CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205098Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	14-Nov-2013
From	Khin Maung U, M.D.
Subject	**Cross-Discipline Team Leader Review**
NDA/BLA #	NDA 205-098
Application Type	505 (b) (1)
Applicant	Provensis Ltd
Dates of Submission	04-Feb-2013
PDUFA Goal Date	04-Dec-2013
Priority Designation	Standard Review
Proprietary Name / Established (USAN) names	Varithena™ / Polidocanol Injectable Foam
Dosage forms / Strength	A canister device to generate 1.0% (weight / volume) of polidocanol injectable microfoam
Proposed Indication	Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below the knee, and to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system
Recommendation:	**Approval**
Advisory Committee Meeting	**Not required**

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

Review Discipline	Reviewer	Team Leader
Clinical	Khin Maung U	Khin Maung U (CDTL)
Statistical	Steven Bai	Hsein Ming J. Hung
Safety (REMS/MedGuide)	Lori Wachter	Mary Ross Southworth
Pharmacology/Toxicology	William T. Link	Albert F. Defelice
Clinical Pharmacology	Peter Hinderling	Rajnikanth Madabushi
CMC	Wendy Wilson-Lee	Kasturi Srinivasachar
BioPharm	Banu S. Zolnik	Sandra Suarez
OPS/NDMS (Microbiology)	Stephen E. Langille	David Hussong
SEALD Endpoints Team	Jessica Voqui	Laurie B. Burke (Director)
OSE-DMEPA	Kimberly De Fronzo	Irene Chan
OSE-DRISK	Jason Bunting	Reema Mehta
OPDP	Emily Baker	Amy Toscano
OSI/DGCP	Sheron K. Gershon	Susan Leibenhaut
Project Manager	Michael V. Monteleone	Edward J. Fromm
OMPQ	Vibhakar Shah	Steven Hertz
CDRH/OC	Andrew Dufor	
CDRH/ODE/DAGRID/HFPMET	QyunhNhu Nguyen	Ron Kaye
CDRH/ODE/DCD/PIBD	Jhumur D. Banik	Kenneth J. Cavanaugh, Jr.
CDRH/OSEL/DCMS	Martin K. McDermott	

1. Introduction

This CDTL review elaborates the rationale for recommending for **approval**, under Section 505(b)(1) of the FD&C Act, NDA 205-098 submitted by Provensis Ltd. for Varithena™ – pending (i) the findings of facilities inspections and reviews of (ii) sponsor's response to an information request by ONDQA and CDRH and (iii) the need for a REMS and labeling review by DRISK.

The approval recommendation is for the indication: "Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below the knee, and to improve symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system."

In the US population, varicose veins due to failure of the terminal (proximal) valve of the great saphenous vein (GSV) at the saphenofemoral junction (SFJ) are very common, affecting up to 25% of adults[1], with the prevalence and severity increasing with age. The extent and severity of the appearance of visible varicosities varies greatly and do not necessarily correspond to the severity of a patient's symptoms which are the result of venous hypertension leading to dilation of veins. The symptoms may include a sensation of tension, feeling tender to touch, swelling, tightness, heaviness, throbbing, aching and itching. Venous hypertension may also lead to progressive damage to the skin, edema, discoloration, hyperpigmentation, eczema and ulceration, which are reported in about 20% of patients with varicose veins in the US. Symptoms motivate patients to seek treatment, with >400,000 patients treated in the US each year.[2]

One modality of management of varicose veins is sclerotherapy with liquid or foam sclerosants {including physician-compounded sclerosant foams prepared by a variety of methods and Varithena™ injectable foam}. Physician-compounded foam sclerosants produced with room air may introduce nitrogen bubbles into the systemic circulation and may lead to gas embolism, or, in the presence of a patent foramen ovale (PFO), may appear as micro-bubbles in the cerebral circulation which may cause stroke, seizure, visual disturbance or a transient ischemic attack, which have been reported in about 2% of patients treated with foam sclerosants[3,4,5].

Varithena™ is a proprietary, engineered injectable foam produced using an aqueous polidocanol solution (in one canister) and a gas mixture of oxygen/carbon dioxide (65:35) (in another canister). A sterile Varithena™ transfer unit (VTU) is incorporated to the two canisters to dispense polidocanol into a syringe at a solution concentration of 1.0% weight/volume as Varithena™ injectable foam of uniform, controlled density and bubble size (median bubble diameter <100 µm and no bubbles >500 µm). Once constituted, the Varithena™ injectable foam in the syringe must be administered by a trained physician within 75 seconds to the patient in the clinic.

After intravenous injection, Varithena™ injectable foam remains as a foam, (b) (4) The Varithena™ injectable foam physically displaces the blood in the vein, allowing polidocanol, which is neither diluted nor de-activated, to act upon the endothelium (in contrast to liquid sclerosants which are diluted and/or deactivated by the blood present in large veins). As a result of the physical properties of the Varithena™ injectable foam, which has a mean density of (b) (4) (approximate liquid:gas ratio of 1:7), Varithena™ injectable foam

empties even large veins of blood and can therefore treat them with a small total dose of the active sclerosant, polidocanol.

The mechanism of action of polidocanol is chemical. As a non-ionic surfactant, the hydrophobic pole of the polidocanol molecule attaches to the lipid membrane of venous endothelial cells and disrupts the osmotic barrier. The resulting cell destruction creates a highly thrombogenic exposed endothelial surface to which platelets attach followed by thrombus formation, obliterating the vein lumen which is later replaced by fibrous tissue.

Varithena™ injectable foam is highly echogenic; with ultrasound the physician can observe the Varithena™ injectable foam filling the targeted segments of the incompetent vein. This allows visually controlled treatment of the incompetent vein segment under ultrasound guidance to ablate the varicose veins.

The volume of Varithena™ injectable foam to be injected depends on the size and extent of the veins to be treated. The maximum recommended volume per treatment session is 15 mL, comprising individual injections up to 5 mL each. Further treatments may be necessary if the extent of the varicose veins requires more than 15 mL of Varithena™ injectable foam; these treatment sessions are to be separated by >5 days.

The submission contains 12 clinical studies of Varithena™ injectable foam in patients with varicose veins, which were conducted using 2 different formulations:

(i) The original formulation (Varisolve OF) (b) (4) and was administered in Studies COM001, 001, 003 and 0005, and to some patients in Study 011 (these studies are not pertinent for efficacy review);

(ii) In 2004, (b) (4) Varithena™ injectable foam (which contained only oxygen and carbon dioxide) was used in some patients in Study 011 (for comparison), and in all subsequent clinical studies of Varithena™ injectable foam: Studies 008, 012 and 014, and in Phase 3 Studies 013, 015, 016 and 017 (and 2 patients treated in the prematurely-discontinued Study 007).

2. Background

The major points in the regulatory history of this Drug Product with FDA are as follows.

The initial IND was filed by BTG International on 11-Oct-2001 with the Division of Dermatology and Dental Products (DDDP) and was placed on clinical hold. A series of clinical hold complete responses by the sponsor followed. On 14-Nov-2003, a complete clinical hold was imposed on Protocol VAP.VV012 for safety concerns related to micro-bubbles detected in the heart (10 patients) and in the internal carotid artery (1 patient with PFO who became symptomatic with visual and cognitive changes).

In March 2005, DDDP consulted DCaRP. I reviewed the sponsor's initial amended protocol and recommended the following changes: (i) that all patients be hospitalized for 24 hours following the Varisolve™ injectable foam procedure, (ii) that the study be restricted to 50 events (of micro-bubbles in the MCA detected by Transcranial Doppler (TCD)), and (ii) that the first five patients be scheduled for MRIs (DWI and PWI) at baseline, 8-24 hours, day 7 and day 28. My review considerations were made in the context of widespread use of sclerosants (in foam form or liquid) for treatment of

varicose veins within the US (off-label treatment at that time) and in Europe, Australia and New Zealand, Japan, Latin America, etc.

The prevalence of PFO in the general population is about 20-30%. However, the published literature and presentations made at the "World Congresses" of Phlebology (involving several thousand patients) reported no occurrence of pulmonary embolism or scotoma (or neurological deficit). The relatively small volume of gas mixture (<20 ml) used for the Varithena™ injectable foam procedure did not appear to pose a high risk of gas embolism. Thus, I considered it appropriate to permit a closely monitored clinical study limited to the assessment of the effect of bubbles in the cerebral circulation.

The IND was transferred from DDDP to DCaRP in May, 2005.

The sponsor submitted a revised protocol (serial # 052) on 16-May-2005 which incorporated these recommendations. Subsequently, in a FDA letter dated 11-July-2005, the clinical hold was lifted.

On 27-Jan-2007, BTG International Ltd contacted me via e-mail to inform that a newly recognized potentially fatal adverse effect, nephrogenic systemic fibrosis, has been associated with gadolinium-based MR contrast agents used for PWI MRI, and that FDA had issued a Public Health Advisory on this topic in December 2006. No patients had yet been enrolled. I advised that PWI MRI, which used gadolinium-based contrast agents, be excluded from this study. On 15-Mar-2007, the sponsor submitted a protocol amendment excluding the PWI MRI procedure.

On 15-Sep-2008, the sponsor submitted a new protocol VAP.VV013 designed to test some of the procedures (e.g., effectiveness of patient blinding for sham procedure, standardization of digital photographic images and Doppler/ultrasound techniques, and correlation between patients' subjective symptoms/cosmetic assessments and objective photographic and ultrasound evaluations) which the sponsor intended to use in future well-controlled trials.

On 20-Aug-2009, the sponsor submitted a new protocol VAP.VV014 for an open-label pilot study to investigate the efficacy of the 0.125% and 0.2% concentrations of Varithena™ injectable foam to be conducted at a single clinical site in the US.

The sponsor submitted two protocols for Special Protocol Assessments (SPAs): (i) on 28-Oct-2009, Protocol VAP.VV015, and (ii) on 11-Dec-2009, Protocol VAP.VV017. The Division issued No-Agreement letters for both due to several flaws with study designs, the saline placebo proposed, the narrow range of doses and the primary endpoints. The sponsor requested withdrawal of their two SPAs on 26-Aug-2010 and 24-Sep-2010.

The sponsor submitted statistical analysis plans (SAPs) for Study VAP.VV016 on 18-Jan-2011, and for Study VAP.VV015 on 13-May-2011.

In response to the Agency's comments, the sponsor also submitted to FDA a Usability Protocol and Instructions for Use for their drug-device product on 20-Feb-2012 and 22-Mar-2012.

Further discussions related to endpoints, safety reports and clinical pharmacology aspects of the NDA were discussed during a pre-NDA meeting between the Agency and the sponsor on 31-Jul-2012.

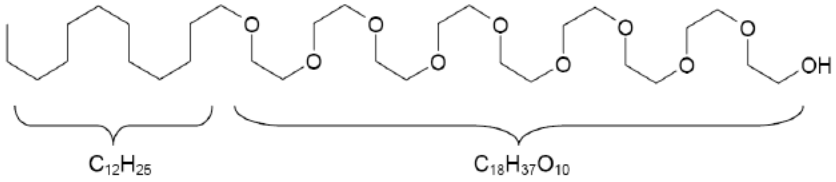
3. CMC/Device

3.1 General product quality considerations

Name of Drug: VARITHENA™ 1%

Active Ingredient: Polidocanol

Drug Product: Polidocanol injectable foam (1.0% w/v)



Structural formula: $=C_{30}H_{62}O_{10}$

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

Mean Molecular Weight: Approximately 600.

Polidocanol, active pharmaceutical ingredient in Varithena™ injectable foam, [(b) (4)] four oligomers (E5, E9, E12 and E14, which have different numbers of ethylene oxide units (5, 9, 12, and 14, respectively) were chosen for quantification.

The initial drug product in this submission ([(b) (4)] was associated with micro-bubbles in the heart and in the cerebral circulation. In 2004, [(b) (4)], using oxygen and carbon dioxide only; the product also added a transfer unit device which delivers a standardized polidocanol foam at a solution concentration of 1% weight per volume for the 1% solution, and was used in clinical trials in the development program.

Although different types of polidocanol foam can offer more effective treatment compared with polidocanol liquid, not all may be safer. Homemade foams had variable gases used (including air or insoluble gases), variable doses of liquid sclerosant in a given volume of foam, and even more variable physical characteristics (i.e., variability in internal cohesion in the dose of liquid sclerosant that a given volume of foam contains in the diameter of the bubble). The diameter of the bubble, the gas-liquid proportion, the internal inter-bubble cohesion, and the type and combination of the gases used, are important parameters contributing to the efficacy and safety of the procedure.

The CMC Reviewer (Wendy I. Wilson-Lee) found that all drug substance analytical procedures are appropriate and validated for their intended use. Based on drug substance stability data, the CMC reviewer recommended granting a [(b) (4)] re-test period for polidocanol drug substance stored at [(b) (4)] and an 18-month expiration date for 1% strength Varithena™ injectable foam stored at controlled room temperature in the commercial packaging.

The CMC reviewer recommended a complete response action in the Quality Review Addendum 1 dated 07-Nov-2013 because:

(i) additional deficiency comments regarding the proposed drug product content uniformity controls fro through canister life, across canisters and across batches

(ii) additional deficiency comments related to the proposed carton and container labels,

(iii) the overall facilities inspection reports by the Office of Compliance is still pending for two manufacturing sites.

On 05-Sep-2013, the CMC reviewer provided the following list of deficiencies which were communicated to the applicant in an information request letter (IR):

(i) 13 new deficiencies,

(ii) response to request for one FDA advice included in 09-Jul-2013 amendment, and

(iii) response to 18 pending deficiencies which have been communicated earlier to the applicant to 18-Jul-2013.

On 05-Nov-2013, an IR was sent to the sponsor to provide the revisions to the carton and container labels, including replacing (b) (4) with "injectable foam," expression of strength on total volume, net contents, route of administration and font changes.

On 07-Nov-2013, **Teshara G. Bouie of CDER/OPS/ONDQA** e-mailed an IR to the sponsor's agent to revise/update sections in the content uniformity proposal to ensure that the content uniformity testing assesses content uniformity through the life of the individual canisters, across canisters in a given batch and across batches.

CDTL comment: **The items (iii), and the sponsor's response to IRs of 05 and 07-Nov will need to be re-reviewed by ONDQA and C&C which may delay the Division's approval action past the PDUFA goal date.**

Review of Microbiology: CDER/OPS/ONDQA/NDMS Review (By Stephen E. Langille) for potential microbiological ingress finds that Polidocanol Injectable Microfoam does not meet the acceptance criteria for USP <51> Antimicrobial Effectiveness testing and may support the growth of microorganisms after a period of approximately (b) (4)

Although the product is sterile, maintained under positive pressure, and the fluid path is shielded with the Varithena™ transfer unit (VTU), the product path will be exposed to the environment intermittently during normal product use, thereby necessitating additional precautions to reduce the risk of microbial contamination and growth along the product path during the proposed 7-day in-use period.

On 12-Aug-2013, the reviewer recommended amending the physician training materials to state that the stem of the shuttle filter assembly should be swabbed with a sterile alcohol pad just prior to the attachment of each new VTU in order to reduce the risk of microbial contamination along the product path during the in-use period.

On 27-Aug-2013, the sponsor submitted an amendment in the "Instructions for use" (page 15) by adding "Swab the uncovered shuttle with a fresh sterile alcohol wipe and immediately place the VTU on top of the Varithena canister….."

The primary reviewer commented that while the drug product is an unpreserved solution for use as a multiple dose product over a period of seven days, the nature of the drug delivery system in the form of the unique container closure configuration, inherent antimicrobial activity of the drug product, aseptic techniques employed during the in-use period, and the precautions taken to avoid contamination during use, have resulted in a minimal risk of product contamination during the 7 day in-use period.

The review identified a potential precedent: "Use of an unpreserved multiple dose injectable over a seven day in-use period." The precedent is applicable to drug products that possess unique container closure systems which do not allow microbial ingress, comprised of formulations that are antimicrobial and employ aseptic techniques during the in-use period. Both the primary reviewer and the secondary reviewer (John Metcalfe) agreed that this precedent is justified.

The reviewer recommended the drug-product for approval in his final review dated 12-Sep-2013, with no recommendation for any phase 4 commitments and/or agreements.

CDTL comment: I concur with the product quality microbiology reviewer's evaluation and recommendation.

3.2 Facilities review/inspection

State whether all facilities inspections have been completed and whether Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable. If not, then the reason(s) for lack of inspections or lack of facilities acceptability should be described here.

OC/OMPQ/DGMPA for manufacturing facilities inspections (to be processed **by Vibhakar J. Shah**): Reports of GMP inspections of two of the four manufacturing sites in the UK (Table 1) are pending (the other two are considered "… may not be needed" and cancelled).

Table 1 Manufacturing facilities scheduled for inspections by ORA

Application	FEI	Establishment	Country	Profile	Stage	Process	Inspection Date	Compliance Status
NDA 205098	3002124545	Biocompatibles UK Ltd.	GBR	(b) (4)	Finished Dosage	Labeler, Manufacturer, Other Tester	Nov 7-15, 2013	PN
NDA 205098	TBA	SCM Pharma	GBR		Finished Dosage	Manufacturer	Oct 28-Nov 05, 2013	PN

CDTL comment: **Any delay in the OC review and determination of the manufacturing facilities inspection findings may carry the Division's approval action past the PDUFA goal date.**

3.3 Other notable issues (resolved or outstanding)

Where a consultative or collaborative review, such as with CDRH has occurred [e.g. a drug/device combination], a summary of the critical issues from the consult may be

included here. Any and all unresolved issues should be stated. If disagreements exist between Centers in regard to any drug/device issue, these also should be described.

CDRH consults:

The following CDRH consult-issues were evaluated by CDRH reviewers, and summaries of their comments (highlighted) are also presented.

(1) For Human Factors and Device Use Safety: CDRH/ODE/DAGRID/HFPMET Review (By QuynhNhu Nguyen): CDRH Human Factors (HFPMET) team provided a comment on an earlier HF/usability validation study conducted with 45 participants (3 user groups: 15 physicians, 15 clinical staff and 15 staff assistants) to provide a characterization of the user tasks that will be performed by the physicians and their clinical staff, and to assess the interaction between the two user groups.

This HF/usability validation study revealed a total of nine use errors, five close calls, and 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention, and the study analyses did not clearly describe their potential negative clinical consequences.

In response to the reviewer's request, the sponsor provided information related to clinical consequences of the observed use errors/close calls/operational difficulties, whether these results were caused by product design, labeling or training, whether modifications will be made, and the conclusions based on the study with regard to whether the device is reasonably safe and effective for the intended users, uses and use conditions. The reviewer found the sponsor's response acceptable.

Later, the sponsor submitted additional changes to the IFU in response to the IRs from DRISK IRs. The HFPMET reviewer then requested the sponsor to provide (i) an analysis of the hazards associated with the aspects of the IFU that have been modified, (ii) the potential clinical consequences if users make errors while performing any tasks that involve the modified instructions, (iii) the mitigations strategies to control all serious use-related hazards and (iv) the methods to validate the effectiveness of those mitigations.

The CDRH reviewer's assessment is that the IR response indicated that the sponsor has analyzed the impact of the changes to the IFU. The reviewer concluded that none of the changes would result in a use-related hazard that would adversely impact patient safety or efficacy. The sponsor provided a table that outlines all of the changes made. Most of the changes were made to allow better flow of the document, to achieve better alignment between the IFU and the information contained in the NDA, to provide explicit language for specific instructional statements, and to comply with IFU content requirement. Apart from three changes that did not fit in the above categories, the sponsor provided a detailed analysis of possible use errors, and associated risks, which were categorized as not significant. The CDRH reviewer found the sponsor's response acceptable.

CDTL comment: I concur with the human factors and device use safety reviewer's evaluation and recommendation.

(2) For chemical interactions of the drug, gas and excipient with the device used

to make the polidocanol injectable microfoam: CDRH/OSEL/DCMS Review (By Martin (Ken) McDermott): The review findings are summarized below:

(i) The O_2 Canister is composed of aluminum with an (b) (4) . The canister holds O_2 at 5.4 bar. The Aluminum and (b) (4) were determined to be stable.

(ii) The Polidocanol Canister is composed of Aluminum. It holds the polidocanol solution for a maximum period of:

a. 18 months in carbon dioxide. The aluminum is stable in the pH range of the polidocanol solution.

b. 7 days in CO_2-O_2 gas mixture after the oxygen canister is attached. Corrosion was not demonstrated to occur within this time.

Aluminum content in the polidocanol solution had not changed at either 25°C or 40°C over a 3 month period. The method for measuring purity level was not discussed and the meaning of NMT (b) (4) was not defined. 4 Week aluminum levels do not change as a function of time.

(iii) Components of the device that generate and deliver the polidocanol foam are composed (b) (4) No degradation products were extracted nor was there a significant change in oligomer size of polidocanol. Surface chemical reactions could possibly alter the interaction between parts such as (b) (4) No change in surface appearance of the (b) (4) suggests that there are no changes in surface properties.

The reviewer commented that adequate responses to requests for additional information by CDRH were received. <u>The ingredients of the polidocanol injectable foam do not appear to be reactive to the materials of the device that stores and produces the foam.</u>

<u>*CDTL comment*</u>: I concur with materials scientist's review and analysis of the chemical interactions of the drug, gas and excipient with the device used to make the polidocanol injectable microfoam, and his recommendation.

(3) For the device design and microfoam generation regarding functional properties of the container closure system and consistency of microfoam characteristics – **CDRH/ODEDCD/PIDB** Review **(By Jhumur D. Banik):** This Engineering Consult Review for functional properties of the container closure system that stores and helps generate the PEM finds that the information provided by the sponsor is adequate regarding the assembly process validation testing and for assessing the functional properties of the container closure system, and that the analytical procedures are appropriate to monitor the respective foam characteristics (i.e. half separation time, bubble size, and foam density). The sponsor's performance testing demonstrated that the container closure system functions as intended and that the device can consistently generate foam according to the specifications. The sponsor

also responded adequately to additional questions by the reviewer during Interactive Review.

The PIDB reviewer concluded that there are no concerns with the device design and foam generation.

CDTL comment: I concur. The above evaluation by the reviewer is accurate.

4. Nonclinical Pharmacology/Toxicology

- ***General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).***

An exhaustive (204-page) review by the **pharm-tox reviewer (William T. Link)** is summarized below for clinically relevant biological effects.

Pharmacodynamic studies

The pharmacodynamics of Varithena™ injectable foam was described in 4 *in vivo* studies in non-rodents.

Study 256277 in the sheep showed no sign of vasospasm in the external jugular vein or saphenous vein when Polidocanol foam was injected. The sheep model was discarded.

The New Zealand rabbit was used (in 3 marginal ear vein Studies 256146, 256696 and KMWW-0001) to model the clinical situation where the vein is occluded, and to investigate the effect of polidocanol (both solution and foam formulations) on vein endothelium *in vivo*. Polidocanol foam at concentrations of 0.25%, 0.5%, 1% and 2% caused sclerosis in a dose-responsive manner with comparable effectiveness at concentrations of 1% and 2%. The foam formulation was found more effective as a sclerosing agent than the polidocanol solution.

No secondary pharmacodynamics studies were conducted.

Safety Pharmacology studies

In vitro safety studies: Three *in vitro* safety pharmacology studies were conducted:

(1) Study 256188 investigated the hemolytic potential of polidocanol (solution and foam) in human blood, and found them to be non-hemolytic at the concentrations evaluated in the study.

The following two studies were part of the program to address the FDA concerns for the effects of microbubbles in the circulation arising from the administration of Varithena™ injectable foam.

(2) Study RD198/23925 assessed polidocanol foam gas absorption into human venous blood. The gas contents of polidocanol foam manufactured with (b) (4) absorbed faster than (b) (4) rate of absorption of half of the gas = 1.4 seconds for (b) (4) vs. 21.3 seconds for (b) (4) and (b) (4) absorbed completely while (b) (4) hardly at all. (b) (4) decayed to a larger residual gas volume at 120 seconds (by 97%, 46% and 27%, respectively), while (b) (4) decayed to zero. (b) (4)

(b) (4)

(3) Study RD198/23926 assessed whether there was a potential for polidocanol to remain in the venous system following the administration of Varithena™ injectable foam. There was no measurable or clinically important excess polidocanol concentration associated with gas bubbles following mixing microfoam *in vitro* with fresh human venous blood.

Standard Pharmacology Safety Studies in Animals

Thirteen *in vivo* safety pharmacology studies were conducted with polidocanol solution and polidocanol foam. Of these, seven standard safety studies were designed to evaluate possible pharmacological effects of polidocanol *solution* on:

- cardio-respiratory system of the anesthetized dog – the Beagle and the Hound (study RCC 767676),
- renal function of the Han Wistar rat (study RCC 767687),
- gastrointestinal motility (study RCC 767698 – charcoal propulsion),
- general behavior (study RCC 767654 – modified Irwin screen test in the mouse)
- central nervous system (study RCC 767665 and study RCC 767654), and
- locomotor activity (study RCC 767665) of the NMR1 mouse.

Summary of findings: Intravenous administration of polidocanol *solution* at doses up to

(i) 3 mg/kg was without biologically relevant effects on renal function in the male Han Wistar Rat,

(ii) 10 mg/kg was without significant pharmacologically relevant effects in the male NMR1 mouse, and

(iii) 20 kg/kg was without effect on systolic blood pressure and heart rate up to 30 minutes post-dose in the anesthetized dog.

A series of standard (study Butler 1, study TMC002) and six specialized cardio-respiratory studies in the dog and rat were conducted with polidocanol ***foam*** to address FDA concerns related to the effect of microbubbles in the circulation, including:

- study TMC003,
- study TMC004,
- study UP001,
- study DVASF001,
- study DVASF002, and
- study CTBR 690666.

Summary of findings: In a 'worst case' scenario study with rapid bolus injection of Varithena™ injectable foam into a peripheral leg vein of dogs, even at the largest dose (equivalent to 180 mL in man w/v) was well tolerated. The 10 mL dose (equivalent to the average human clinical dose of 30 mL 1% foam) resulted in no significant changes in pulmonary hemodynamic measurements. Larger doses produced increasingly large changes in measurements suggesting reflex pulmonary vascular occlusion; these changes rapidly returned to normal values without sustained deleterious effects.

The transient appearance of microbubbles seen in trans-esophageal echocardiography

following infusions in three experiments with the anesthetized dogs showed that the opacification time was dose dependent, and that the hemodynamic and gas exchange responses produced by higher doses (45 to 150 mL total dose) of Varithena™ injectable foam were consistent with transient occlusion of the pulmonary arterioles with microbubbles and initiation of compensatory effects. However, the histopathology of lung, liver, heart and kidney observed was the same in Varithena™ injectable foam-treated dogs (up to 10 times the clinically relevant dose) as in untreated control animals, suggesting that under acute conditions, Varithena™ injectable foam NF1 had no effect on cardiopulmonary hemodynamics at total doses of 10 mL and 20 mL administered intravenously, while transient and minor pulmonary obstruction was observed at a total dose of 80 mL (equivalent (v/w) to 12 times the therapeutic dose).

An *in vivo* canine model to evaluate the association of polidocanol with the gaseous component of Varithena™ injectable foam showed that following treatment with either Varithena™ injectable foam (<1% N_2) or Varithena™ injectable foam (approximately (b) (4) N_2), there were no significant differences in the mean ratio of polidocanol concentration between the bubble-rich portion of the plasma sample and the bubble-depleted portion of the plasma sample. This suggests that systemically circulating gas bubbles were *not* associated with more polidocanol than the surrounding plasma, and that residual bubbles that circulate to the lung following polidocanol foam sclerotherapy will not cause an increase in polidocanol toxicity to the lung vasculature.

Varithena™ injectable foam NF1 and Varithena™ injectable foam OF were without effect on the arteriolar microcirculation as typified by the cremaster muscle, at doses up to 400 µL (i.e., equivalent to 20 times the amount of polidocanol foam estimated to cross a 20% PFO assuming the improbable migration of the entire clinical dose of 20 mL to the right atrium) whereas foam generated by foaming liquid polidocanol with room air occluded microvascular arterioles at a dose of 50 µL, the lowest dose tested. These experiments suggest that sclerosant alone also had no effect on classic agonist-induced arteriolar responses.

The effect of intra-arterial administration of Varithena™ injectable foam NF1 on subclinical cerebral effects was evaluated in a rat model (previously shown to display cerebral ischemia and infarction in response to intra-carotid injection of atheroembolic particles). Morphological evidence of cerebral infarction was not seen at a 5 µL dose of Varithena™ injectable foam NF1 at both Day 1 and Day 7 following treatment; minimal ischemia was observed at 24 hours in 1 out of 8 rats but completely absent in all rats at Day 7. This suggests that the no adverse effect dose of Varithena™ injectable foam NF1 is 5 µL (i.e., 11.6 times the amount of Varithena™ injectable foam NF1 expected to enter the arterial circulation, assuming the entire dose traversed an estimated 20% PFO).

- ***Carcinogenicity***

The drug product is intended for single or infrequent use. Carcinogenicity studies were not required or performed.

- ***Reproductive toxicology***

Study 493003 and 493017 – Effects on fertility in male and female Sprague-Dawley rats: There was no effect of polidocanol treatment on mating performance, male

reproductive organ weights, fertility index or pregnancy performance at any of the dose levels tested up to 27 mg/kg/day.

Study 492832 – Effects on embryonic fetal development in rats: Intravenous injection of polidocanol via lateral tail vein for 11 days at a dose of 27 mg/kg/day, as required for the subsequent developmental toxicity study, was not possible due to the marked reaction of the tail and difficulty in finding the vein.

Subsequent development toxicity studies (below) were conducted by infusion following femoral vein catheterization.

Study 19467 and 493265 – Polidocanol developmental toxicity study in Sprague-Dawley rats: There were no effects of treatment with polidocanol on pregnancy performance, fetal weight, or incidence of fetal abnormalities and variants, or the state of skeletal ossification at doses up to 27 mg/kg/day. The incidence of fetuses at 10 mg/kg/day with complete 13th supernumerary ribs was marginally greater than Control.

Study 493134 – Polidocanol peri- and post-natal study in Sprague-Dawley rats: At 27 mg/kg/day, all animals showed signs of reaction to treatment such as mastication, a fixed stare, irregular respiration, red cage staining, subdued behavior, chin rubbing and salivation. Animals 74 and 79 were found dead, respectively, on Days 20 and 17 of gestation after showing similar signs. Animal 107 was found dead on Day 19 of lactation, and had the typical signs, but the necropsy findings included an ulcer in the colon; it was not possible to attribute this death to treatment.

At 9 mg/kg/day, many animals had mastication and irregular respiration, 8 had subdued behavior and 7 had a fixed stare. Other clinical signs of reaction to treatment included salivation, a pale appearance, lying flat, fitting, crawling on paws and red cage staining. One animal (Number 106) was killed on Day 4 of lactation due to its condition.

At 3 mg/kg/day, three animals had mastication, and there was a single instance of a fixed stare, salivation, piloerection and rolling gait.

There were no obvious effects of treatment on duration of gestation, litter size or pup survival, or the pre-weaning physical or functional development of the F1 pups.

Special toxicology studies – Polidocanol antigenicity studies of active systemic anaphylactic (ASA) reaction and passive cutaneous anaphylactic (PCA) reaction in the albino guinea pig: No antigenic potential was detected in the ASA and PCA tests after treatment with 1% stock solution of Polidocanol. Polidocanol is considered not to be a functional antigen. The clinical signs noted after intravenous treatment with Polidocanol are regarded as toxic responses and not as immunological responses. (Ovalbumin confirmed its antigenic potency throughout the ASA and PCA test.)

- ***Other notable issues (resolved or outstanding)***

None

CDTL comment: I concur with pharmacologist's analyses of the non-clinical pharmaco-dynamic and toxicological studies, and his determination that the product is approvable.

5. Clinical Pharmacology/Biopharmaceutics

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

OCP – The Clinical Pharmacology reviewer (Peter H. Hinderling) evaluated the following PK studies.

(a) *In vivo* PK studies:

(i) Study 008 is the pivotal PK study which evaluated the to-be-marketed formulations of Varithena™ injectable foam: the plasma concentrations of 4 polidocanol oligomers were determined using a sensitive enough assay method, and the possible impact of polidocanol on QTc and the other ECG intervals was also investigated.

(ii) Studies 005 and 011 were pilot PK studies, which used a less sensitive assay and/or too short a duration of the plasma concentration profiles of the polidocanol oligomers (limited to 60 minutes) after injection. No PK review was done.

(b) *In vitro* PK studies: There were 7 *in vitro* studies comprising 3 on metabolism, 1 on plasma protein binding and red blood cell partitioning, 1 on absorption of the gaseous constituents of Varithena™ injectable foam in whole blood, 1 on hemolytic effects of polidocanol and 1 examining the possibility of high concentrations of polidocanol remaining in the venous system after injection of Varithena™ injectable foam.

(c) A mass balance study in 4 male dogs that were administered 20.5mg ^{14}C-polidocanol intravenously showed a disposition half-life of about 1.5 - 2.0 h for total radioactivity representing polidocanol oligomers and generated metabolites in the dog during the 0 - 6 h post injection interval, and indicated that the polidocanol oligomers during the 0 - 6 h interval after injection undergo elimination not just distribution into tissues.

The key PK findings included the following:

- The 4 selected oligomers of polidocanol, E5, E9, E12 and E14 tend to exhibit a less than dose proportional pharmacokinetics in males and females. The respective apparent terminal $t_{1/2}$ of the oligomers range between 1 and 2.5 h. The respective dominant half-lives of the oligomers are shorter.
- Plasma protein binding of polidocanol is saturable.
- The predominant route of elimination of the selected oligomers is through metabolism.
- Body weight, but not gender, is a covariate for the pharmacokinetics of the oligomers.
- Polidocanol does not significantly prolong the QT_{cF} interval. (See Section 8.4.)

The Clin-Pharm reviewer concluded that the submitted clinical pharmacology package supports approval of NDA 205-098.

CDTL comment: I concur with the above evaluation by the Clin-Pharm reviewer and his determination that the submitted clinical pharmacology data support approval.

ONDQA – Biopharmaceutics reviewer (Banu S. Zolnik) evaluated the applicant's requests for biowaiver of any bioequivalence study that would be required to bridge the formulation changes (from the liquid formulation of the FDA-approved Asclera (NDA 21-201) drug product to the Varithena™ injectable foam formulation in this application).

The reviewer concludes that based on the fact that review of this NDA for Varithena™ injectable foam does not rely on the efficacy and safety data from the Asclera NDA, but on the pivotal Phase III clinical trials VAP.0015 and VAP.VV016 submitted in this application, the biowaiver requests are not relevant.

CDTL comment: I concur. The above determination by the reviewer is appropriate.

5.2 Drug-drug interactions

No drug interaction studies were conducted.

6. Clinical Microbiology

See Section 3.1 – Review of Microbiology.

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. The primary clinical reviewer and the primary statistical reviewer (Steven Bai) are in agreement.

The submission contains 12 clinical studies of Varithena™ injectable foam in patients with varicose veins which were conducted using two Varithena™ injectable foam formulations:

(i) The original formulation (Varisolve OF) used a gas mixture that contained (b) (4) and was administered in Studies COM001, 001, 003 and 0005, and to some patients in Study 011 (all of which are not pertinent for clinical review), and

(ii) A new formulation (Varithena™ injectable foam which used a low-nitrogen gas mixture and was intended for licensure) was used in some patients in Study 011 (for comparison), and in all subsequent clinical studies of Varithena™ injectable foam: namely, Studies 008, 012 and 014, and in Phase 3 Studies 013, 015, 016 and 017 (and 2 patients treated in the prematurely-discontinued Study 007).

The efficacy data is derived from two pivotal studies: Study 015 (which evaluated Varithena™ injectable foam 0.5%, 1.0% and 2.0%) and Study 016 (which evaluated Varithena™ injectable foam 0.5% and 1.0%) as randomized, blinded, multi-center studies at 20 and 12 US sites, respectively.

The primary endpoint for both studies is "the improvement of symptoms as measured by the absolute change from baseline in the average 7-day electronic daily diary Varicose Vein Symptoms Questionnaire (VVSymQ) score at Week 8 in patients treated with

Varithena™ injectable foam (pooled treatment groups) compared with Vehicle placebo."

Both Study 015 and Study 016 individually, as well as the integrated analyses, show that the primary efficacy endpoint of symptom improvement is statistically significantly (*P*<0.0001) greater in the pooled Varithena™ injectable foam treatment group, and in each of the individual Varithena™ injectable foam dose-concentration groups compared to the Vehicle placebo group.

Treatment with Varithena™ injectable foam also resulted in statistically significantly greater improvement in appearance (the co-secondary endpoints) as assessed by (i) the patient using the Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V^3) instrument (*P*<0.0001), and (ii) three blinded physicians using the Independent Photography Review – Visible Varicose Veins (IPR-V^3) instrument (*P*<0.0001) to rate photographs of the treated legs.

The results for the tertiary efficacy analyses – improvements in (i) duplex ultrasound response, (ii) clinician assessment of severity of venous disease using Venous Clinical Severity Score (VCSS), and (iii) patient-completed quality of life questionnaire (modified Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms [VEINES-QOL/Sym]) – were highly statistically significant (*P*<0.0001) in favor of Varithena™ injectable foam vs. Vehicle placebo (or, for duplex ultrasound response, vs. Varithena™ injectable foam 0.125% control).

The effect of pooled Varithena™ injectable foam concentrations on the primary, secondary and tertiary efficacy endpoints are summarized in **Table 2**.

Table 2 Summary of results from the primary, secondary and tertiary endpoints in pivotal studies

Study Endpoint		Study 015[a]			Study 016[a]		
Change from Baseline to Week 8[b] in:		Treatment Effect	[95% CI]	*P*-value	Treatment Effect	[95% CI]	*P*-value
Primary	VVSymQ (LOCF)	-3.31	[-4.31,-2.30]	<0.0001	-3.53	[-4.63,-2.42]	<0.0001
Co-Secondary	IPR-V3 (LOCF)	-0.80	[-0.98,-0.62]	<0.0001	-0.79	[-0.98,-0.60]	<0.0001
	PA-V3 (LOCF)	-1.44	[-1.75,-1.12]	<0.0001	-1.50	[-1.81,-1.19]	<0.0001
Tertiary	Duplex Response (LOCF)[c]	32.4%	not calculated	<0.0001	25.1%	not calculated	0.0002
	VCSS	-3.21	[-3.88,-2.54]	<0.0001	-3.58	[-4.35,-2.80]	<0.0001
	VEINES-QOL	13.50	[9.97,17.02]	<0.0001	14.18	[10.47,17.89]	<0.0001

CDTL comment: **The statistical reviewer, Stephen Bai**, did not find any statistical issues with the data and analysis quality. I concur with his assessment.

Using Patient Global Impression of Change (PGIC for VVSymQ and PA-V^3) and Clinical Global Impression of Change (CGIC for IPR-V^3) instruments as anchor-based methods, the primary endpoint (VVSymQ score) and co-secondary endpoints (PA-V^3 and IPR-V^3) in Studies 015 and 016 were found to show "clinically meaningful changes" in symptom burden and appearance based on the following:

- The percent of patients achieving at least moderate improvement favored Varithena™ injectable foam.
- Treatment with Varithena™ injectable foam 0.5%, 1.0% and 2.0% led to clinically meaningful (and statistically significant) improvements in both symptoms and appearance of varicose veins.

- Cumulative distribution curves plotting the percent of patients for VVSymQ, IPR-V^3 and PA-V^3 scores showed that the percent of patients with improvement was higher for the pooled Varithena™ injectable foam treatment groups vs. Vehicle placebo group throughout the distribution.

There were also positive correlations between the symptom improvement {VVSymQ score (and individual symptoms)} and the improvement in appearance {the IPR-V^3 and PA-V^3 scores} and the functional improvement {the Duplex ultrasound response}, which are statistically significant (**Table 3**).

Table 3 Correlation between Duplex Response and change from baseline in VVSymQ, IPR-V3, PA-V3 and Individual VVSymQ Symptoms at Week 8 in Study 015 and Study 016

	Change in VVSymQ	Change in IPR-V^3	Change in PA-V^3	Individual VVSymQ Symptoms				
				Heaviness	Achiness	Swelling	Throbbing	Itching
Study 015								
Kendall's Tau Correlation Coefficient, r (p-value)								
Duplex Response	-0.193 (<0.0001)	-0.299 (<0.0001)						
Change in Daily Diary VVSymQ		0.176 (0.0002)						
Change in IPR-V^3			0.343 (<0.0001)	0.204 (<0.0001)	0.138 (0.005)	0.188 (0.0002)	0.101 (0.043)	0.041 (0.421)
Spearman Rank Correlation Coefficient, r (p-value)								
Duplex Response	-0.235 (<0.0001)	-0.315 (<0.0001)						
Change in Daily Diary VVSymQ		0.227 (0.0002)						
Change in IPR-V^3			0.393 (<0.0001)	0.261 (<0.0001)	0.178 (0.005)	0.235 (0.0002)	0.129 (0.040)	0.051 (0.418)
Study 016								
Kendall's Tau Correlation Coefficient, r (p-value)								
Duplex Response	-0.228 (<0.0001)	-0.364 (<0.0001)						
Change in Daily Diary VVSymQ		0.163 (<0.002)						
Change in IPR-V^3			0.324 (<0.0001)	0.095 (<0.077)	0.126 (0.018)	0.125 (0.020)	0.115 (0.033)	0.102 (0.062)
Spearman Rank Correlation Coefficient, r (p-value)								
Duplex Response	-0.279 (<0.0001)	-0.381 (<0.0001)						
Change in Daily Diary VVSymQ		0.206 (<0.002)						
Change in IPR-V^3			0.383 (<0.0001)	0.121 (0.0755)	0.162 (0.017)	0.161 (0.017)	0.146 (0.031)	0.127 (0.062)

Table 4 Primary efficacy endpoint (VVSymQ scores) by CEAP classification (Integrated Efficacy Population)

CEAP Grade	Number PEM treated	Number Placebo treated	Estimate (95% CI)
2 (varicose veins)	122	41	-2.96 (-4.12, -1.79)
3 (edema)	81	43	-3.09 (-4.34, -1.83)
4 (skin changes)	68	20	-3.94 (-5.57, -2.30)
5 & 6 (skin changes with healed and active ulceration)	10	5	-8.48 (-12.34, -4.61)

For all CEAP classification subgroups (Table 4), the pooled Varithena™ injectable foam

treatment group showed consistently improved VVSymQ scores at Week 8, compared to Vehicle placebo with the higher CEAP classifications showing the largest improvements in symptoms. However, the sample size for Grade 5 & 6 groups was much smaller than the other groups to make valid comparisons.

For all GSV diameter categories, too, the pooled Varithena™ injectable foam treatment group showed consistently greater improvement in symptoms at Week 8, as measured by the VVSymQ, compared to Vehicle placebo with the larger GSV diameter groups of (10 to <12 mm) and (≥12 mm) showing the largest improvements in symptoms; however, the sample sizes for both of these groups were the smallest (Table 5).

Table 5 Primary efficacy endpoint (VVSymQ scores) by GSV Diameter (Integrated Efficacy Population)

Baseline GSV diameter	Number PEM treated	Number Placebo treated	Estimate (95% CI)
< 5mm	50	20	-2.28 (-3.98 , -0.59)
5 to <8 mm	106	49	-3.79 (-4.91, -2.66)
8 to <10 mm	54	17	-2.17 (-4.03, -0.32)
10 to <12 mm	27	6	-7.45 (-10.36, -4.54)
≥12 mm	37	15	-4.80 (-6.77, -2.83)

CDTL comment: The primary clinical reviewer and the primary statistical reviewer agree that the efficacy findings support approval.

7.2 Discussion of notable efficacy issues both resolved and outstanding

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

Regarding dose recommendation, there was a statistically significant linear trend across Varithena™ injectable foam concentrations from 0.125% to 2.0% for the improvement in appearance endpoints (IPR-V^3 and PA-V^3).

However, the Varithena™ injectable foam 0.5%, 1.0% and 2.0% dose concentration were not substantially different from one another with regard to improvement in VVSymQ score. For the secondary endpoints of improvement in appearance, too, there were no significant differences in the reduction (i.e., mean change at Week 8 from the baseline values) in the IPR-V^3 or PA-V^3 scores between the Varithena™ injectable foam 0.5%, 1.0%, and 2.0% dose groups.

On the other hand, the percent of Duplex responders increased as the Varithena™ injectable foam dose increased from 0.125% (control; (51% Duplex responders) to 0.5% (72% Duplex responders) and 1.0% (84% Duplex responders), at which the dose-response trend reached a plateau and the Duplex responder rate for Varithena™ injectable foam 2.0% (83%) was nearly identical to that for 1.0%.

Also, there was an apparent inverse dose response relationship in patients who required subsequent open-label treatment: 74% of patients treated with blinded Varithena™ injectable foam 0.125% (control) required subsequent open-label treatment compared with 63%, 56% and 51% for patients treated with blinded Varithena™ injectable foam 0.5%, 1.0%, or 2.0%, respectively.

The sponsor argued that the Varithena™ injectable foam 1.0% dose showed:

(i) the least number of treatment failures (SFJ Reflux >0.5 seconds),
(ii) the least number of partial treatment failures (GSV incompetence), and
(iii) the highest rate of Duplex ultrasound response compared to the other doses of Varithena™ injectable foam, and,
(iv) from a safety perspective, Varithena™ injectable foam 1.0% was associated with the lowest frequency of venous thrombosis adverse events.

Based on these review findings, I think it is reasonable to select the 1% dose of Varithena™ injectable foam.

CDTL comment: The primary clinical reviewer and the primary statistical reviewer agree that the efficacy findings support approval of the 1% dose of Varithena™ injectable foam.

8. Safety

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

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)

The Safety Population is defined as all patients who received at least 1 study treatment (i.e., Varithena™ injectable foam, saline or Vehicle placebo, or other study treatment) in any of the 12 clinical studies pooled (See section 5.3 of Clinical review). Two patients who participated in a clinical study of Varithena™ injectable foam that was prematurely discontinued, (Study 007 at a single study site in the United Kingdom with open-label Varithena™ injectable foam 1.0% as part of the study investigator training procedure), were excluded from the Safety Population.

Safety data in the current submission is based on 1,333 patients who received Varithena™ injectable foam, of which 907 were followed for ≥91 days, 527 for ≥6 months and 483 for ≥1 year.

Saline and Vehicle solutions were used as placebo (and referred to as “Placebo”) in the placebo-controlled studies of Varithena™ injectable foam.

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

No deaths or non-fatal serious adverse events (SAEs) attributed to the study treatment were reported. However, there were four deaths: 3 in patients treated with Varithena™ injectable foam and 1 patient treated with comparator sclerotherapy. All deaths occurred several months post-treatment: three were related to comorbid conditions (heart failure, cirrhosis liver and prostate cancer) and one death was from a motor-vehicle accident.

There were 36 patients who experienced 46 SAEs including the 4 deaths, of which 26 patients were treated with Varithena™ injectable foam and 10 were treated with a

comparator. The non-fatal SAEs included spinal osteoarthritis, venous thrombosis limb (3 patients), gastric obstruction, cellulitis (in untreated leg), diverticulitis, sick sinus syndrome, trachea-bronchitis, breast cancer and recurrence of lymphoma.

There were 13 early discontinuations due to an AE (of which 12 were treated with Varithena™ injectable foam), including the 4 deaths.

Of 797 patients treated with Varithena™ injectable foam 1%, 56 (7%) had one or more severe AEs including pain in the extremity (26 patients), headache (10 patients), muscle spasms (4 patients), venous thrombosis limb (3 patients) and inflammation, tenderness, paresthesia, pruritis and vein pain (2 patients each).

Varithena™ injectable foam is injected in small volumes at low total doses for a local sclerotic effect, usually only once, and, therefore, does not reach significant levels in the systemic circulation. The total dose of polidocanol in each volume of Varithena™ injectable foam administered to patients in the clinical trials exposed the patients to very small doses (<19.5 mg) of polidocanol {i.e., less than $1/5^{th}$ of the polidocanol contained in the maximal dose of liquid polidocanol formulation (Asclera®)}.

The AEs most commonly observed in the clinical studies of Varithena™ injectable foam are local AEs which include infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, and superficial thrombophlebitis

In the clinical studies of Varithena™ injectable foam, the only signal for a treatment-related change in laboratory parameters was a slight but consistent decrease from baseline in hemoglobin (by 0.1 to 0.3 g/dL), and hematocrit (by 0.2% to 1.0%) in Varithena™ injectable foam treated patients.

No unexpected safety signals were found.

8.3 Immunogenicity

Not applicable.

8.4 Special safety concerns

The submission-specific AEs included the potential for stroke, neurological events, deep vein thrombosis, anaphylactic reactions and local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses and pigmentation).

Potential for stroke: Among 1,333 patients exposed to Varithena™ injectable foam, which included 60 patients with confirmed patent foramen ovale (PFO) and micro-bubbles detected in the middle cerebral artery by Transcranial Doppler, only one patient complained of “twinky lights” lasting about 20 seconds about one hour after treatment, and one more patient (treated with Varithena™ injectable foam containing up to (b) (4) reported TIA-like symptoms in the hours following treatment, but did not report for further medical care and had no sequelae.

Extensive screening for neurological effects with diffusion-weighted MRI at 24 hours and T2 MRI imaging at 28 days post treatment in a study of 82 patients (60 had PFO) did not reveal abnormalities in the MRIs on post-treatment scans. 89% of patients with right-to-

left shunt and 29% of patients with no right-to-left shunt had bubble emboli detected by Transcranial Doppler (TCD). TCD detected ≤5 microbubbles in MCA in (34/60) 57% of patients and ≤50 microbubbles in MCA in (56/60) 93%; this is much less than >150 microbubbles detected using 1 ml room air in 10 ml agitated saline injected intravenously and monitored for 15 cardiac cycles after injection (with and without Valsalva maneuver).

Table 6 Neurological events reported with foam sclerotherapy in clinical trials and case reports

Year	Study (ref)	Total number Treated	Transient neuro-deficit TIA	Visual	Migraine	Stroke	Left-to-Right shunt
2008	Sponsor's IND study (with TCD and MRI evaluations)	83	-	1	-	-	60
2008	Sponsor's Phase 2 and Phase 3 studies (1333-83)	1,250	1	-	-	-	Not studied
2005	French Polidocanol Registry (Guex et al, *Dermatol Surg* 2005; 31: 123-8)	12,173 (6,739)*	-	-	-	-	Not studied
2012	Literature review study (Sarvanathan et al, *J Vasc Surg* 2012; 55:243-251)	10,819	9		29	12	11
2002	Air-based polidocanol foam study (Henriet et al, *Phlebologie* 2002; 52: 277-282)	10,000	1	8	7	-	Not studied
2011	Ultrasound-guided foam therapy (Beckett et al, *Euro J Endovasc Surg* 2011;42:11-19)	2,500	-	4	-	-	Not studied
2002	Air-based foam therapy (Frullini et al, *Dermatol Surg* 2002; 28: 11-15)	(Monfreux) 257 (Tessari) 196	3 -	3 1	- -	-	Not studied
2004	Reticular veins treatment (Kern et al, *Dermatol Surg* 2004; 30: 367-372)	150 (51)*	-	2	-	-	Not studied
2001	Air-based STS foam treatment (Tessari et al, *Dermatol Surg* 2001;27(1):58-60)	77	-	2	-	-	Not studied
2008	Large volume air-based foam therapy (Morrison et al, *J Vasc Surg* 2008;47(4):830-6)	100	-	2	-	-	Not studied
	Total neurological events in clinical trials	**37,605**	**14**	**23**	**36**	**12**	**71**

Year	Study (ref)	Total number	Transient neuro-deficit			Stroke	Left-to-Right shunt
	Case report studies						
2011	Three ischemic strokes with STS foam (Ma et al, *Phlebology* 2011 Oct; 26(7):280-284)	3	3				3
2010	One case of cerebral infarct (Picard et al *J Neurol Neurosurg Psych* 2010;81:582-3)	1				1	1
2010	One case of reversible ischemic stroke (Hahn et al, *Vasa* 2010; 39:108-110)	1	1				1
2001	Two cases of amaurosis fugax (Ramelet, AA. *Venous Digest* 2001; 8:2-3)	2		2			---
2003	Four cases of visual migraine (Ratinahirana et al, *Cephalalgia*, 2003; 23:850-851)	4			4		---
2006	One case of ischemic stroke (Forlee et al, *J Vasc Surg* 2006; 43(1):162-164)	1				1	1
2004	One case of stroke (Hanisch et al, *Eur J Med Res* 2004; 9:282-284)	1				1	1
2008	Two neurologic reactions - air-based foam (Bush et al, *Phlebology* 2008;23(4):189-192)	2	1			1	1
1994	One TIA with elevated Coagulation factors (Van der Plas et al, *Lancet* 1994; 343:428)	1	1				No PFO
2004	Seizure after air-based STS therapy (Kritzinger, PM. *Canadian Soc Phlebol* 2004, oral presentation)	1	1	1			--
2009	Reversible aphasia after foam sclerotherapy (Hartmann K et al, *Eur J Vasc Endovasc Surg* 2009; 38(5):648-9)	1	1				1
	Total neurological events in case report studies	**18**	**8**	**3**	**4**	**4**	**9**

*number of patients who were foam-treated

Table 6 shows that while there are individual case reports in the medical literature of neurological events following sclerotherapy, most patients recover from stroke with only 4 patients sustaining non-reversible neurological deficits. On the other hand, none of the large studies and randomized clinical trials (totaling > 37,000 treatments of varicose veins) in the medical literature reported any major neurological complications.

One explanation for transient neurological symptoms may be the release of endothelin induced by polidocanol foam bubbles acting on the endothelium or as they pass through a PFO. The endothelin quickly flows into the cerebral cortex and may initiate symptoms of migraine with aura, including visual, speech, and motor disturbances.

In the Varithena™ injectable foam clinical trials submitted in this NDA, there was no signal that Varithena™ injectable foam treatment was associated with an increase in neurological adverse events.

Table 7 Coding of thrombi in or distal to the common femoral vein

Medical Terminology Used in the ISS	Location	Colloquial	MedDRA Preferred Term	N (%) PEM-treated patients (n=1333)	Total %
Common femoral vein thrombus extension	Common femoral vein	eHIT 1-3[a] (non-occlusive)	*Venous thrombosis limb*	41 (3.1%)	3.1%
Proximal Deep vein thrombosis	Common femoral vein	eHIT 4 (occlusive)	*Deep vein thrombosis*	0	2.9%
	Femoral vein	Proximal DVT	*Deep vein thrombosis*	14 (1.1%)	
	Popliteal vein	Proximal DVT	*Deep vein thrombosis*	8 (0.6%)	
Distal Deep vein thrombosis	Posterior tibial vein	Distal DVT	*Deep vein thrombosis*	13 (1.0%)	
	Anterior tibial vein	Distal DVT	*Deep vein thrombosis*	1 (0.08%)	
	Peroneal vein	Distal DVT	*Deep vein thrombosis*	2 (0.15%)	
IGSVT	Gastrocnemius vein	Calf muscle vein	*Thrombosis*	17 (1.3%)	1.4%
	Soleal vein	Calf muscle vein	*Thrombosis*	1 (0.08%)	

[a] Of note, a Class 1 eHIT does not meet the criteria specified in the Sponsor's coding convention for the MedDRA Preferred Term Venous thrombosis limb, because it does not extend into the deep venous system. However, because there is no better MedDRA Preferred Term for this event, the single Class 1 eHIT that occurred in the studies of PEM was coded to this term.
DVT: deep vein thrombosis; eHIT: endovenous heat-induced thrombus; IGSVT: isolated gastrocnemius and soleal vein thrombosis
Source: ISS Coding Conventions and Venous Thrombus AE Classification Document, which is located in ISS Appendix K.

Venous thrombosis: In the Varithena™ injectable foam clinical Studies 015, 016, 017 and 008, duplex ultrasound surveillance of the leg veins was made at screening and on a minimum of 3 occasions following the initial study treatment and twice more after optional open-label treatments. The ultrasound images were reviewed by the Venous Thromboembolic Event Review Board (VTERB). 96 of 1,333 (7.2%) patients had venous thrombus detected by ultrasound following Varithena™ injectable foam treatment (**Table 7**); 2 patients had venous thrombus AEs 53 days to 9 months after treatment. Thus, 94 patients (7.1%) had treatment emergent venous thrombus AEs. Of the 1,170 patients treated with Varithena™ injectable foam 1.0%, 6.1% (71 patients) had venous thrombus AEs, a per-treatment session rate of 5.1%.

The most common type of venous thrombus was asymptomatic, non-occlusive, common femoral vein thrombus observed in 39 (2.9%) Varithena™ injectable foam -treated patients. The second type of venous thrombosis was the isolated gastrocnemius and soleal vein thrombosis (IGSVT) which were observed in 1.4% (19 patients) during detailed duplex ultrasound evaluations of the calf, and caused no symptoms.

Deep vein thromboses (DVT) were detected by ultrasound in 38 of 1,333 (2.8%)

Varithena™ injectable foam treated patients: distal DVT in 1.1% and proximal DVTs in 1.7%. One percent of 1,333 Varithena™ injectable foam-treated patients had proximal, symptomatic thrombi.

No patient had a diagnosis of pulmonary embolism.

The venous thrombi that occurred in the Varithena™ injectable foam studies were small (median thrombus volume = 0.7 cm^3, median length = 24.5 mm, largest thrombus volume = 5.41 cm^3, giving an average Marder scale of 5, compared to much larger thrombus volumes reported in the literature with an average Marder scale of 20).

The male sex was statistically significantly (P=0.021) associated with the occurrence of venous thrombus AEs following Varithena™ injectable foam treatment. There is an incremental association between increasing volume of Varithena™ injectable foam administered and incidence of venous thrombus AE; however, this was not statistically significant (P=0.095). There was no increased risk of venous thrombus AEs in patients who received multiple treatment sessions.

In **Table 8**, 51 of 97 patients with venous thrombus AEs were treated with anti-coagulants. About 70% of patients with proximal DVT (thrombus in femoral vein or popliteal) received anticoagulants; the median time to stabilization or resolution was 87 days. Most patients with DVT (79%) and most with IGSVT (84%) did not receive anticoagulants; half of the patients with common femoral vein thrombus extensions were managed with ultrasound observation and did not receive anticoagulants.

Table 8 Treatment for venous thrombosis events

	Observation / Stockings only	NSAIDS; ASA	Anticoagulation (<1 month)	Anticoagulation (long term)	Total
Proximal Symptomatic					
Venous thrombosis limb	0	0	0	3	3
DVT	0	0	3	7	10
Proximal Asymptomatic					
Venous thrombosis limb	11	5	13	8	37
DVT	2	1	4	4	11
Distal Symptomatic					
Thrombosis	2	1	1	0	4
DVT	1	3	2	1	7
Distal Asymptomatic					
Thrombosis	8	4	2	0	14
DVT	8	0	1	2	11
Total	32	14	26	25	97

The venous thrombi AEs resolved or stabilized rapidly (median of 29 days) irrespective of whether or not the patient was treated with anticoagulants in all but 3 patients. The time to resolution of venous thrombus AEs in the Varithena™ injectable foam studies are shown in Table 9. All vein thrombus events resolved or became stable with the exception of 1 patient with proximal DVT and 2 with IGSVT.

Table 9 Time to resolution of venous thrombus AEs

Venous Thrombus AE Location	N	Resolved or Stable		Resolved		Stable		Not Resolved or Stable
		N	Median Days (Range)	N	Median Days (Range)	N	Median Days (Range)	N
Common femoral vein thrombus extension	39	39[a]	21 (4, 103)	39[a]	21 (4, 103)	0	NA	0[a]
Proximal deep vein thrombosis[b]	22	21	87 (16, 380)	15	90 (16, 380)	6	69.5 (23, 197)	1[c]
Distal deep vein thrombosis[d]	14	14	49 (14, 99)	9	50 (19, 99)	5	49 (14, 93)	0
Isolated gastrocnemius & soleal vein thromboses	19	17	36 (8, 337)	14	33.5 (8, 337)	3	50 (22, 50)	2[e]

[a] Patient 012-1100 in Study 001 had a venous thrombus of the common femoral vein that resolved 77 days after diagnosis. This patient's resolution information is updated information provided in the narrative for this patient following the cut-off for the 3 Month CSR and is therefore not in the pooled ISS database.
[b] Includes venous thrombi of the femoral and popliteal veins.
[c] Patient 081-8028 in Study 001
[d] Includes thrombi of the posterior tibial, anterior tibial, and peroneal veins
[e] Patient 01-116 in Study 0005 and Patient 11-1114 in Study 013
AE: adverse event; OL: open-label; PEM: Polidocanol Endovenous Microfoam
Source: Sponsor's ISS Tables 38 and 47.2.3.1

Anaphylactic or hypersensitivity reactions: In the 1,333 patients treated with Varithena™ injectable foam, there were no anaphylactic or major hypersensitivity reactions. Five patients experienced severe possible hypersensitivity events (two experienced localized swelling, and one each reported chest discomfort, cough and pruritus); 2 more patients reported AEs of "allergy." Seventeen (3.9%) of 427 Varithena™ injectable foam treated patients and 9 (6.0%) of 151 placebo-treated patients experienced possible hypersensitivity reactions (pruritus, edema peripheral, and rash) within 1 day of study treatment. These possible hypersensitivity reactions appeared to increase with the Varithena™ injectable foam dose-concentration.

The AEs most commonly observed in the clinical studies of Varithena™ injectable foam are events that would be expected in patients undergoing a minimally-invasive medical procedure for the treatment of GSV incompetence. These include infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, and superficial thrombophlebitis. In contrast to endovenous thermal ablation (ETA), no patient required anesthesia or sedation prior to study treatment. Post-procedural pain resolved within 1 week in 80% of the cases reported, and a few Varithena™ injectable foam -treated patients were treated with opioid analgesics within 10 days of the study treatment procedure (1.3% of Varithena™ injectable foam -treated patients in the pooled, placebo-controlled studies).

In the pooled clinical studies of Varithena™ injectable foam, the only signal for a treatment-related change in laboratory parameters was a slight but consistent decrease from baseline in hemoglobin and hematocrit in Varithena™ injectable foam -treated patients; for hemoglobin, this decrease ranged from 0.1 to 0.3 g/dL, and for hematocrit it ranged from 0.2% to 1.0%. It is possible that they are related to the mobilization of peripheral fluid due to post-procedural use of compression stockings, or to the hemolysis of red blood cells caused by contact with the Varithena™ injectable foam.

With regard to vital signs, there were no clinically important changes in diastolic blood pressure (BP), oral temperature, pulse rate or respiratory rate. Some patients had

transient decreases in systolic BP of ≥20 mmHg; none were associated with symptoms or classified as an AE.

In lieu of a formal thorough QT study, confirmation of QT safety was ascertained by obtaining well-standardized ECGs in triplicate at peak plasma concentration during the PK study (VAP.VV008), which showed no dose-related effect of Varithena™ injectable foam on QT_{cF}. (See Clinical Review Section 9.4.5 and Table 43 in which the QT_{cF} interval showed an average change of -4.8 ~ -5.0 ms, with no subjects having (i) an abnormal U-wave or (ii) new morphological changes or (iii) new >500ms change in QT_{cF} or (iv) a >60 ms or 30-60 ms change from baseline.)

Also, the results of ECG, Holter monitoring, cardiac enzymes, transthoracic ultrasound, oxygen saturation and end-tidal CO_2 evaluations consistently demonstrate no adverse cardiac or cardiopulmonary effects following treatment with Varithena™ injectable foam.

My conclusion is that there were no unexpected safety signals in the clinical trial data in the submission.

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)

There are no outstanding notable safety issues.

9. Advisory Committee Meeting

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 symptom and cosmetic improvement of varicose veins, which is not of significant 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.

(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, an advisory committee meeting is not necessary.

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.

At the PeRC meeting on 30-Oct-2013, the PeRC agreed with the Division to grant a full waiver in all pediatric patients because studies would be impossible or highly impractical. The PeRC also recommended that the Division ask the sponsor if there are any other potential uses of this product in pediatric patients.

10.3 Consults

Consults were made to the following review divisions in CDER and CDRH:

CDER (Reviews discussed under Section 3 CMC, Section 11 Other Relevant Regulatory Issues, and Section 12 Labeling):

- OC/OSI (for GCP inspections),
- OC/OMPQ/DGMPA (for manufacturing facilities inspections),
- SEALD team (for validation methods, results and clinical significance of the changes in VVSymQ (primary efficacy endpoint)),
- OPS/ONDQA/NDMS (for potential microbiological ingress),
- OSE DMEPA {(i) Proprietary Name, (ii) Usability Study, label, labeling and packaging},
- OSE/DRISK

CDRH (Reviews discussed under Section 3 CMC/Device):

- ODE/DAGRID (for Human Factors and Device Use Safety),
- OSEL/DCMS (for chemical interactions of the drug, gas and excipient with the device),
- ODE/PIDB (for functional properties of the container closure system and consistency of PEM microbubbles generated),

11. Other Relevant Regulatory Issues

Financial disclosure: The sponsor submitted certification that 57 clinical investigators who participated in the following studies had no disclosable financial interest: VV003, VV008, VV012, VV013, VV014, VV015, VV016 and VV017.

The sponsor submitted that all study sites and investigators remained fully blinded throughout the study, and that no blinded or unblinded information was provided to these (or any other participating) investigators during the study.

Office of Compliance/Office of Scientific Investigation audits (by Sharon K Gershon): The Division requested OSI for GCP inspections of the conduct of the pivotal studies VAP.VV015 and VAP.VV016 at five sites which enrolled large numbers of patients, showed strong positive results, and had relatively large number of protocol violations in addition to having patients who discontinued early and patients whose data were excluded from efficacy analysis.

A clinical inspection summary from OSI dated 28-Jun-2013 informs that no regulatory violations were found during the inspections at Sites #37 and #75, and minor regulatory violations were found at Sites #33, and #39. For Site #74, the regulatory violation consisted of using screening VVSymQ scores instead of the baseline score to calculate the primary efficacy endpoint in six subjects. The inspectional (FDA Form 483) observations indicated no major issues with protocol compliance or reporting of AEs, and that they are unlikely to significantly impact the primary efficacy or safety analyses.

CDTL comment: I concur. The above determination by the OSI reviewer is appropriate.

Study Endpoints and Labeling Development (SEALD) review (by Jessica Voqui): The Division requested that SEALD review the validation methods and results, clinical significance of the changes in VVSymQ scores as related to the Patient Global Impression of Change (PGIC) with respect to symptoms. Some key concerns were in regard to the item reduction from the 9 core symptoms to 5 symptoms, lack of diverse demographics in the qualitative research, and whether it was more appropriate to assess symptoms using duration/frequency or severity. The 5-item VVSymQ score (duration) was compared to score configurations that used 7- and 9-item scores (intensity and duration sets of items were compared). The 5-item summary score demonstrated high correlation with the other score configurations in terms of Baseline score and changes, indicating that the shorter instrument may be acceptable. In regard to the demographics of the study population in the qualitative studies, these were comparable to the demographics of the patients who enrolled in the phase 3 clinical trials. Additionally, the psychometric properties of the instrument appear to be adequate in regard to reliability, construct validity, and ability to detect change. The results of the responder analyses appear to support that patients experienced a clinically meaningful change in symptoms as a result of using the treatment. The review concludes that the evidence submitted by the sponsor has addressed previous concerns about the instrument and is adequate to demonstrate that the VVSymQ measures symptoms of superficial venous disease in the stated context of use.

CDTL comment: I concur. The above determination by the SEALD reviewer is accurate.

The Division of Medication Error Prevention and Analysis (DMEPA) – Usability Study, Label, Labeling, and Packaging Review (by Kimberly DeFronzo): The Division of Medication Error Prevention and Analysis was requested to evaluate the results from the validation usability study and the proposed labels and labeling. The reviewer commented that the Applicant had not demonstrated usability of the intended commercial version of this combination product. On the other hand, DMEPA recognized that the proposed product has advantages over the currently available therapies and may offer benefits that outweigh the potential risk of device failures.

DMEPA's analysis of the usability data submitted by the Applicant found:

(i) 19 use errors, of which 5 occurred with initiating gas transfer, waiting for gas transfer, and removal of the oxygen canister, and 11 occurred during priming, flushing/filling the syringe, and inspection of microfoam;

(ii) 23 operational difficulties, including 10 reported with initiating gas transfer, waiting for gas transfer, and removal of the oxygen canister, 8 reported with attaching the VTU to the canister, and 2 with the sample canisters to twist and assemble, (the last for which the root cause analysis suggested that users with compromised hand strength or dexterity may encounter difficulty with using this product). The Applicant provided new commercial grade versions of the canisters which appeared to demonstrate improvement in ease of assembly, twisting, and removal of the oxygen canister; however, this version has not been validated; and,

(iii) 5 close calls, of which 4 were associated with flushing/filling the syringe.

DMEPA provided recommendations to be implemented *prior to* approval of the application, which will further minimize the risk for use errors and promote the safe use of the product, including the following:

- broaden the training program, both online and in person, to include all users,
- improve the proposed labels and labeling to provide clarity and increase the readability and prominence of important information on the label; and
- add clarity and bring prominence to specific information in the Instructions for Use (IFU).

If continued failure or difficulty with gas transfer, removal of the oxygen canister or VTU attachment is found during Postmarket surveillance, DMEPA may require the Applicant to investigate and make further design changes to the device, labels, labeling, or packaging.

CDTL comment: I concur with DMEPA reviewer's recommendations, which were forwarded to the applicant.

DRISK review (by Jason Bunting): The reviewer informed verbally during a meeting on 13-Nov-2013 that the review is completed and is pending management sign off after filing in DARRTS. The DRISK reviewer's recommendation is that a REMS is not required.

CDTL comment: I concur. The above determination by the reviewer is appropriate.

12. Labeling

12.1 Proprietary name

The Division of Medication Error Prevention and Analysis (DMEPA) review (by Kimberly De Fronzo on 13-Feb-2013 and, again, on 18-Jun-2013) found the proposed proprietary name of **Varithena™** acceptable from both a promotional and safety perspective.

CDTL comment: I concur. The above determination by the reviewer is accurate.

12.2 Address important issues raised by brief discussion of OPDP and DMEPA comments

See sections 11, 12.1 and 12.3.1 of this CDTL review.

12.3 Physician labeling

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

DMEPA (reviewer Kimberly DeFronzo) recommended changes to the Polidocanol Canister Label, Oxygen Canister Label, Bi-Canister Pouch Label, Bi-Canister Carton Label, Administration Box Label, Commercial Presentation Carton Label, Microfoam Transfer Unit (MTU) Lid Label and Instructions for Use (IFU).

CDTL comment: I concur with the DMEPA reviewer's recommendations, which were forwarded to the applicant.

As mentioned in Section 3.1 of this CDTL review, the CMC reviewer identified a list of deficiencies which were communicated to the applicant in information request letters sent to the sponsor on 05-Sep-2013 and 05-Nov-2013, to provide the revisions to the carton and container labels, including replacing (b) (4) with "injectable foam," expression of strength on total volume, net contents, route of administration and font changes.

CDTL comment: **The sponsor's response to IRs of 05-Sep and 05-Nov will need to be re-reviewed by CMC, C&C, and OMPT which may delay the Division's approval action past the PDUFA goal date.**

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

A Medication Guide is not required. See Section 13.3 of this CDTL review.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is **approval** (§21 CFR 314.110) pending the sponsor's response to the IRs and subsequent FDA review, the proposed postmarketing study commitments (PMCs) and the changes suggested in the proposed labeling.

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 benefits of treatment with Varithena™ injectable foam seen in Studies 015 and 016 are improvement in:

- The symptoms of chronic venous insufficiency, as measured by a validated, patient-completed Varicose Vein Symptoms Questionnaire (VVSymQ);
- The appearance of visible varicosities, as evaluated by a blinded, independent panel of clinicians (IPR-V^3) and by patients using a validated questionnaire (PA-V^3);
- Hemodynamic function of superficial venous, (elimination of SFJ reflux and/or occlusion of the incompetent vein) as assessed by duplex ultrasonography;
- Clinical severity of venous disease, as evaluated by the physician using the Venous Clinical Severity Score (VCSS), and
- Patient quality of life, as measured by the patient using the Modified Venous Insufficiency Epidemiologic and Economic Study – Quality of Life/Symptoms (VEINES-QOL/Sym) instrument.

Statistically significant correlations are found between the improvement in symptoms and (i) the appearance of visible varicosities, and (ii) duplex ultrasound response.

Treatment with Varithena™ injectable foam 0.5%, 1.0% and 2.0% led to clinically meaningful improvements in both symptoms and appearance as evaluated by anchor-based responder analyses.

Treatment benefits of Varithena™ injectable foam were similar across sub-groups for all efficacy endpoints.

The risks of Varithena™ injectable foam treatment are predominantly local adverse events (AEs) such as infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, superficial thrombophlebitis and venous thrombus. Extravasation of Varithena™ injectable foam in 25 patients was not associated with necrosis or adverse sequelae, probably because of the small amount of polidocanol in each mL of Varithena™ injectable foam (1.3 mg).

Venous thrombosis is a clinically important AE related to Varithena™ injectable foam treatment. It was observed in 7.2% of Varithena™ injectable foam treated patients and 5.2% of Varithena™ injectable foam treatment sessions. In the 1,333 Varithena™ injectable foam treated patients evaluated with ultrasound studies:

- Common femoral vein thrombus extensions occurred in 2.9%;
- Proximal Deep vein thrombosis AEs occurred in 1.7%;
- Distal Deep vein thrombosis AEs occurred in 1.1%; and
- Isolated gastrocnemius and soleal vein thrombi occurred in 1.4%.

No pulmonary emboli were diagnosed.

Small, consistent and dose-dependent decreases in hemoglobin and hematocrit were observed in treated patients; these did not require intervention in any patient.

In 1,333 patients treated with Varithena™ injectable foam, there were no deaths or life-threatening SAEs, and no significant hypersensitivity events attributed to the study treatment or procedure. The risk of serious hypersensitivity reactions to Varithena™ injectable foam was low.

Despite the potential for neurological or visual events, transient ischemic attacks and strokes, which have been reported in patients treated with physician-compounded sclerosant foams, treatment with Varithena™ injectable foam was not associated with neurological or visual AEs in the placebo-controlled studies.

In summary, Varithena™ injectable foam at the dose-concentration (1.0%) and maximum volume (15 mL) per treatment session proposed for the treatment of patients with incompetence of the great saphenous vein, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee appears to provide a reasonable balance of benefit and risk for the treated patients.

13.3 Recommendation for Postmarketing Risk Management Activities (includes restricted distribution, RiskKAPs, REMS)

The sponsor voluntarily submitted a risk management plan to mitigate the risks of proximal DVT and common femoral vein thrombus extension, pulmonary embolism, hypersensitivity and anaphylactic reactions, neurological events and accidental intra-arterial injection.

In this NDA, there is no finding of an increased risk of neurological or visual events, and no AEs of pulmonary emboli, or anaphylactic reactions. DVTs and venous thrombus AEs were detected by ultrasound evaluations only, and were mostly asymptomatic and resolved or stabilized rapidly. Intravenous injection of Varithena™ injectable foam under ultrasound guidance prevented intra-arterial injection. Thus, there is NO reason to recommend a REMS for this NDA.

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 Varithena™ injectable foam treatment for varicose veins, a Medication Guide will not serve this purpose because this drug is not taken by the patient. Varithena™ injectable foam is injected to a maximal volume of 15 mL per treatment session, performed under visual ultrasound guidance by a qualified and trained physician. At the low total doses (19.5 mg maximum) used, polidocanol does not reach significant levels in the systemic circulation.

A Physician Communication Plan does not help the patient or the physician because the application-specific safety issues of neurological events, deep venous thromboses or anaphylactic reactions are exceedingly rare with this drug product.

In >55 million sclerotherapy exposures to polidocanol injections (including various foam forms of polidocanol) spanning half a century of treatment in different clinical settings in many countries reported in the medical literature, there is no evidence that neurologic events, venous thromboembolic events and anaphylactic reactions are more frequent than one would expect with any other parenteral drug for cosmetic purposes (e.g., botulinum toxin (Botox) to treat glabellar lines) which do not require a REMS.

Based on the clinical data in the application and comprehensive safety data reported in the medical literature, my recommendation is that a REMS is not necessary for approval.

13.4 Recommendation for other Postmarketing Study Commitments

None.

13.5 Recommended Comments to Applicant

The sponsor will submit to FDA a complete training manual and video that will be used to provide education and training to health care providers (physicians and clinical staff).

The sponsor voluntarily offered that only physicians who have completed this training will be able to order Varithena™ injectable foam from the designated distributor to administer or supervise administration of the Varithena™ injectable foam.

My recommendations to the sponsor are that they

(i) conduct an assessment of spontaneous reports of death, stroke, neurological or visual event, pulmonary embolism, deep vein thrombosis, and anaphylactic reaction in patients treated with Varithena™ injectable foam, and submit periodic safety update reports / periodic adverse drug event reports (PSURs/PADER).

(ii) respond to the carton and container label issues and comments raised by FDA reviewers, and

(iii) make changes to the labeling as recommended by FDA.

REFERENCES

[1] Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, Golomb BA. Chronic venous disease in an ethnically diverse population: The San Diego Population Study. *Am J Epidemiol* 2003; 158(5):448-456.

[2] Millennium Research Group, 2009. US markets for varicose vein treatment devices. Millennium Research Group, Toronto, ON.

[3] SarvanathanT, Shepherd AC, Willenberg T, Davies AH. Neurological complications of sclerotherapy for varicose veins. *J Vasc Surg* 2012; 55:243-251.

[4] Bush RG, Derrick M, Manjoney D. Major neurological events following foam sclerotherapy. *Phlebology* 2008; 23(4): 189-192.

[5] Forlee MV, Grouden M, Moore DJ, Shanik G. Stroke after varicose vein foam injection sclerotherapy. *J Vasc Surg* 2006; 43(1): 162-164.

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
11/14/2013
Recommendation: approval

THOMAS A MARCINIAK
11/14/2013