</th>
<th>Scleremo®</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN</td>
<td>Lauromacrogol 400</td>
<td>Sodium tetradecyl sulfate</td>
<td>Glycerin and chrome alum</td>
</tr>
<tr>
<td>Number of ischaemic AEs with the liquid</td>
<td>39</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Number of ischaemic AEs with the foam</td>
<td>13</td>
<td>0</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Total number of ischaemic AEs</td>
<td>52</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Reporting rate per litre sold</td>
<td>$63.10^{-5}$</td>
<td>$36.10^{-5}$</td>
<td>$56.10^{-5}$</td>
</tr>
</tbody>
</table>

Conclusion: The signal from spontaneous reporting is relatively weak but real. However, a strong signal is found in the literature. In addition, the chronology of its appearance is very significant. Thus, the risk of ischaemic complications at a distance from the point of injection, observed whatever the pharmaceutical form administered, can be considered a class effect which is relatively rare. It is still difficult to differentiate between the safety profiles of the foam and liquid forms. Several mechanisms in favour of the causal role of sclerosing agents have been mentioned (vasospasm, migration of the product or cellular debris via the right heart to the pulmonary circulation, or across a patent foramen ovale (creating communication between the two atria in 20% to 35% of adults). Finally, the literature and reporting do not show any dose-dependent effect. However, most authors mention their concern to administer the lowest possible doses so as to limit the effects.

Following that survey, the following proposal was made: harmonising the SPCs, carrying out additional studies (i/ to determine the nature of the circulating particles and their effects on haemostasis, ii/ in larger populations so as to determine the frequency and dose dependence of adverse effects, and iii/ to determine the usefulness of physical means of preventing adverse effects) and, for the vascular physicians involved in the evaluation, guidelines for these future clinical studies.
Amendments to the SPC were made in March 2011, following this pharmacovigilance survey, and are presented in Appendix 1. They concern mainly sections 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects”. The contraindications added are as follows:
- Patients suffering prolonged immobilisation
- A recent thromboembolic episode
- Progressive cancer
- Known symptomatic patent foramen ovale
- Erysipelas and lymphangitis in the area to be treated.

6.3.2 Safety data supplied by the company (PSUR)

The company supplied safety data covering the period from 1 January 2002 to 31 January 2007 (PSUR). More than 2,000,000 ampoules were sold in that period. A total of 16 cases were reported, 9 of them serious with probable or possible attributability (mainly serious allergic reactions and general malaise).

The company also supplied safety data covering the period from 1 February 2007 to 30 October 2008 (line listings). More than 800,000 ampoules were sold in that period. A total of 18 serious adverse effects were reported, concerning mainly the skin and subcutaneous tissue (n = 7).

Since September 2008, two cases have been reported to the company:
- pulmonary embolism
- pain and eruption at the injection site.

6.3.3 Data from the literature

A study\(^\text{14}\) performed over 8 weeks (+ 1 month’s follow-up) included 12,173 sessions of sclerotherapy (all sclerosing agents together) using the liquid form (5434 sessions) or the foam form (6395 sessions) or both forms (344 sessions) was published. The frequency of the adverse events observed was 0.1% for the liquid form and 0.3% for the foam form, with mainly reversible visual disorders (0.07% for the liquid form and 0.25% for the foam form). A femoral venous thrombosis was observed after use of the foam form.

6.4. Conclusion

TROMBOVAR used in liquid form has been the subject of very few randomised double-blind studies. The clinical studies available are generally of poor methodological quality: period of patient follow-up too short to evaluate long-term efficacy, dosages that do not correspond to those of the MA, endpoint not relevant, insufficient populations, poorly described methodology (no echo-Doppler measurement of vein diameter) or even no statistical calculation. In addition, all the published data evaluated the elimination of reflux, the improvement in symptoms (such as pain or discomfort) and the aesthetic improvement but cannot be used to evaluate the impact on the frequency and timing of recurrences, on progression to chronic complications such as trophic disorders (including ulceration) and acute complications such as superficial vein thrombosis (which can progress to deep peripheral vein thrombosis or pulmonary embolism) and varicose haemorrhages.

In view of all these data, the level of evidence of the efficacy of TROMBOVAR is low. Its level of effect and clinical relevance cannot be assessed accurately. The level of evidence of the available data does not allow recommendation of the use of one treatment rather than another, whatever the diameter of the vein. No difference in efficacy was clearly demonstrated between the different sclerosing agents.

Sclerosing agents have a risk of ischaemic adverse effects, whatever the form used (foam or liquid), which is regarded as a relatively rare class effect (national pharmacovigilance survey, French Healthcare Product Safety Agency (AFSSAPS)).
7. TRANSPARENCY COMMITTEE CONCLUSIONS

7.1. Actual benefit

Varicose veins are the commonest physical sign of chronic venous insufficiency. They are most often essential, more rarely secondary to an abnormality of the deep venous network (postthrombotic syndrome). They can be asymptomatic and cause no aesthetic impairment or be accompanied by symptoms such as a sensation of heaviness, swelling, cramps or restless legs and be located in the lower limbs. They are a chronic disease which can progress with a worsening of symptoms and more rarely with trophic disorders (the main complication of which is ulceration), and/or superficial vein thromboses and varicose haemorrhages. Varicose disease is not directly life-threatening, but can be indirectly through its complications. Superficial vein thrombosis of varicose veins, if untreated, spreads to the sapheno-femoral junction in 3.4% of cases and is combined with deep vein thrombosis or pulmonary embolism in 1.3% of cases.¹⁵

These proprietary products are intended as curative treatment.

The efficacy/adverse effects ratio is moderate.

The actual benefit of TROMBOVAR remains moderate.

7.2. Therapeutic use

The international CEAP classification (clinical, aetiologic, anatomic, pathophysiologic) can be used to specify the clinical stage of the varicose disease and as a guide to its correct treatment. A distinction is made between the following stages:

C0: no visible or palpable signs
C1: telangiectasia and reticular veins
C2: “true” varicose veins
C3: oedema
C4: trophic disorders such as hypodermitis, white atrophy, lipodermatosclerosis
C5: healed venous ulcer
C6: active venous ulcer

The National Health Accreditation and Evaluation Agency (ANAES), in its report of 2004 concludes that sclerotherapy and surgery are recommended for the treatment of grade C varicose veins.¹⁶ However, surgery and sclerotherapy do not necessarily correspond to the same indications. Thus, the working group proposed a strategy for the management of lower-limb varicose veins (Table 6).

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¹⁶ ANAES. Traitements des varices des membres inférieurs [Treatments of lower-limb varicose veins. June 2004]
### Table 6: Working group’s proposal for the choice of techniques in the management of lower-limb varicose veins (ANAES 2004)

<table>
<thead>
<tr>
<th>CEAP classification</th>
<th>Reflux</th>
<th>Technique proposed**</th>
<th>Other possible techniques</th>
<th>Current limits of the techniques</th>
</tr>
</thead>
</table>
| **AS2** (above-knee great saphenous vein) C2 to C6 | Ostial and trunk reflux | Crossectomy and stripping (with phlebectomy of the branches) | - Echosclerotherapy  
- Radiofrequency ablation  
- Laser | - Diam. > 10-12 mm***  
- Diam. > 12 mm  
- Substantial sinuosity of the varicose vein |
| **AS3** (below-knee great saphenous vein) C2 to C6 | Trunk reflux without ostial reflux | Echosclerotherapy | - Stripping without crossectomy (with phlebectomy of the branches)  
- Radiofrequency ablation  
- Laser | - Diam. > 12 mm  
- Substantial sinuosity of the varicose vein |
| **AS4** (small saphenous vein) C2 to C6 | Ostial and trunk reflux | Crossectomy and stripping (with phlebectomy of the branches) | - Echosclerotherapy  
- Laser  
- Laser  
- Laser | - Diam. > 10-12 mm***  
- Substantial sinuosity of the varicose vein |
| **AS5 and saphenous branches C2 to C6** | Isolated reflux on the other saphenous and nonsaphenous branches | Sclerotherapy | - Phlebectomy  
- Echosclerotherapy | |
| **Special case**: anterior accessory femoral vein of GSV, C2 to C6 | Ostial and trunk reflux from the anterior accessory femoral vein of GSV with no reflux from the great saphenous vein | Phlebectomy of the anterior saphenous vein and ligature at the level of the cross with no other phlebectomy or crossectomy combined with preservation of the saphenous trunk | Echosclerotherapy  
Sclerotherapy | |
| **AP 17** | Reflux from the perforating femoral veins | Ligature by direct approach + phlebectomy | Echosclerotherapy | |
| **AP 18 (C3, C5)** | Reflux from the perforating veins in the leg | Ligature by direct approach + phlebectomy | Echosclerotherapy | |
| **AP 18 (C4, C6)** | Reflux from the perforating veins in the leg | Endoscopic surgery of the subfascial perforating veins | Echosclerotherapy  
Perforating vein at the level of the ulcer | |

* The table mentions only varicose vein destruction techniques, since the working group was not able to reach a decision on conservative techniques because of the inadequacy of the literature.

** The techniques proposed were defined by the working group as techniques that should be chosen as comparators in a controlled treatment study in the indication considered. This choice was based either on the historical reference technique or, for recently identified indications, on the most relevant suitability criterion for the physiopathological target.

*** Corresponds to the limit most often found in clinical studies of sclerotherapy.

The German Phlebology Society considers that sclerotherapy (without differentiating the liquid from the foam form) is a method of choice for the treatment of small-diameter varicose veins (reticular veins, telangiectasia)17.

The Vascular Surgery Society and the American Venous Forum18 recommend liquid or foam sclerotherapy in the treatment of tributary veins, for the same reason as phlebectomy (grade 1B).

Overall, the place of sclerosing agents in liquid form and of TROMBOVAR in therapeutic use in lower-limb varicose veins is not clearly established.

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According to expert opinion, TROMBOVAR does not seem suited to the treatment of telangiectasia (which is, moreover, mainly an aesthetic treatment) and reticular veins because of its concentrations (1% and 3%) but is intended for varicose veins of larger diameter. The main limit is however varicose veins with a diameter of more than 8-10 mm and/or ostial reflux.
TROMBOVAR has a place in therapeutic use for the treatment of certain varicose veins of the lower limbs, as a first- or second-line therapy according to the CEAP classification stages (C2 to C6) and the different concentrations of the product adapted to the diameter of the varicose vein.
Moreover, TROMBOVAR has its place in the treatment of tributary veins in addition to and at a distance from classic or endovenous surgery, or in the event of contraindications.

7.3. Target population

The number of patients who underwent a sclerotherapy procedure in France in 2011 was estimated using the general sample of beneficiaries (EGB).
The following CCAM procedures were used: sclerosis session in lower-limb vein, by transcutaneous intravenous injection with echographic guidance (ENJN001) and sclerosis session of a lower-limb varicose vein, transcutaneous intravenous injection without guidance (EJNF002).
According to these EGB data extrapolated to the French population,19 the number of persons who underwent at least one sclerotherapy procedure in private practices and establishments in 2011 is estimated to be **312,336 (95% CI 300,909 and 323,764)**.
This estimate does not include sclerotherapy procedures carried out as outpatient care in public hospitals.

7.4. Transparency Committee recommendations

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

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19 The EGB is a representative sample of French people covered by national insurance. It contains anonymous information about the demographic characteristics of those persons, the benefits paid and chronic (long-term) conditions since 2003. The extrapolation of EGB data to the French population was done 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 is 1/109.36.
### Appendix 1: SPC comparative table (September 1998 vs. March 2011)

**TROMBOVAR 1% and 3%**

<table>
<thead>
<tr>
<th>SPC of September 1998</th>
<th>SPC of March 2011</th>
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<tbody>
<tr>
<td><strong>4.2 Posology</strong></td>
<td><strong>4.2 Posology</strong></td>
</tr>
<tr>
<td>For intravenous administration. Injection must start with the administration of a test dose of 1 ml of TROMBOVAR 1% solution. The 1% solution is more commonly used than the 3% solution; the use of TROMBOVAR 3% must be restricted to the sclerosis of large varicose veins and varicose veins resistant to treatment with the 1% solution. The usual dosage is 0.5 to 2 ml of injectable solution per session at points 6 to 12 cm apart, without exceeding, particularly for TROMBOVAR 3%, a total dose of 10 ml per session. Injections must be repeated every week or every two weeks, increasing the injection sites and progressively increasing the total dose per session.</td>
<td>Strictly for intravenous administration. It is desirable to start each injection session by administering a minimal test dose. The 1% solution is more commonly used than the 3% solution; The use of TROMBOVAR 3% must be restricted to the sclerosis of large varicose veins and varicose veins resistant to treatment with the 1% solution. The usual dosage is 0.5 to 2 ml of injectable solution per session at points 6 to 12 cm apart, without exceeding, particularly for TROMBOVAR 3%, a total dose of 10 ml per session. Injections must be repeated every week or every two weeks, increasing the injection sites and progressively increasing the total dose per session.</td>
</tr>
</tbody>
</table>

| **4.3 Contraindications** | **4.3 Contraindications** |
| • History of hypersensitivity to Trombovar 1 or 3% | Known allergy to sodium tetradecyl sulfate or any of the excipients |
| • Children younger than 3 years: | • Patients suffering prolonged immobilisation |
| • Very large veins and veins that are difficult to reach | • A recent thromboembolic episode |
| • Phlebitis | • Progressing cancer |
| • Febrile conditions | • Known symptomatic patent foramen ovale |
| • Intra-articular injection | • Erysipelas and lymphangitis in the area to be treated. |
| • Erysipelas and lymphangitis in the area to be treated. | • Children younger than 3 years. |

| **4.4 Special warnings and precautions for use** | **4.4 Special warnings and precautions for use** |
| Warnings: Injections must be given by an experienced doctor. Any injection outside a vein can cause serious necrosis. Intra-articular injection is particularly serious and may lead to a need for amputation. | Special warnings: Injections must be given only by an experienced doctor. Echographic guidance is recommended. Sclerotherapy is not recommended in patients with: Intra-articular injection is particularly serious and may lead to a need for amputation. Since there is a possibility of the product or cellular debris passing into the right heart, the presence of PFO may promote the occurrence of arterial accidents. Consequently, a check for patent foramen ovale is recommended before sclerotherapy in patients with a history of stroke, PAH or migraine with aura. |

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18/20
Precautions for use: Special care is needed in patients with a history of allergy.

Look out for symptoms such as pruritus on the face and extremities, conjunctival redness and any irritation occurring within a few minutes after the injection.

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4.8 Undesirable effects

- Risk of allergic reaction or anaphylactic shock (cf Warnings and special precautions for use)
- Possibility of residual pigmentation especially in case of overdose.

Undesirable effects, observed with different frequencies, are listed below by organ class.

- **Immune system disorders**: anaphylactic shock, angioedema, urticaria, asthma
- **Nervous system disorders**: headaches, migraine, paraesthesia, loss of consciousness, confusional state, vertigo
- **Eye disorders**: phosphenes, scotoma, amaurosis
- **Cardiac disorders**: palpitations. In view of the arrhythmogenic properties of lauromacrogol, possibility of cardiovascular collapse associated with systemic passage of the substance.
- **Vascular disorders**:
  - neovascularisation, haematoma
  - superficial thrombophlebitis, phlebitis
  - deep vein thrombosis
  - pulmonary embolism
  - vasovagal syncope
  - vasculitis, leucocytoclastic vasculitis.
- **Respiratory, thoracic and mediastinal disorders**: dyspnoea, sensation of tightness
- **Gastrointestinal disorders**: dyseusia, nausea
- **Skin and subcutaneous tissue disorders**:
- Hyperpigmentation of the skin, ecchymosis
- Allergic dermatitis, contact urticaria, erythema
<table>
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<tr>
<th>5.1</th>
<th>VASCULAR PROTECTOR/VENOUS SCLEROSING AGENT FOR LOCAL INJECTION</th>
</tr>
</thead>
</table>

Hypertrichosis (in the treated area).

General disorders and administration site conditions:

- Pain at the point of injection (short-term), thrombosis at the point of injection (local intravaricose blood clots)
- Induration, oedema
- Local necrosis-type reactions particularly in the skin and the underlying tissue (and, in a few rare cases, in the nerves) have been observed in the treatment of varicose veins of the legs after inadvertent injection into the surrounding tissue (paravenous injection). The risk increases with an increase in the concentrations and volumes injected
- Fever, hot flushes

Investigations:

- Abnormal blood pressure
- Lesions and intoxications: lesion of a nerve

The injection causes local destruction of the endothelium, generally accompanied by vasospasm then thrombus.