

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-201s000**

**CROSS DISCIPLINE TEAM  
LEADER REVIEW**

# Cross-Discipline Team Leader Review

<b>Date</b>	18-Dec-2009
<b>From</b>	Khin Maung U, M.D.
<b>Subject</b>	<b>Cross-Discipline Team Leader Review</b>
<b>NDA/BLA #</b>	NDA 21-201
<b>Application Type</b>	505 (b) (1)
<b>Applicant</b>	Chemische Fabrik Kreussler & Co., GmbH
<b>Dates of Submission</b>	21-Jul-2008; 10-Jul-2009
<b>PDUFA Goal Date</b>	08-Jan-2010
<b>Priority Designation</b>	Priority Review
<b>Proprietary Name / Established (USAN) names</b>	Asclera® (Polidocanol)
<b>Dosage forms / Strength</b>	0.5% & 1.0% solution for injection
<b>Proposed Indication</b>	Sclerotherapy of C <sub>1</sub> veins: Group S: (<1 mm diameter; spider veins, [REDACTED], very small varicose veins) Group R <sup>(U)</sup> <sub>(4)</sub> 1–3 mm diameter; reticular varices and small varicose veins)
<b>Recommendation:</b>	<b>Approval</b>
<b>Advisory Committee Meeting</b>	<b>Not required</b>

This CDTL review is based on completed reviews for the following disciplines:

<b>Review Discipline</b>	<b>Reviewer</b>	<b>Team Leader</b>
Clinical	Khin Maung U	Stephen Grant
Statistical	John P. Lawrence	Hsein Ming J. Hung
Safety (REMS/MedGuide)	Meg Pease-Fye	Mary Ross Southworth
Pharmacology Toxicology	William T. Link	Albert F. Defelice
Clinical Pharmacology	Peter H. Hinderling	Rajnikanth Madabushi
Chemistry, Manufacturing and Controls	Wendy Wilson	Kasturi Srinivasachar
OPS/NDMS (Microbiology)	Vinayak B. Pawar	James McVey
SEALD	Debra Beitzell	Laurie B. Burke
OSE-DMEPA	Shirley A. Zeigler	Laura Pincock
OSE-DRISK	Gita Toyserkani	Claudia B. Karwoski
DDMAC	Michelle Safarik (Group I) Zarna Patel (Group II)	Michael Sauers (Group I) Marcy Kiester (Group II)
DSI/GCP	Lauren Iacono-Connor	Tejashri Purohit-Sheth
Project Manager	Michael V. Monteleone	Edward J. Fromm

## 1. Introduction

This CDTL review elaborates the rationale for recommending, under Section 505(b)(1) of the FD&C Act, **approval** of NDA 21-201 submitted by Chemische Fabrik Kreussler & Co., GmbH for Asclera<sup>™</sup> (polidocanol) 0.5% & 1.0% solution for injection for the indication of sclerotherapy of C<sub>1</sub> veins: (a) Group S: (<1 mm diameter; spider veins, (b) (4) very small varicose veins), and (b) Group R (b) 1–3 mm diameter; reticular varices and small varicose veins).

Varicose veins (C<sub>1</sub>-C<sub>6</sub>, according to CEAP-classification) of the lower limbs are a chronic circulatory condition that can produce a poor quality of life if left untreated. Superficial varices can cause pain, swelling, persistent itching, deep vein thrombosis (DVT), phlebitis, eczema and leg ulcers. Superficial thin-walled veins may rupture and hemorrhage. Even small varices (C<sub>1</sub>, spider veins or reticular veins) are unattractive and can cause considerable embarrassment.

Sclerotherapy is the targeted elimination of intracutaneous, subcutaneous, and/or trans fascial varicose veins (perforating veins) as well as the sclerosation of subfascial varicose vessels in the case of venous malformation by the injection of a sclerosant.

Polidocanol is a long chain fatty acid originally developed as a local anesthetic. The mechanism of action of polidocanol is chemical (as a non-ionic surfactant) and not pharmacological. The hydrophobic pole of the polidocanol molecule attaches to the lipid cell membrane and disrupts the osmotic barrier of cells causing cell destruction. When injected intravenously, polidocanol at concentrations ranging from 0.5% to 3% induces endothelial damage with denudation of the vein lining. The absence of endothelial cells results in failure of nitric oxide production, with loss of smooth muscle relaxation leading to venospasm. The exposed surface is highly thrombogenic; platelets aggregate at the site of damage and attach to the venous wall. A mesh of platelets, cellular debris, and fibrin occludes the vessel. The vein is obliterated and is replaced later with connective fibrous tissue. Compression treatment is advisable after injection of the sclerosant to close the vein lumen and facilitate the development of fibrous tissue formation.

The purpose of sclerotherapy is not just thrombosis of the vein which can recanalize, but transformation of the vein into a fibrous cord which can not recanalize. The action corresponds to the surgical removal of a varicose vein as far as the functional result is concerned. Sclerotherapy is effective to treat varicose veins of all sizes, is simpler than surgery to perform, has a lower morbidity, and is less expensive.

Many alternative types of treatment of varicose veins are available.

For treating small, superficial, (C<sub>1</sub>, spider veins or reticular) varicose veins:

- *Another liquid sclerosant, Sotradecol<sup>®</sup>* – with similar mechanism of action albeit a different chemical class of detergent – had been approved for treatment of varicose veins by the FDA Office of Generics in 2004. Sotradecol<sup>®</sup> is used as a positive control in the pivotal and supportive clinical trials in the current NDA.
- *Laser surgery* sends very strong bursts of light onto the vein, making the vein slowly fade and disappear. Lasers are very direct and accurate. The proper laser controlled by a skilled physician will damage only the area being treated. Laser surgery is appealing to some patients because it does not use needles or incisions. However,

when the laser hits the skin, the patient feels a heat sensation that can be quite painful. Cooling helps reduce the pain. A laser treatment may take 15 to 20 minutes. Depending on the severity of the veins, two to five treatments are generally needed to remove spider veins in the legs. As with sclerotherapy, patients can return to normal activity right after treatment. Possible adverse effects of laser surgery include redness or swelling of the skin right after the treatment which usually disappears within a few days, discolored skin that will usually disappear in one to two months, and, rarely, laser burns and scars. For spider veins > 3 mm, laser therapy is not practical, but sclerotherapy can be used.

For treating larger (> 3mm) and superficial veins, surgical treatment modalities available include:

- *Surgical ligation and stripping* - Problematic superficial veins of the leg are tied shut and completely removed from the leg under local or general anesthesia in an operating room on an outpatient basis. The disadvantages include: problems associated with general anesthesia, bleeding, wound infection, inflammation, permanent scars, perivascular nerve tissue damage causing numbness, burning, or paresthesia, DVT, pain in the leg, and a long recovery time of one to four weeks.
- *Endoscopic vein surgery / Ambulatory phlebectomy* – With this surgery, a small fibre-optic probe is inserted into the vein to mark its location. Then the varicose vein is removed through small cuts made in the skin, and surgical hooks pull the vein out. The vein usually is removed in one treatment. Very large varicose veins can be removed with this treatment which leaves only very small scars. Patients can return to normal activity the day after treatment. People who have this surgery need epidural, spinal, or general anesthesia. Patients can return to normal activity within a day to a few weeks. The disadvantages are those of surgery, general anesthesia, bruising, and temporary numbness.

For treating the deeper varicose veins of the legs which are not visible on the surface, *endovenous techniques (radiofrequency and laser)* are used. The doctor puts a fiber-optic probe through a needle in the vein. Once inside, the probe emits radiofrequency or laser energy as it is pulled out, heating the vein wall and causing the collagen in the wall to shrink and the vein to close and become sealed. Collateral veins around the closed vein restore blood flow, thereby providing relief from symptoms of the varicose veins. Veins on the surface of the skin that are connected to the treated deep varicose vein will also shrink after treatment. When needed, these connected varicose veins are treated with sclerotherapy or other techniques.

## 2. Background

NDA 21-201 has a long history with FDA. Initially, the sponsor had submitted MICA (**M**ichigan and **C**alifornia) and OHIO trials as pivotal trials to the Division of Dermatology and Dental Drug Products, first on 10/01/1999, and re-submitted – after 21 amendments – on 11/10/2003.

On 08/02/2004, the Office of Drug Evaluation III issued a non-approvable letter because

- (i) the efficacy of polidocanol was not demonstrated as superior or non-inferior to the reference drug Sotradecol<sup>®</sup>,

- (ii) there was little or no assessment of risk of deep vein thrombosis (DVT) following injection with polidocanol,
- (iii) FDA GCP inspections revealed problems with data integrity or data quality at two (Michigan and California) of three sites inspected,
- (iv) controls were inadequate to prevent micro-organisms surviving the sterilization procedures, and
- (v) pivotal pharmacokinetic results were not reliable to meet *in vivo* bioavailability requirements under 21 CFR 320.

In May 2005, NDA 21-201 and related IND 35,139 were transferred to DCaRP. The Division guided the sponsor to develop a protocol evaluated by a SPA, and a plan of clinical and bio-pharm studies and CMC actions to address the issues stated in the non-approvable letter of 2004.

Table 1 lists the clinical trials in the NDA submitted by the sponsor on 07/21/2008.

**Table 1 Number of patients involved in clinical trials of polidocanol**

Study	Polidocanol*			Sotradecol <sup>®</sup>				Placebo (Saline) <sup>†</sup>			Total studied	Comments
	0.5% (S)	1% (R)	Total	0.25% (S)**	0.5% (R)**	1% <sup>†</sup> (S+R)	Total	(S)	(R)	Total		
<b>Controlled, randomized, single-blind trials</b>												
EASI	94	86	180	-	-	105	105	27	26	53	338	Pivotal trial
OHIO	25	25	50	25	25	-	50	-	-	-	150#	Also studied 3% polidocanol and 1.5% Sotradecol <sup>®</sup>
<b>Total</b>	119	111	230	25	25	105	155	27	26	53	438	Number for analysis of blinded studies
<b>Open-label, concentration-controlled trials in Japan</b>												
ASK-94-002 <sup>§</sup>	18/20	44/50	62/70	-	-	-	-	-	-	-	161 <sup>α</sup>	<sup>α</sup> Also studied 2% and 3% polidocanol
ASK-96-001 <sup>§</sup>	50/51	29/29	79/80	-	-	-	-	-	-	-	100 <sup>β</sup>	<sup>β</sup> Also studied 0.25% polidocanol
<b>Total</b>	68/71	73/79	141/150	-	-	-	-	-	-	-	141	Number studied in open-label trials
<b>All clinical trials of polidocanol</b>												
<b>Grand Total</b>	187	184	371	76	79	-	155	27	26	53	579	Number studied in all controlled trials
<b>Trials not useful for efficacy analyses</b>												
MICA <sup>Δ</sup>	29	31	60	33	32	-	65				179	54 patients received 3% polidocanol and 1.5% sotradecol <sup>®</sup>
ASK-97-01-00 <sup>‡</sup>	-	-	-	-	-	-	-	-	-	-	30	<b>Only studied 3.0% polidocanol</b>
AET-AS25/4 <sup>‡</sup>	-	-	-	-	-	-	-	-	-	-	40	<b>Only studied 0.25% polidocanol</b>
AET-P2/1/US	-	-	-	-	-	-	-	-	-	-	10	<b>Only studied 2.0% polidocanol</b>
French Registry	-	-	-	-	-	-	-	-	-	-	-	Post-treatment survey for safety data only

(S)= spider veins; (R)= reticular veins; \*Patients enrolled in EASI, OHIO, ASK-94-002 and ASK-96-001; \*\*Patients enrolled in EASI and OHIO; <sup>†</sup>Patients enrolled in EASI only; <sup>#</sup>includes 50 patients at other doses; <sup>§</sup>Open-label, drug concentration-controlled trials in Japan; <sup>α</sup>includes 89 patients at other doses; <sup>β</sup>includes 20 patients at other doses; <sup>Δ</sup>FDA GCP inspections revealed major data integrity issues, data not acceptable; <sup>‡</sup>Open-label, uncontrolled, using doses other than 0.5% & 1.0%.

Of the listed clinical trials, five trials have data relevant to efficacy evaluation: EASI (the

pivotal trial), OHIO, MICA, ASK-94-002 and ASK 96-001. Three trials, ASK-97-01-00, AET-AS25/4 and AET-P2/1/US were open-label, uncontrolled studies of polidocanol at doses other than 0.5% and 1.0% intended for this indication. The French Registry Study is a questionnaire survey to provide long-term safety data after sclerotherapy in patients in the French Polidocanol Registry 2008 (FPR 2008).

The pivotal **EASI** {Efficacy and safety of **A**ethoxysklerol<sup>®</sup> (polidocanol) compared to **S**odium tetradecyl sulfate and **I**sotonic saline (placebo) for the treatment of reticular veins and spider veins} trial is a placebo-and comparator-controlled, double-blind, multicenter trial. It was conducted at 19 centers in Germany, and randomized 338 patients with C<sub>1</sub> varicose veins (reticular veins and spider veins) to polidocanol (180 patients), Sotradecol<sup>®</sup> (105 patients) and placebo (53 patients), including 22 patients (called Group C) who were treated open-label at one center to determine PK (pharmacokinetic) data. Patients with spider veins were treated with polidocanol liquid 0.5% and those with reticular veins were treated with polidocanol liquid 1%.

Safety data in the current submission is based on: (i) 338 patients in the pivotal EASI trial, (ii) 685 patients in seven clinical studies which had been submitted earlier to FDA in 2003, and (iii) The French Polidocanol Registry of 1,605 patients who were surveyed using standardized questionnaires, then recorded on case report forms, to evaluate long-term AEs following 6,444 sclerotherapy sessions these patients underwent in 2003-2004, including 2,041 sessions treated with liquid polidocanol.

On 08/18/2008, an Acknowledgement of Incomplete Response to an Action Letter was issued informing the sponsor of the Division's decision to refuse to file because of manufacturing issues: namely, the sponsor had changed the manufacturer from (b) (4) to (b) (4) and had not submitted validation and requalification reports.

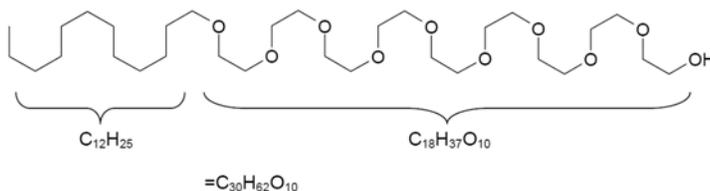
The review process was restarted after the sponsor submitted an acceptable complete response on 07/10/2009.

### 3. CMC/Device

#### 3.1 General product quality considerations

**Name of Drug:** Aethoxysklerol<sup>®</sup> 1% and Aethoxysklerol<sup>®</sup> 0.5%

**Active Ingredient:** Polidocanol (0.5% & 1.0%) (INN: lauromacrogol 400), a detergent.



**Structural formula:**

**Molecular formula:**  $C_{12}H_{25}(OCH_2-CH_2)_nOH$  where  $n$  has an average value of 9.  
Nominally,  $C_{30}H_{62}O_{10}$ .

**Mean Molecular Weight:** Approximately 600.

An additional modern facility, called (b) (4), was constructed adjacent to the original (b) (4) facility. The sponsor submitted documentation

that all of the equipment that had been used to manufacture ASCLERA<sup>™</sup> were relocated and revalidated/requalified.

The CMC reviewer (Wendy Wilson) recommended approval of the 0.5% and 1.0% polidocanol injection packaged in 2 ml, Type I, glass ampoules, and granted a 36-month (b) (4) for expiry of the drug product when stored at USP controlled room temperature (15°C – 30°C (59°F-86°F)) in the approved container closure system.

### **3.2 Facilities review/inspection**

This new facility has been inspected recently for GMP. The inspection findings are not yet available.

### **3.3 Other notable issues (resolved or outstanding)**

Following the sponsor's conversion to the polidocanol assay using HPLC method as the regulatory method for identification of polidocanol in the finished drug product, the CMC reviewer (Wendy Wilson) considered that the use of relative retention time alone as the test for identification is not specific as outlined in ICH Q6A. The CMC reviewer advised the sponsor to revise the drug product specification for both strengths to include another polidocanol identification test in addition to the current HPLC method, and suggested that the addition of a specification "UV absorbance spectrum matches that of the reference standard" is an acceptable approach.

The CMC reviewer found the sponsor's rationale for the lack of extractables testing acceptable; the sponsor is not required to perform extractables testing.

The CMC reviewer also found sponsor's rationale for the inclusion of bacterial endotoxins and sterility testing at the beginning and end of the stability program acceptable; the sponsor is not required to perform additional annual testing for these as part of the stability program.

The CMC reviewer has no Phase 4 (Post-Marketing) CMC recommendations.

In response to the statement in the "non approval" letter in 2004 that "controls are inadequate to prevent micro-organisms surviving the sterilization procedures," the sponsor submitted documentation that all of the sterilization processes – including performance requalification data summary from the relocated sterilizers (i.e. (b) (4) (b) (4) now show successful sterilization and depyrogenation of containers, closures, filling equipment and components which come in direct contact with the product when these equipment are re-qualified after installation at the new facility.

However, requalification of (b) (4)

The OPS/NDMS microbiology reviewer (Vinayak Pawar) recommended the submission approvable only after the sponsor submits evidence that the sterilization program at (b) (4) for NLT (b) (4) for a required (b) (4) results in adequate heat penetration of the ampoules and neutralization of the biological indicators. A written response was requested from the sponsor by letter dated 30-Nov-2009.

[REDACTED]

The microbiology reviewer found this explanation acceptable.

#### 4. Nonclinical Pharmacology/Toxicology

A previous Pharm/Tox review in 2004 (review in DARRTS, authors: David Allen and Norman See) considered this NDA approvable. The current Pharm/Tox reviewer (William T. Link) agrees with their conclusions and recommendations, and considers that the labeling adequately addresses the need for technical training regarding the administration and use of ASCLERA<sup>™</sup>, as well as the dangers inherent with intentional or accidental misuse such as delivery of large boluses into veins or arteries.

#### 5. Clinical Pharmacology/Biopharmaceutics

##### 5.1 General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

One of the conditions for which a previous application for polidocanol was issued a “non approval” letter in 2004 was that “pivotal pharmacokinetic results are not reliable to meet *in vivo* bioavailability requirements under 21 CFR 320.”

In the EASI trial, 22 patients were enrolled in a subgroup (Group C) at a separate center. They were given open-label polidocanol (12 patients with spider veins were injected with 0.5% polidocanol at volumes of 0.33 to 1.9 ml (doses of 1.5 to 9.0 mg), and 10 patients with reticular veins were injected with 1.0% polidocanol at 1.3 to 2.0 ml (doses of 13 to 20 mg). Blood samples were taken at Visit 1 to determine plasma polidocanol concentrations using a validated LC-Ms/MS assay.

The sponsor’s analysis of the data alleged that the maximum plasma polidocanol levels were detected at 5 minutes after injection in all patients. From 30 minutes to 3 hours after injection, the values declined, and returned to initial values or were slightly above initial values at 6 hours after application. At 6 hours after injection, plasma polidocanol concentrations were <100 ng/ml in 20 of 22 cases (the other two values being 103.5 and 126.8 ng/ml). There was no dose proportionality for polidocanol 0.5% and 1%, with (1) the dose adjusted  $AUC_{(0-inf)}$  for polidocanol 0.5% being nearly three times higher compared to polidocanol 1%, (2)  $t_{1/2}$  approximately twofold higher, and (3) the mean values of the dose-adjusted  $C_{max}$  for polidocanol 0.5% and 1% approximately similar.

However, the Clin-Pharm reviewer (Peter Hinderling) noted that (1) the PK parameters showed large inter-subject variability, (2) positive pre-dose levels were 2% to 67% of  $C_{max}$  (for which there was no explanation), and (3) in 8 patients with spider veins the extrapolated AUC was >20% of AUC. These findings suggest that the estimates for AUC may be biased.

Using an arbitrary acceptability criteria that subjects must have (i) negative pre-dose concentrations and (ii) extrapolated AUC <0.2, to be eligible to provide acceptable PK data, the Clin-Pharm reviewer found that only 4 of these 22 subjects had acceptable PK data, and that only the data for  $t_{1/2}$  was considered reliable.

The Clin-Pharm reviewer commented that local entrapment of the drug (by venospasm) aided by compression (required by the protocol) could reduce the amount of polidocanol reaching the systemic circulation significantly, limiting the interpretability of  $C_{max}$ , CL and  $V_{ss}$ . The Clin-Pharm reviewer has reservations regarding the reliability of the PK data in the submission because the doses used in subgroup C were lower than the maximum dose of (b) (4) mg per treatment day/session in the proposed label.

The Clin-Pharm reviewer concluded that the substudy provided limited PK information only, and that the results of the PK study do not provide acceptable  $C_{max}$  and AUC data.

During discussions at team meetings, the Clin-Pharm reviewer was informed by other members of the team (including myself) that there had been no safety signals of liquid polidocanol administered to patients with different types of varicose veins at doses larger than that in the pivotal trial, sometimes in multiple treatment sessions, in many countries over the past several years (see Section 8.1).

My opinion is that polidocanol has been used with a broad spectrum of doses over several years to treat varicose veins in many clinical settings so that there is no need for a repeat bioavailability study. This is particularly true because (i) the drug is used for its local “chemical” action, and (ii) the drug’s mechanism of action (venospasm) limits its access to the systemic circulation. To create an artificial situation to induce high plasma levels of polidocanol just to be able to determine its PK characteristics is not justified.

Taking these discussions into consideration, the Clin-Pharm reviewer concluded in his review that “... given that the safety data of polidocanol in humans is unremarkable and the value of PK information from a repeat bioavailability study is uncertain, another bioavailability study is not warranted.”

## 5.2 Drug-drug interactions

No drug interaction studies were conducted. Polidocanol is a local anesthetic, which, combined with other anesthetics within 24 hours after sclerotherapy, may theoretically give rise to a risk of an additive anesthetic effect on the cardiovascular system. The labeling states (b) (4)

(b) (4)

(b) (4)

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

### 7.1 Discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.

Note: CDTL and the primary clinical reviewer are the same.

In the EASI trial, the primary efficacy endpoint was improvement of the treated veins on standardized digital photographic images at 12 ( $\pm$  2) weeks after injection evaluated on a 5-grade scale by each investigator and two independent blinded medical experts (comparison of change from baseline between polidocanol and isotonic saline). Assuming the effect of polidocanol 0.5% on spider veins and polidocanol 1% on reticular veins are equal, a pooled, stratified analysis was done using stratified Wilcoxon-Mann-Whitney test.

Of the 316 patients enrolled in the EASI trial (excluding 22 patients in Group C), 313 patients (155 treated with polidocanol, 105 with Sotradecol<sup>®</sup>, and 53 with placebo) had valid assessments of digital images at 12 ( $\pm$  2) weeks (full analysis (FA) data set). 47 patients in FA data set were excluded due to protocol deviations; 266 patients (135 treated with polidocanol, 84 with Sotradecol<sup>®</sup>, and 47 with placebo) comprise the per protocol (PP) data set.

The primary efficacy analysis of the FA data set showed statistically significant ( $P < 0.0001$ ) superiority of polidocanol over placebo for the mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) evaluated by the investigator and two independent medical experts at 12 ( $\pm$  2) weeks (Table 2). The same is true for Sotradecol<sup>®</sup>, suggesting adequate *assay sensitivity* of the EASI trial.

Table 2 Improvement of veins in digital photographs after 12 weeks and 26 weeks

<b>Digital Photograph Scores at 12<math>\pm</math>2 weeks</b>			
<b>Full Analysis data set</b>			
<b>Treatment Group</b>	<b>Polidocanol (N=155)</b>	<b>Sotradecol<sup>®</sup> (N=105)</b>	<b>Placebo (N=53)</b>
<b>Mean <math>\pm</math> SD (N)</b>	4.52* $\pm$ 0.65 (154)	4.47* $\pm$ 0.74 (104)	2.19 $\pm$ 0.68 (53)
<b>Per Protocol data set</b>			
<b>Treatment Group</b>	<b>Polidocanol (N=135)</b>	<b>Sotradecol<sup>®</sup> (N=84)</b>	<b>Placebo (N=47)</b>
<b>Mean <math>\pm</math> SD (N)</b>	4.55* $\pm$ 0.63 (135)	4.45* $\pm$ 0.75 (84)	2.09 $\pm$ 0.41 (47)
<b>Digital Photograph Scores at 26 weeks</b>			
<b>Full Analysis data set</b>			
<b>Treatment Group</b>	<b>Polidocanol (N=155)</b>	<b>Sotradecol<sup>®</sup> (N=105)</b>	<b>Placebo (N=53)</b>
<b>Mean <math>\pm</math> SD (N)</b>	4.54* $\pm$ 0.67 (155)	4.45* $\pm$ 0.77 (105)	2.19 $\pm$ 0.68 (53)
<b>Per Protocol data set</b>			
<b>Treatment Group</b>	<b>Polidocanol (N=135)</b>	<b>Sotradecol<sup>®</sup> (N=84)</b>	<b>Placebo (N=47)</b>
<b>Mean <math>\pm</math> SD (N)</b>	4.55* $\pm$ 0.69 (135)	4.51* $\pm$ 0.77 (84)	2.11 $\pm$ 0.48 (47)

\* $p < 0.0001$  compared to placebo (Wilcoxon-Mann-Whitney test); \*\*For patient 437 the evaluation of one of the medical experts was not available and therefore the median of the evaluation of the investigator and one of the medical experts was 4.5.

The PP data set shows the same statistically significant ( $P < 0.0001$ ) superiority of polidocanol over placebo for the mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) at 12 ( $\pm$  2) weeks (Table 2). The results for

Sotradecol<sup>®</sup> which are similar suggest adequate *assay sensitivity* of the EASI trial.

This statistically significant superiority of polidocanol over placebo for the mean *change* in digital photograph scores at 12 ( $\pm 2$ ) weeks from baseline was maintained at 26 weeks (Table 2), documenting that the cosmetic benefit is sustained.

Patients' subjective perception of their satisfaction with treatment (on a scale of 1 to 5) showed that a significantly ( $p < 0.0001$ ) larger proportion of patients treated with polidocanol were "satisfied" or "very satisfied" at 12 weeks (88%) and 26 weeks (84%), compared to patients treated with Sotradecol<sup>®</sup> (64% at 12 weeks and 63% at 26 weeks) or placebo (13% at 12 weeks and 11% at 26 weeks).

The Spearman's correlation coefficients showing the correlations between improvement in digital photographs and patients' satisfaction scores were statistically significant ( $p = 0.0381$  to  $p < 0.0001$ ).

The collective findings of (i) a highly significant ( $p < 0.0001$ ) success rate in objective photographic evaluations, and (ii) a highly significant ( $p < 0.0001$ ) patient satisfaction rate, (iii) which are significantly ( $p = 0.0381$  to  $p < 0.0001$ ) correlated, are persuasive of the efficacy of polidocanol in the treatment of C<sub>1</sub> varicose veins (reticular and spider veins).

The OHIO trial was a randomized, double-blind, active-controlled trial with valid data for efficacy evaluation in the earlier (2003) submission to FDA. It did not have a placebo group. The OHIO trial showed that polidocanol and Sotradecol<sup>®</sup> produced relatively similar rates of disappearance of spider and reticular veins, although the trial was not designed to demonstrate statistical non-inferiority. While the results of the OHIO trial do not contribute to the efficacy analyses, they may be considered to imply that the efficacy of polidocanol and Sotradecol<sup>®</sup> in patients in the United States appeared to be generally comparable to that observed in patients in Europe in the pivotal EASI trial.

## **7.2 Discussion of notable efficacy issues both resolved and outstanding**

*Note: CDTL and the primary clinical reviewer are the same.*

Many of the patients required more than one treatment session. Of 86 patients with reticular veins treated with 1% polidocanol, 38 (44.2%) patients had one treatment session, 30 (34.9%) patients had two treatment sessions, and 18 (20.9%) patients had three treatment sessions. Of 94 patients with spider veins who were injected with 0.5% polidocanol, 17 (18.1%) patients had one treatment session, 33 (35.1%) patients had two treatment sessions, and 44 (46.8%) patients had three treatment sessions.

At each treatment session, patients needed multiple injections: the *number of injections* of polidocanol 1% given to patients with reticular veins ranged from 5.1 to 6.5, and that of polidocanol 0.5% to patients with spider veins ranged from 7.9 to 10.0 injections. The *mean $\pm$ SD volume* injected in patients with reticular veins was  $1.5 \pm 0.5$  ml of 1% polidocanol, and that in patients with spider veins was  $1.1 \pm 0.8$  ml of 0.5% polidocanol.

I think that the need for multiple injections of liquid polidocanol can be considered comparable to the need for multiple laser sessions (generally 2 to 5 treatments) to remove spider veins in the legs.

## 8. Safety

### **8.1 Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)**

In this context, I think the following information related to safety of polidocanol found in the medical literature should be taken into consideration:

- (1) There is a large body of experiential data (published and unpublished) from widespread use of sclerosants (liquid and foam) to treat varicose veins in Australia, China, Europe, Latin America and New Zealand which showed that adverse events and/or technical complications of the procedure have been **very rare**.
- (2) A single-arm prospective study of > 2 years of polidocanol (0.5%, 1% and 3%) injected into C<sub>1</sub> and C<sub>2</sub> varicose veins in 16,804 limbs by 98 investigators in Australia revealed no deaths and no cases of anaphylaxis. AEs in patients treated with polidocanol were less frequent and less severe than in those treated with sodium tetradecyl sulfate<sup>1</sup>.
- (3) In a prospective, randomized multicenter trial<sup>2</sup> of 3% polidocanol *foam* (45 patients) vs. 3% *solution* of polidocanol (43 patients) to determine the rates of elimination of reflux in the Greater Saphenous Vein (GSV), AEs were rare. At 6 months, 2 patients in the polidocanol *foam* group had re-canalized, vs. 6 in the polidocanol *solution* group, with no additional recanalization in either group at one year.
- (4) A recent prospective multicenter registry of 12,173 sclerotherapy treatments<sup>3</sup> in France including 5,434 sessions with liquid sclerosants (75% using polidocanol) showed that there were no instances of anaphylaxis, no deaths and, for patients who had sclerotherapy with liquid polidocanol, no cases of deep vein thrombosis.
- (5) In a recently completed ESACHina trial<sup>4</sup>, 288 Han Chinese patients with C<sub>1</sub> (spider and reticular) or C<sub>2</sub> veins at 3 centers in China were randomized (3:1) to treatment with polidocanol 0.5% (spider vein), 1.0% (reticular vein) and 3% (C<sub>2</sub> vein) vs. placebo during December 2007 and February 2009. There were no SAEs and no cases of anaphylaxis. AEs consisted of mild to moderate local tenderness, pain, pigmentation and nausea.
- (6) The FDA ODS (Office of Drug Safety) investigation comparing the safety data for polidocanol (Aethoxysklerol<sup>®</sup>) in the WHO Vigisearch database and in published and unpublished literature vs. AERS reports for the liquid sclerosant Sotradecol<sup>®</sup> (approved by FDA Office of Generic Drugs in 2004) shows no signal that liquid polidocanol is more unsafe than Sotradecol.

In this NDA, safety data submitted for review are from:

- (i) the pivotal EASI trial (338 patients, of which 180 patients received one dose of liquid polidocanol),
- (ii) the seven earlier clinical studies previously submitted to FDA (685 patients of which 501 patients had been administered one dose of liquid polidocanol), and

(iii) a subsample of 1,605 patients in the French Polidocanol Registry who had received at least one polidocanol injection in 6,444 sclerotherapy sessions during 2004, who were surveyed with a questionnaire for AEs they had experienced during the survey period of 4 years (April 2004 to April 2008), which covered 3,357 patient-years.

No pooling of data across studies was done due to differences in evaluation of the safety data in these three sets of data.

## **8.2 General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

There were no deaths in any of the three sets of safety data (above) in the NDA.

In the EASI trial, there were two SAEs: one patient was hospitalized for exacerbation of existing fibromyalgia, and another was hospitalized for severe urticaria requiring parenteral administration of corticosteroids and antihistamines.

Withdrawals due to AEs were reported for two patients: one patient was diagnosed with borrelia infection and another with intermittent tachycardia 7 days post-sclerotherapy.

In the seven earlier clinical studies, there were significant AEs in 5 patients treated with 4 to 8 ml of polidocanol 3% and in 2 patients treated with Sotradecol<sup>®</sup>. These included ecchymoses and hyperpigmentation (4 AEs), local pain, inflammation, swelling and itching (1 AE), superficial vein thrombosis and neovascularization (2 AEs) and possible allergic reaction manifested as tongue or lip feeling numb, or hives or sneezing (3 AEs).

In the French Polidocanol Registry, 54 patients reported 68 AEs during 58 sessions, of which 51 AEs in 37 patients during 41 sessions were associated with polidocanol. Of these, 46 AEs were associated with polidocanol foam, and 5 AEs were associated with polidocanol liquid (p=0.0033). The five AEs associated with polidocanol liquid were one visual disturbance, one cramp and two inflammatory reactions observed soon after administration, and one hyperpigmentation observed as a delayed AE.

Common AEs observed in the EASI trial were local AEs: hematoma, hyperpigmentation and neovascularization, and local sensations or symptoms (itching, pain, warmth and burning). In the seven earlier clinical studies, too, the common AEs were local reactions (redness, inflammation, swelling, skin necrosis, itching, induration, incrustation, blister, dermatitis, ecchymoses, hyperpigmentation and neovascularization). Systemic AEs were rarely reported, which included taste perversion, paresthesia and cramps.

There were no clinically important laboratory abnormalities or changes in vital signs in the EASI trial, the seven earlier clinical studies or the French Polidocanol Registry.

In lieu of a thorough QT study, patients in EASI trial had ECGs done at screening and at 30±15 minutes after treatment at Visit 1. The QT intervals were measured, and QT<sub>C<sub>B</sub></sub> and QT<sub>C<sub>F</sub></sub> values calculated. There were no QT<sub>C<sub>F</sub></sub> values >480 ms, no differences in QT<sub>C<sub>F</sub></sub> between treatment groups, and no marked changes in QT<sub>C<sub>F</sub></sub> duration between screening and Visit 1. The range of change in QT<sub>C<sub>F</sub></sub> is from -1 ms to 2.7 ms.

There were no unexpected safety signals in this submission. The safety profile of liquid polidocanol appears to be as safe as that of Sotradecol<sup>®</sup>, another liquid sclerosant approved for treatment of varicose veins by the FDA Office of Generics in 2004.

### 8.3 Immunogenicity

Not applicable.

### 8.4 Special safety concerns

The special safety concerns for polidocanol liquid – which is injected in small volumes for a local cosmetic effect without reaching any significant levels in the circulation – are (i) allergic reactions, (ii) local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses, pigmentation), (iii) deep vein thrombosis, and (iv) anaphylactic shock/reaction and cardiac arrest (the last reported in MedDRA).

Allergic reactions including urticaria, numbness in tongue and/or lips, and local reactions reported in the EASI trial, the seven earlier clinical studies and the French Polidocanol Registry survey are reviewed in sections 7.3.2, 7.3.3 and 7.3.4 (above).

Deep vein thrombosis (DVT) was an AE of specific concern. DVT was not sought for in the seven earlier clinical studies previously submitted to FDA, which was one of the reasons for non-approval in 2004. DVTs are known to occur largely during the first week after injection of sclerosant, and many DVTs are asymptomatic so that historical or symptom data may under-report DVT following treatment with polidocanol liquid.

In the EASI trial, DVT was evaluated prospectively by ultrasound evaluations at screening visit (baseline), Visit 1a (one week  $\pm$  3 days after injection of study drug) and at Visit 4 (12 weeks  $\pm$  2 weeks after injection). No case of DVT was found by ultrasound evaluation following treatment with polidocanol or Sotradecol<sup>®</sup> or placebo.

In the French Polidocanol Registry (Table 3), 14 DVTs were associated with *foam* sclerosants, of which 8 were noted in relation to polidocanol *foam*. Two DVTs were associated with liquid sclerosants, both with *other* liquid sclerosants. No DVT was reported in any patient who had been treated with polidocanol liquid.

**Table 3 Number (%) of patients with AEs and DVTs in The French Polidocanol Registry**

Adverse events	Foam (4,403 sessions)		Liquid (2,041 sessions)	
	N	% in relation to total number of foam sessions	N	% in relation to total number of liquid sessions
All adverse events	60	1.363%	8	0.392%
Deep Vein Thrombosis	14	0.318%	2	0.098%

For one DVT reported medium-term after administration of polidocanol *foam*, the physician's notes stated that the patient suffered from Thrombophilia (heterozygote Factor V Leiden), with history of prior DVT before sclerotherapy. The patient had stopped taking anticoagulant therapy; sclerotherapy was performed during this period when she was not taking anticoagulants. It is likely that the DVT detected was the previously diagnosed DVT which persisted due to termination of anticoagulant therapy.

### 8.5 Discussion of primary reviewer's comments and conclusions

Note: CDTL and primary clinical reviewer are the same. See sections 8.1 to 8.4.

## **8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

Note: CDTL and primary clinical reviewer are the same. See section 8.7.

## **8.7 Discussion of notable safety issues (resolved or outstanding)**

The issue of anaphylaxis following injection with polidocanol remains a subject of discussion with three different opinions from three reviewers as follows:

The first opinion is by the OSE reviewer (Mary Ross Southworth), who suggests that because polidocanol is given for "... an utterly cosmetic reason,..." "... the threshold for accepting serious risk is high even if the rate of the risk is rare." The OSE reviewer suggests changes to the Warning label, to be bolded, as follows:

*Cases of severe allergic reactions have been reported in association with polidocanol use, some have included anaphylaxis, cardiac arrest, and death. These reactions may be more likely with larger volumes (> 3 ml), therefore the dose of polidocanol should be limited to the minimum necessary to treat the vein. Use in veins larger than 3mm should be avoided. The physician should be prepared to treat anaphylaxis appropriately and should have emergency resuscitation equipment readily available.*

*Patients who demonstrate any sign of hypersensitivity to polidocanol (wheezing, sneezing, generalized urticaria) should not receive the drug again.*

With regard to a boxed warning, the OSE reviewer comments that "... there are no clear criteria for boxing safety information," and suggests "...further discussion within the review team."

The OSE reviewer recommends "A REMS should be required as part of the approval that would include a Communication Plan to physicians describing the risk associated with polidocanol and directing prescribers to limit the volume administered, have emergency equipment available, and to not re-administer in patients displaying signs of hypersensitivity." "The Communication Plan should be distributed for a finite period of time after approval (2 to 3 years), should be distributed periodically (every 6 months), and should be sent to all prescribers that the sponsor plans to market / to detail."

Please see section 12.3.2 for the OSE reviewer's discussion on a Medication Guide.

The OSE reviewer suggests that "Elements to assure safe use (restricted distribution) is not necessary as this product is intended to be administered by physicians in their practice settings."

The second opinion is by the DRISK reviewer (Gita Toyserkani), who recommends a boxed warning because it "...would have a greater impact on marketing (limiting reminder advertisement) and ensuring that the safety message is captured in the promotional materials that would be distributed in various settings targeted to both patients and healthcare providers."

The DRISK reviewer does not recommend a REMS Communication plan because (i) at

the time of prescribing and administering (the polidocanol injection), healthcare providers would be more likely to refer to the labeling than recall a communication plan that was sent to them (reinforces the usefulness of strong labeling) (ii) a communication plan, whether one time or repeated, would not ensure that the product is not dispensed in inappropriate settings and most likely would not reach those settings, and (iii) "... a communication plan, such as a DHCP letter, it could be requested outside of a REMS."

Please see section 12.3.2 for the DRISK reviewer's discussion on a Medication Guide.

The third opinion is given by the clinical reviewer (myself) and supported by the Deputy Director (Stephen Grant) and Division Director (Norman Stockbridge) of DCaRP. Our position is that that apart from mentioning the risk of anaphylaxis (as in the Sotradecol<sup>®</sup> label) and having emergency treatment available on site, neither a black box warning nor a REMS (Communication Plan, Medication Guide) is necessary for approval.

In team discussions regarding the action to take for anaphylaxis associated with polidocanol, I have presented the following four considerations:

First, data in the NDA did not show any patient had anaphylaxis: The data submitted for review in the NDA for the C<sub>1</sub> (spider and reticular) varicose veins with the specified dose, concentration and volume showed **no deaths or anaphylaxis** in:

- 338 patients (108 treated with liquid polidocanol) in the pivotal EASI trial,
- 685 patients (501 treated with liquid polidocanol) in 7 earlier clinical trials, and
- 1,605 patients who were a subsample of over 3,000 patients in the French Polidocanol Registry who had received at least one polidocanol injection in 6,444 sclerotherapy sessions during 2004, in a questionnaire survey to determine the AEs they had experienced.

Recently, in the ESACHina trial<sup>4</sup> during December 2007 and February 2009, 288 Han Chinese patients with C<sub>1</sub> (spider and reticular) or C<sub>2</sub> veins at 3 centers in China were randomized (3:1) to treatment with polidocanol 0.5% (spider vein), 1.0% (reticular vein) and 3% (C<sub>2</sub> vein) vs. placebo. There were **no SAEs and no cases of anaphylaxis**.

Secondly, the issue of "anaphylaxis" arises from post-marketing reports in *other* countries using *other* forms/doses/concentrations/volumes and for *other* diseases (large varicose veins or "medical" uses to stop bleeding from esophageal varices, gastric and duodenal ulcer, etc.). The sponsor submits that about (b) (4) patients have been treated with one or the other form/concentration of polidocanol during 1987 to 2009.

To understand the risk factors, time course and clinical determinants of anaphylaxis or cardiac arrest and/or deaths associated with use of polidocanol to treat varicose veins in these patients, we asked the sponsor to provide information related to (1) disease(s) for which polidocanol was used (e.g., esophageal varices, leg vein varices - C<sub>1</sub> or C<sub>2</sub>), (2) co-existing diseases, (3) concomitant medications, (4) time course of clinical events/symptoms following injection of polidocanol, (5) dose (mg, concentration) and form (liquid or foam) of polidocanol used, (6) cause of death – (whether anaphylaxis or upper GI bleed or hepatic failure/coma in patients with cirrhosis, etc.), (7) temporal relationship between injection of polidocanol and death/shock, and between other drugs and death, (8) agents used to treat anaphylaxis, if any, and (9) response to re-challenge, if done.

FDA received the following information from the sponsor in December, 2009:

Cases associated with death:

The sponsor provided a list and CIOMS forms of 19 patients who died in which polidocanol was one of the drugs administered. Of these:

- five patients were treated for leg varices, (one died of “anaphylactic shock”, one of “cardiac arrest” not related to polidocanol (CIOMS form not available), one of cardiac arrest (autopsy showed an arrhythmogenic right ventricle), one of pulmonary embolism, and one of angiosarcoma several years after polidocanol treatment);
- seven patients were treated for esophageal varices (one died of esophageal cancer, one from persisting bleeding, one from pleural effusion, one from cardiac failure, one from asystole, one from multi-organ failure and one from anaphylactic shock);
- four patients were treated for bleeding gastric or duodenal ulcer (two died from sepsis, one died from ulcer bleeding and one from small bowel necrosis); and
- one patient was treated for hemorrhoids (died during delivery of a male baby with anencephalos);
- one patient was treated for facet coagulation of spine (and died from meningitis), and
- one patient was treated for an unknown diagnosis, (and died of cardiac failure).

Of these 19 patients, I found only one death that was associated with anaphylactic shock following injection of 2% polidocanol for treatment of “leg varices.” I note that this was not associated with use of 0.5% or 1% polidocanol under consideration in this NDA, and not with treatment of C<sub>1</sub> (spider or reticular) varicose veins.

I think that the seven patients with esophageal varices, the four patients with gastric or duodenal ulcer bleeding and the patient with bleeding hemorrhoids were too sick to receive the proper surgical treatment (e.g., Tanner's gastric transection for esophageal varices, ligation of gastroduodenal artery or its branches for persistent gastric or duodenal ulcer bleeding, etc.). This suggests that these patients had received injection of polidocanol as a last resort or stop gap palliative measure to combat uncontrolled bleeding. I do not think we can determine risk-benefit without having the data to evaluate any potential benefit this treatment could have provided.

Cases NOT associated with death:

The sponsor provided a list and CIOMS forms of 29 patients (none died) who had experienced some form of allergic reaction including anaphylactic shock, angioedema, urticaria, or shortness of breath following injection with polidocanol in different forms or doses/concentrations for a variety of diseases in addition to varicose veins. Of these:

- eight patients experienced angioedema (one patient received 2% polidocanol, three received 1%, one received 0.5%, and three received unknown concentration/doses; three patients had previous allergic conditions with angioedema),
- six patients experienced urticaria or pruritus (one patient received 2% polidocanol, one received 1% polidocanol foam, one received 0.5%, and three received unknown doses; three of these patients had previous allergic reactions to *other* substances; four were treated for leg varices, one for reticular veins, and one for bleeding hemorrhoids),

- seven patients experienced dyspnea or bronchospasm (three patients received 1% polidocanol, one received 0.25%, and three received unknown doses; five were treated for “probably” leg varices, one for esophageal varices, and one for bleeding hemorrhoids),
- eight patients experienced some form of “anaphylactic shock or anaphylactic reaction” (three patients received 2% polidocanol, two received 0.5% (one as polidocanol foam erroneously mixed with Lavasept – a cleaning agent and disinfectant), and three received unknown concentrations; one patient was on digoxin which could have caused a ventricular arrhythmia).

Thus, of the eight patients who had experienced some form of anaphylactic reaction, four had received polidocanol in other forms (3 as 2% and one as foam erroneously mixed with Lavasept – a cleaning agent and disinfectant), and another four had received unknown concentrations or doses. Only one patient (ae008J07, a 28 year-old Japanese woman) had been treated with 0.5% polidocanol. This patient did not actually go into shock but had hypotension (BP 92/71; HR 87 bpm) accompanied by “discomfort” without a decrease in SpO<sub>2</sub>; the symptoms resolved with rest and IV infusion of Acetate Ringer 500 ml. The patient was permitted to go home after one hour, then felt discomfort after a short walk; she rested for another hour and went home.

Thirdly, while the indication for this drug is cosmetic, there are other parenteral drugs for cosmetic purposes which have been associated with anaphylaxis, but had been approved by FDA without a REMS for anaphylaxis. E.g., for Botulinum toxin injection to treat glabellar lines, the Botox label does not have a REMS for anaphylactic reactions. The extent of FDA action was to include the following paragraph in the Botox label under WARNINGS: “*Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One **fatal** case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted.*”

Fourth, I think the purpose of a REMS is to help the patient and/or the physician reduce the risks of a potentially fatal or serious adverse event. In the case of polidocanol injection for varicose veins, a Medication Guide will not serve this purpose because this drug is not taken by the patient. A physician communication plan does not help the patient or the physician because anaphylaxis is not easily preventable. Some of the CIOMS forms show that patients who experienced anaphylactic or allergic reactions had “negative” responses to prior skin testing with polidocanol.

Rapid injection of a large volume (or dose) is not the issue. Polidocanol is injected in small volumes at low total doses for a local cosmetic effect, and does not reach significant levels in the systemic circulation. The injection cannot be given rapidly because of (1) small bore of needle, (2) small diameter of vein (<1 mm for spider veins and 1-3 mm for reticular veins), (3) tortuousness of the spiders/ [REDACTED], (4) need to prevent puncture (which is extremely painful to the patient), and (5) the relatively thicker consistency of polidocanol compared to saline or water.

I think we have to put the above considerations in the context of more than [REDACTED] (b) (4)

sclerotherapy exposures to polidocanol injections (including treatment of miscellaneous medical conditions) spanning half a century of treatment in many different types of clinical settings in many countries without any evidence of anaphylactic or allergic reactions more frequent than one would expect with any other parenteral drug.

Thus, based on objective evaluation of clinical and post-marketing data, my opinion (and that of the Director and the Deputy Director of DCARP) is that a REMS is not necessary for approval.

## 9. Advisory Committee Meeting

ASCLERA<sup>™</sup> (polidocanol) is a first-of-a-kind, first-in-class drug product for human use which, under Section 505(s) of the Federal Food, Drug and Cosmetic Act, requires referral to an advisory committee. I present below three major reasons which justify the Division not requesting an advisory committee meeting:

First, another liquid sclerosant, Sotradecol<sup>®</sup> – a detergent in a different chemical class but with similar mechanism of action to that of polidocanol – had been approved for treatment of varicose veins by the FDA Office of Generics in 2004. This approval was based on “an expedited review” of bioequivalence data (of Bioniche Pharma USA’s product compared to an earlier preparation manufactured by Elkin Sinn which had been withdrawn) submitted in an “abbreviated new drug application (ANDA).” The reason for the expedited review was that there was “... a nationwide shortage of this medically necessary drug product.” In the current NDA, Sotradecol<sup>®</sup> is used as a positive control in the pivotal and supportive clinical trials. The data does not suggest that liquid polidocanol is more unsafe than Sotradecol<sup>®</sup>.

Secondly, polidocanol had been registered in Germany since 1966 as a sclerosing agent under the name Aethoxysklerol<sup>®</sup> (and re-approved in 2004). It is currently licensed for treatment of varicose veins in 13 countries including Argentina, Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, the Netherlands, Spain, Sweden and Switzerland, and is currently available in more than 50 countries. Thus, there is a large body of post-marketing and experiential data (published and unpublished) on the efficacy and safety of polidocanol in the treatment of varicose veins in many clinical settings.

Thirdly, according to the FDA Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings (Draft Guidance, August 2008), “*When considering whether to convene such a meeting, FDA should consider the following three factors:*

(a) *Is the matter at issue of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency’s regulatory decision-making process?*

Reviewer’s Answer: No. The indication in this NDA is cosmetic improvement of small C<sub>1</sub> varicose veins, which is not of high public interest.

(b) *Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency’s regulatory decision-making process?*

Reviewer’s Answer: No. There are no major controversial issues. The data does not

suggest that liquid polidocanol is more unsafe than Sotradecol<sup>®</sup>, another liquid sclerosant already approved by FDA in 2004 for treatment of varicose veins.

*(c) Is there a special type of expertise that an advisory committee could provide that is needed for the agency to fully consider a matter?*

Reviewer's Answer: No.

Since none of the above factors is met, the matter at issue does not call for a request to convene an advisory committee meeting.

## 10. Pediatrics

### 10.1 Peds exclusivity board review - PPSR/WR

Not applicable.

### 10.2 PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment

The sponsor requested a full waiver from the requirements of 21 CFR 314.55 and the Pediatric Research Equity Act of 2007, as allowed under 21 CFR Section 314.55 (C)(2) because varicose veins of the lower extremities is a disease that is not present in pediatric populations.

Following PERC review as required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the pediatric study requirement for this application is waived because necessary studies are impossible or highly impracticable, since varicose veins of the lower extremities is a disease not present in pediatric populations.

### 10.3 Consults

Consults were made to DSI (for GCP inspections), OSE DMETS (for carton container label evaluation), OSE DMEPA (for proposed trade name evaluation), DDMAC (for labeling evaluation), OPS PARS (for microbiology of drug product).

## 11. Other Relevant Regulatory Issues

**DSI audits:** From the Clinical Inspection Summary filed by DSI on 18-Nov-2008, GCP inspections of the two investigator sites, the sponsor and the CRO found "... records and procedures were clear, complete and well organized, that reporting of AEs/SAEs appeared adequate, and a review of monitoring reports found no major issues."

At the study sites, the GCP inspections found minor protocol violations (for some patients, the protocol-specified number of injections per visit was exceeded; and thrombophilia tests results were not available before injections) and record-keeping deficiencies (incorrect times of injections, AEs such as hematoma or hyperpigmentation were reported not at the time of occurrence but at the patients' next visit). These do not appear to be serious 483 observations. The clinical investigators' verbal explanations of the incorrect times (that the computer clock and the wall clock showed different times by some minutes) appear to be plausible.

The sponsor submitted information that the protocol-specified maximum number of injections was exceeded in a few patients which could be attributed to injections of varicose veins outside the area of record for the study protocol.

There were no data integrity issues in a "systematic" manner. Even using the worst case scenario for these two sites and discarding their data from efficacy analyses, the efficacy outcome is not effected because polidocanol still wins over placebo with a very high level of statistical significance ( $P < 0.0001$ ).

**Financial disclosure:** The sponsor submitted certification that all of the 19 clinical investigators who participated in the EASI study had no disclosable financial interest.

## 12. Labeling

### 12.1 Proprietary name

The initial proposed proprietary name, (b) (4), was found unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) because the name evokes the (b) (4)

(b) (4) ns (letter dated 07/16/2009 by Carol Holquist).

Subsequently, the second proposed proprietary name ASCLERA<sup>™</sup> was found acceptable by the DMEPA reviewer (Shirley A. Zeigler).

### 12.2 Address important issues raised by brief discussion of DDMAC and DMETS comments

Not applicable.

### 12.3 Physician labeling

#### 12.3.1 Carton and immediate container labels (if problems are noted)

The CMC reviewer (Wendy Wilson) identified the following issues and requested a written response from the sponsor by letter dated 19-Nov-2009:

- Include the drug product dosage form "Injection" in the drug product name, and enclose "polidocanol" in parentheses in the drug product name.
- Include the expression of content per total volume prior to and more prominently than the expression of content per mL.
- Include the statement "Each ampoule intended for immediate use in a single patient" on the carton and container labels.
- As the USAN name for the drug substance is polidocanol, remove the reference to (b) (4) from all carton and container labels intended for the US market.

The sponsor submitted corrected carton and ampoule labels by e-mail on 10-Dec-2009. The corrections appear acceptable.

The CMC reviewer and the DMEPA reviewer recommended more changes which were communicated to the sponsor on 16-Dec-2009. The important changes that are

recommended include the following:

Carton label:

- Relocate the statement “Each ampoule intended for immediate use in a single patient” on the back panel of the carton label to the front on the principal display panel and replace it with “Single use: Discard unused portion”.
- Ensure the established name is at least ½ the size and prominence of the proprietary name to comply with 21 CFR 201.10(g)(2).
- Revise the white font color to another prominent color to provide adequate contrast to make clearer the presentation of strength on the container label, “0.5%”.
- Add a net quantity statement such as, “contains 5 ampules each containing 10 mg/2 mL”, to the principal display panel.
- Revise the unit “ml” for milliliter to read as “mL”. (The lowercase letter ‘l’ can be confusing and look like the number ‘1’.)
- Revise the manufacturer name to be identical and consistent on all labels and labeling
- Revise the strength statements “5 mg/1 ml” and “10 mg/1 ml” to read as “5 mg per mL” and “10 mg per mL” (or “5 mg/mL” and “10 mg/mL”) in accord with the United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25).

Container label:

- The abbreviation “IV” should be spelled out as “Intravenous” on all of the labels and labeling to reduce the potential for misinterpretation of the abbreviation.
- The vial label lacks information regarding the manufacturer of Asclera. The manufacturer information should be included on all labels and labeling.
- Other changes recommended are similar to those mentioned under Carton Label.

### **12.3.2 Patient labeling/Medication guide (if considered or required)**

With regard to a Medication Guide, there are different opinions.

The OSE reviewer (Mary Ross Southworth) comments that “... practically, this drug will be dispensed by the physician administering the drug and discussions of risk/benefit would take place prior to administering the drug, in the office or practice setting. This drug is not administered chronically and hypersensitivity reactions appear within minutes of the injections, so the need for a Medication Guide becomes obsolete after the patient receives the dose. Input on the utility of a Medication Guide should be obtained from the Division of Risk Management (DRISK).”

The DRISK reviewer (Gita Toyserkani) comments that the DRISK group had some dissention regarding a Medication Guide for polidocanol, with the majority considering that “... a Medication Guide would be necessary to inform patients about the risk and enable the patient to decide whether to use or not to use the product,” in the event that “...there is a risk of anaphylaxis for the approved indication...”

I agree with the OSE reviewer that a Medication Guide would not be useful. My reasoning is that this drug is not taken by the patient, and anaphylaxis is not a preventable or predictable condition. Some of the CIOMS forms show that patients who

experienced anaphylactic or allergic reactions in post-marketing studies had had “negative” responses to prior skin testing with polidocanol.

## 13. Recommendations/Risk Benefit Assessment

### 13.1 Recommended regulatory action

This is a new molecular entity for a new indication. Based on review of the clinical data submitted in this NDA, my recommendation is **approval** (§21 CFR 314.110) pending the sponsor’s response to comply with the changes recommended in:

- (a) the proposed labeling: in (1) Indications and Usage, (2) Dose Considerations, (3) Contraindications and (4) Warnings and Precautions sections, and
- (b) the carton and ampoule label.

The regulatory reason to approve is:

*There is substantial evidence consisting of adequate and well-controlled investigations, as defined in §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling {§ 21 CFR 314.125(b)(5)}.*

### 13.2 Risk Benefit Assessment

The EASI trial showed that polidocanol was significantly superior to placebo for the primary efficacy endpoint of success rate {defined as mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) at 12±2 weeks} for the full analysis data set ( $4.52 \pm 0.65$  for polidocanol vs.  $2.19 \pm 0.68$  for placebo;  $p < 0.0001$ ) and the per-protocol data set ( $4.55 \pm 0.63$  for polidocanol vs  $2.09 \pm 0.41$  for placebo;  $p < 0.0001$ ).

The same is true also for the active comparator Sotradecol<sup>®</sup> compared to placebo suggesting adequate *assay sensitivity* of the EASI trial.

This cosmetic benefit was maintained when evaluated again at 26 weeks (6 months).

Patients’ satisfaction with treatment (graded on a scale of 1 to 5) showed that a significant ( $p < 0.0001$ ) proportion of patients treated with polidocanol were “satisfied” or “very satisfied” at 12 weeks (88%) and 26 weeks (84%), compared to patients treated with Sotradecol<sup>®</sup> (64% at 12 weeks and 63% at 26 weeks) or placebo (13% at 12 weeks and 11% at 26 weeks).

The success rate (by objective photographic evaluations) and the subjective patient satisfaction rates were significantly correlated ( $p = 0.0381$  to  $p < 0.0001$ ). Thus, the efficacy results demonstrate consistent and sustained cosmetic benefit.

From the safety perspective, there were no deaths, no events of anaphylaxis, very few SAEs, a few limited local AEs, and no clinically important laboratory abnormalities or QTc<sub>F</sub> changes in the clinical studies in this application. DVT, a specific concern with this type of drug product, was not found with prospective ultrasound screenings in the EASI trial at one and 12 weeks after injection of polidocanol. Also, DVT was not found with

liquid polidocanol in the French Polidocanol Registry study (in which 14 DVTs were associated with foam sclerosants and 2 with other liquid sclerosants).

The sustained cosmetic benefit obtained by treatment of C<sub>1</sub> spider and reticular veins using polidocanol liquid appears to exceed the risk of local AEs which were minor and transient in nature. The absence of DVTs in patients treated with polidocanol liquid further alleviates safety concerns.

The efficacy and safety profile of polidocanol liquid appears to be no worse than that of Sotradecol<sup>®</sup>, another liquid sclerosant which was approved for the treatment of varicose veins by FDA Office of Generic Drugs in 2004.

### **13.3 Recommendation for Postmarketing Risk Management Activities**

Please see Section 8.7 for discussions on the need or not for (1) a black box warning, and (2) REMS (Communication Plan). Please see Section 12.3.2 for discussions on the need or not for a Medication Guide.

### **13.4 Recommendation for other Postmarketing Study Commitments**

In accordance with §21 CFR 314.81 (b)(1)(ii), the postmarket reporting requirement for “... *information concerning any bacterial contamination, or significant chemical, physical or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application,*” the sponsor had submitted a signed commitment to:

- (1) conduct stability studies,
- (2) add one commercial batch yearly on a rotating principle,
- (3) provide annual reports of post-approval stability testing,
- (4) report information concerning bacterial contamination, significant chemical, physical or other deterioration in the drug product or failure to meet established product specifications, and,
- (5) withdraw any batch of drug product from the market that fails to meet specifications during the course of stability testing.

The CMC reviewer has other no Phase 4 (Post-Marketing) CMC recommendations.

The OSE reviewer (Mary Ross Southworth) recommends that the sponsor “... submit an analysis of all serious hypersensitivity events on an annual basis for review by the Agency. All serious hypersensitivity reactions should be reported as 15-day reports.”

### **13.5 Recommended Comments to Applicant**

I have the following recommendations to be communicated to the sponsor:

- (1) Comply with the signed post-marketing commitments.
- (2) Respond to the carton and container label issues raised by FDA reviewers.
- (3) Make changes to the labeling as recommended by FDA.
- (4) Submit to FDA all information related to serious adverse events, serious anaphylactic or hypersensitivity reactions including anaphylactic shock, and deep

vein thrombosis within 15 days of receipt as 15-day expedited reports, and submit adverse event reports under the AERS.

### **REFERENCES**

- 
- <sup>1</sup> Conrad P, Malouf GM, Stacey MC. The Australian polidocanol (aethoxysklerol) study. Results at 2 years. *Dermatol Surg* 1995; 21(4): 334-6 (abstract).
  - <sup>2</sup> Hamel-desnos C, Desnos P, Wollmann J-C, Ouvry P, Mako S, Allaert F-A. 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; 29: 1170-1175.
  - <sup>3</sup> Guex J-J, Allaert FA, Gillet J-L, Chleir F. Immediate and midterm complications of sclerotherapy: Report of a prospective multicenter registry of 12,173 sclerotherapy sessions. *Dermatol Surg* 2005; 31: 123-8.
  - <sup>4</sup> Jiwei Z, Schliephake DE, Malouf GM, Otto J, Zaiping J, and Yong-quan G. Polidocanol/lauromacrogol 400 vs. placebo for sclerotherapy of C<sub>1</sub> and C<sub>2</sub> non-saphenous trunk varicose veins: a double-blind, randomized, controlled, multi-center clinical trial (ESACHina Study). Presented at *World Congress of the International Union of Phlebology (UIP) in September 2009* in Monaco. (Source: Sponsor's abstract of the trial and the set of slides presented at the UIP conference.)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

KHIN M U  
12/18/2009  
Recommend approval of this NDA 21-201.