

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205098Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	November 21, 2013
Reviewer(s):	Jason Bunting, PharmD Division of Risk Management
Team Leader:	Kimberly Lehrfeld, PharmD Division of Risk Management
Division Director:	Claudia Manzo, PharmD Division of Risk Management
Subject:	Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	Varithena™ (polidocanol endovenous microfoam)
Therapeutic Class:	venous sclerosant
Dosage and Route:	1.0% solution (weight per volume) intravenous injection
Application Type/Number:	NDA 205-098
Applicant/sponsor:	Provensis Ltd.
OSE RCM #:	2013-1381

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the proposed risk management plan for New Drug Application (NDA) 205-098, for Varithena™ (polidocanol endovenous microfoam) injectable microfoam, and assesses the need for a Risk Evaluation and Mitigation Strategy (REMS). The proposed risk management plan submitted by Provensis Ltd, received on February 1, 2013, consists of both routine and additional risk minimization activities including pharmacovigilance, addressing the risks of concern in labeling, Sponsor mandated physician training and education, and restricted distribution of Varithena only to those physicians who are trained and credentialed.

1.1 BACKGROUND

Varithena, polidocanol endovenous microfoam (PEM), is an engineered microfoam formulated from an aqueous polidocanol solution and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The proposed indication is for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee. Varithena is a venous sclerosant that destroys the venous endothelium through disruption of the osmotic barrier, causing venospasm and ultimately occlusion of the treated vein which becomes a fibrotic cord (sclerus). Upon administration, it remains coherent and displaces blood in the treated vein.

Superficial venous insufficiency develops because of the failure of one or more valves separating the deep venous system from the superficial venous system including the great saphenous vein (GSV), small saphenous vein (SSV), and their tributaries. The occurrence is common, affecting up to 25% of the United States (US) adult population, and causes progressive dilation and elongation of the superficial veins, leading to swelling, discomfort, and the well-known bulging appearance of varicose veins. The appearance of visible varicosities varies greatly and does not necessarily correspond to the severity of clinical symptoms which can include veins that may be tender to touch, edema causing lower leg swelling and tightness, a sensation of heaviness, throbbing, aching, and itching.

Currently, the management of chronic superficial venous disease includes compression stockings, superficial vein surgery, and endovenous thermal ablation (ETA) techniques including endovenous radiofrequency ablation (ERFA) and endovenous laser ablation (EVLA). Ablation of veins by injection of sclerosant solutions is also performed, most commonly, using Sotradecol® (sodium tetradecyl sulphate) or Asclera® (polidocanol); however, they are indicated for the treatment of small, uncomplicated varicose veins.

The use of "hand-made" foamed sclerosants has become increasingly popular because, unlike liquid sclerosants, foam can displace the intravascular blood and does not become diluted; thus, the concentration of the agent in the vessel is known and controlled. Foamed sclerosants also homogeneously distribute within the vessel lumen and provide a generous surface area of the agent in contact with the endothelium. Phlebologists began converting polidocanol solution into a "home-made" foam formulation and using it as an endovenous sclerosant as early as the late 1960's. However, it did not become popular

until the mid-1990's when the methods for transforming liquid sclerosing solutions into foam were well described. Foamed sclerosants are created from the solution by mechanical agitation of the liquid in the presence of a gas. Commonly, this is achieved by using room air as the gas and rapid displacement of the mixture between two syringes joined by a stopcock. This creates a foam containing 79% nitrogen and 21% oxygen and having a wide bubble size distribution (Eckmann, 2009). If approved, Varithena would be the first FDA approved foam sclerosant marketed in the U.S.

Following administration of these "hand-made" sclerosant foams made with room air, there have been case reports of patients with significant neurological events including stroke, seizure, and transient ischemic attack. It is believed that these adverse events are due to the high nitrogen content of room air and the creation of large bubbles in the foam.

Varithena is supplied in a canister device which generates injectable microfoam, delivering polidocanol at solution concentration of 1.0% weight per volume. The canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, Varithena is generated via the container system that produces microfoam of controlled density and bubble size. Both a low nitrogen content and small, uniform bubble size reduce the risk of neurological adverse events.

The volume of Varithena injected depends on the size and extent of the varicose veins. The maximum recommended volume per individual injection is 5 mL and the maximum per treatment session is 15 mL. If more than 15 mL of Varithena is required, further treatment sessions would be necessary and should be separated by a minimum of 5 days.

A risk management plan was submitted with the application and consisted of proposed labeling, educational materials for physicians, a sponsor mandated physician training program, and distribution that is restricted to trained physicians. A formal REMS proposal was not submitted.

1.2 REGULATORY HISTORY

- July 31, 2012 - A Type B Pre-NDA meeting was held with the Sponsor to discuss the proposed NDA for Varithena for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee, and improvement of symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system. The sponsor stated that they did not believe a REMS was necessary for Varithena. The Agency responded by stating that the need for a REMS would be determined during review of the application.
- February 1, 2013 - Provensis Ltd. submitted NDA 205-098, for Varithena. The application was filed on April 5, 2013 and granted a standard review with a user fee goal date of December 4, 2013. A risk management plan was submitted with the NDA; however, a formal REMS was not submitted.
- April 11, 2013 - A Filing Communication (74-day) letter was sent to the Sponsor and included the following comments from DRISK:

The Division of Risk Management is reviewing your proposed risk management plan. Your proposal suggests there are risks associated with

polidocanol that may require mitigation strategies beyond labeling and routine pharmacovigilance (e.g., elements to assure safe use). If you feel additional risk mitigation is necessary to assure safe use of polidocanol, please refer to the following Guidance for Industry for the correct format and content for your proposal and resubmit accordingly.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.

Furthermore, we note that your proposed risk management plan includes a list of training forms and materials. In order to facilitate an efficient review of a proposed risk mitigation plan, all materials identified within the proposal that will be necessary to implement the plan should be submitted.

- June 25, 2013 - The Sponsor responded to DRISK's comments in the 74-day letter and stated the following:

Provensis Ltd does not believe that there are risks uniquely identified to our product, Polidocanol Injectable Microfoam, that requires mitigation strategies beyond labeling and routine pharmacovigilance.

- November 13, 2013 – DRISK met with DCRP to discuss labeling recommendations.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Provensis Ltd. Integrated Summary of Efficacy for Verithena (polidocanol endovenous microfoam), received February 4, 2013
- Provensis Ltd. Integrated Summary of Safety for Verithena (polidocanol endovenous microfoam), received February 4, 2013
- Provensis Ltd. Risk Management Plan for Verithena (polidocanol endovenous microfoam), received February 4, 2013
- Provensis Ltd. Draft Prescribing Information for Verithena (polidocanol endovenous microfoam), received February 4, 2013
- Povensis Ltd. Varithena Delivery System Instructions for Use, received September 24, 2013

3 REVIEW FINDINGS FOR VARITHENA

3.1 OVERVIEW OF CLINICAL PROGRAM

There were two pivotal Phase 3 studies of Varithena completed:

- Study VAP.VV015 (Study 015) - A randomized, blinded study to evaluate PEM 0.5%, 1.0%, and 2.0% for the treatment of both symptoms and appearance in patients with saphenofemoral junction (SFJ) incompetence due to reflux of the GSV or major accessory veins compared with Vehicle placebo

- Study VAP.VV016 (Study 016) - A randomized, blinded study to evaluate PEM 0.5% and 1.0% for the treatment of both symptoms and appearance in patients with SFJ incompetence due to reflux of the GSV or major accessory veins compared with Vehicle placebo

The primary efficacy endpoint in Studies 015 and 016 is the improvement of symptoms as measured by the absolute change from baseline in the average 7-day electronic diary (e-diary) Varicose Vein Symptoms Questionnaire (VVSymQ) score at Week 8 in patients treated with PEM, compared with Vehicle placebo. The VVSymQ score is a patient-reported outcome measure based on daily patient assessment of 5 varicose vein symptoms: heaviness, achiness, swelling, throbbing, and itching. Patients rated their experience of each symptom using a 6-point (i.e., 0 to 5 points) duration scale, and the ratings were summed to generate a 0 to 25-point scale, where 0 = "no symptoms" and 25 = "all 5 symptoms experienced all of the time."

The co-secondary endpoints in Studies 015 and 016 are the improvement of appearance as measured by both the absolute change from baseline in the central Independent Photography Review – Visible Varicose Veins (IPR-V³) score at Week 8 and the Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V³) score at Week 8 in patients treated with PEM, compared with Vehicle placebo. The IPR-V³ is a clinician-reported outcome measure. The IPR-V³ score was the median of the appearance ratings assigned by 3 trained, fully blinded physician assessors, the Independent Photography Review (IPR) Panel. Each IPR Panel member individually rated standardized photographs of the medial view of each patient's study leg before and after treatment using the IPR-V³ instrument. Scores ranged from 0 (no visible varicose veins) to 5 (very severe visible varicose veins). The PA-V³ is a patient reported outcome measure. The PA-V³ score is based on the patient's rating of the appearance of their varicose veins in the medial segment of their leg on a scale that ranged from 0 (no visible varicose veins) to 5 (extremely noticeable visible varicose veins).

Key efficacy findings:

Primary endpoint (VVSymQ score)

For study 015, the PEM 0.5%, 1.0%, and 2.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P < 0.0001$) with an adjusted mean change from baseline in VVSymQ score of -5.44 points versus -2.13 points, respectively. For Study 016, the PEM 0.5% and 1.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P < 0.0001$) with an adjusted mean change from baseline in VVSymQ score of -5.53 points versus -2.0 points, respectively. For both Study 015 and 016, each of the individual PEM dose concentrations were also statistically significantly superior to Vehicle placebo ($P \leq 0.0001$) in reduction of VVSymQ score.

Co-secondary endpoints (IPR-V³ score and PA-V³ score)

For study 015, the PEM 0.5%, 1.0%, and 2.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P < 0.0001$) with an adjusted mean change from baseline in IPR-V³ score of -0.81 points versus -0.01 points, respectively.

For study 016, the PEM 0.5% and 1.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P<0.0001$) with an adjusted mean change from baseline in IPR-V³ score of -0.86 points versus -0.07 points, respectively.

For study 015, the PEM 0.5%, 1.0%, and 2.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P<0.0001$) with an adjusted mean change from baseline in PA-V³ score of -1.58 points versus -0.15 points, respectively. For study 016, the PEM 0.5% and 1.0% dose concentrations (pooled) were statistically significantly superior to Vehicle placebo ($P<0.0001$) with an adjusted mean change from baseline in PA-V³ score of -1.82 points versus -0.32 points, respectively.

Key safety findings:

Treatment-emergent adverse events (TEAE) that occurred more frequently in the PEM treatment groups (pooled), compared with the placebo group, with a difference of $\geq 5\%$ were infusion site thrombosis (10.5% vs. 0%), thrombophlebitis superficial (9.2% vs. 1.3%), pain in extremity (14.9% vs. 9.3%), and venous thrombosis limb (5.5% vs. 0%).

A total of 13 patients (3.0%) in the PEM treatment groups (pooled) had a severe adverse event (SAE), compared with only one patient (0.7%) in the placebo group. Most SAEs occurred in only one patient with the exception of venous thrombosis limb (4 PEM-treated patients) and deep vein thrombosis (2 PEM-treated patients).

There were three deaths in PEM-treated patients during or following participation in the clinical studies of PEM. All three deaths occurred several months following study treatment; two deaths were related to concomitant conditions (hepatic cirrhosis and heart failure) that pre-dated the patient's participation in the study and one death was accidental (motor vehicle accident).

3.2 SAFETY CONCERNS

3.2.1 Venous Thrombus Adverse Events

Localized thrombosis of the vein treated with Varithena, other sclerosants, or other treatment modalities such as ETA is an expected result of those treatments. However, with the creation of a thrombus in the target superficial vein, there is a risk of causing thrombosis in a non-target deep vein (i.e., deep vein thrombosis (DVT)) by either active sclerosant reaching a non-target vein or by the thrombus of a treated vein bulging into the lumen of a non-target vein. DVTs have the potential to result in PE.

Of the 1333 Varithena treated patients, 94 patients (7.1%) experienced a venous thrombus AE with 36 patients (2.7%) classified as having a DVT. During the main treatment period, those patients that received the 2.0% dose concentration of Varithena had a higher incidence of venous thrombus AE (10.7%) than those receiving the lower concentrations (5.7%). Of note, 5.9% of patients receiving Varithena 1.0% (the dose sought for approval in this application) had a venous thrombus AE.

There was a statistically significant ($P=0.021$) association between the male sex and the occurrence of venous thrombus AEs.

Most venous thrombus AEs detected were asymptomatic (72 of 94 patients, 77%) and resolved or stabilized on average within one month, with or without anticoagulation treatment. There were 3 patients that had neither stabilized nor resolved at the time of the last study contact.

No patient was diagnosed with a pulmonary embolism (PE).

There was no clearly identifiable threshold volume of Varithena above which venous thrombus AEs were markedly increased. In addition, the DCRP medical officer review states in his clinical review (Khin U, July 11, 2013) that there is data supporting the safety of this product when up to a 60 mL dose was used in patients during the clinical trials. However, in one Varithena study, DVTs were eliminated when practitioners used smaller volumes of microfoam (<5 mL per injection and <15 mL per treatment session) and stopped the microfoam injection once the foam reached 5 cm distal to the termination of the trunk vein (Wright, 2006). Given this study and the successful efficacy outcomes and safety demonstrated in the pivotal studies using 15 mL, the Sponsor recommends a maximum microfoam volume per treatment session of 15 mL, divided into aliquots of up to 5 mL. If the patient requires more than 15 mL to treat their varicosities a second treatment session, separated by at least 5 days, could be performed.

Administration technique may also be associated with an increase in DVT in Varithena treated patients. Based on the lack of DVTs observed in the previously mentioned study, the Sponsor recommends stopping the injection of microfoam once the foam reaches 3-5 cm distal to the saphenofemoral junction (SFJ).

Reviewer comment: DVT can occur with almost any treatment for varicose veins though rates of occurrence are debatable. One retrospective study showed that surgery, the most popular treatment for varicose veins, carries a risk of DVT of about 1 in 200 patients (0.5%) (Critchley, 1997). Another prospective study detected DVTs postoperatively in 5.3% of patients (Rij, 2004). This compares to 36 (2.7%) of the 1333 patients treated with Varithena in clinical trials that experienced DVT.

3.2.2 Ischemic Cerebrovascular Conditions

In Studies 015 and 016, nervous system disorders occurred at similar rates in the Varithena 1.0% treated patients (7.4%) and the placebo treated patients (8.6%). There was a higher incidence of headache in the Varithena 1.0% treated patients (5.4%) than in the placebo treated patients (2.6%). This may be significant because it is believed that the same mechanism (i.e., bubbles passing into the arterial circulation and to the brain) by which more severe neurological events may occur is also responsible for the occurrence of headache.

There were no stroke, seizure, or TIA reported in the pivotal trials.

In contrast, serious neurological events including stroke, seizure, and transient ischemic attack (TIA) have been reported with the use of foamed sclerosants made by agitating a sclerosant liquid in the presence of room air. It is believed that these adverse events are due to the presence of insoluble gas (nitrogen) in the room air and the creation of large bubbles in the foam. While all patients treated with sclerosant foam will have bubbles circulating in the venous system, they are normally filtered out by the lung. However, in

the presence of right to left cardiac shunt (i.e., patent foramen ovale (PFO)), bubbles can pass into the arterial circulation and then to the brain.

To address this issue, Varithena has been formulated to have a low nitrogen content and small, uniform bubble size. To confirm the Varithena formulation was less likely than hand-made foam to obstruct vessels, a study in rats was performed to determine the relationship between microfoam formulation and arteriolar embolization bubble lodging and clearance. It was found that the hand-made foam had larger bubbles that were more likely to obstruct vessels than Varithena foam (Eckmann, 2006). Additionally, a Phase 2 safety study, Study VAP.VV012 (Study 012), was performed to determine whether treatment of varicose veins with Varithena in patients with right to left cardiac shunt experienced any neurological adverse events. Transcranial Doppler ultrasound was used during administration of Varithena to detect bubbles which have passed into the arterial circulation and to the brain. A total of 82 patients were treated where 60 patients had one or more bubbles detected in the middle cerebral artery (MCA). One subject complained of an episode of "twinkly lights" in their peripheral vision approximately one hour after treatment, which lasted for 20 seconds. Subsequent ophthalmologic examination of this patient was normal. No new abnormalities were observed in any patient with respect to cardiac markers or ECG parameters following treatment, nor were there any new abnormalities on brain magnetic resonance imaging (MRI), neurological examination, fundoscopy, or visual fields.

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE SPONSOR

A risk management plan proposed by the Sponsor consists of:

- appropriate labeling to address the issue of concern,
- a sponsor-mandated physician training program,
- sponsor verification of physician credentials and completed training, and
- restricted distribution of Varithena to trained and credentialed physicians.

3.3.1 Appropriate labeling to address the issue of concern

Table 1 below describes the Sponsor's proposed labeling for the identified and potential risks of concern.

Table 1



(b) (4)

3.3.2 Sponsor-mandated physician training program

The mandated training program includes on-line modules with knowledge assessments and a video demonstrating Varithena administration with a knowledge assessment. Items covered in the on-line modules and videos of the training program are:

- vein disease knowledge and management,
- venous ultrasound interpretation,
- venous ultrasound examination,
- ultrasound-guided venous access,
- endovenous treatment and sclerotherapy,
- device description and instructions for use of the device,
- patient set-up, in-office patient management and facility resource requirements,
- administration demonstrated by an expert, and
- post-procedure management.

To address the risk of DVT, described in Section 3.2.1 above, the physician training video demonstrates the procedure using a duplex ultrasound and reiterates that the maximum recommended microfoam volume per treatment session is 15 mL, divided into aliquots of up to 5 mL. The training video also helps physicians to visualize the recommended rate of injection (1 mL/second in the GSV and 0.5 mL/second in accessory veins or varicosities) and when to stop the injection (3-5 cm distal to the SFJ when treating the GSV). Post-procedure patient care targeted to prevent DVT is also demonstrated in the video.

To mitigate the risk of ischemic cerebrovascular events, described in Section 3.2.2 above, the physician training video shows the appropriate creation of microfoam using the canister device and reinforces the importance of visual inspection for bubbles and the time limit to injection once the microfoam is created (75 seconds).

The Sponsor has also proposed instructions for use (IFU) of the device and completed a validation usability study (Study SP2277) of the IFU. Under separate cover, the Division of Medical Error Prevention and Analysis (DMEPA) has reviewed the validation

usability study of the proposed labels and labeling including the IFU for Varithena and concluded:

"...the Applicant has not demonstrated usability of the intended commercial version of this combination product. However, we recognize the proposed product has advantages over the current available therapies and may offer benefits that outweigh the risk of device failures."

The Center for Devices and Radiological Health (CDRH), Human Factors Team, also provided a review of the human factors study (Study SP2277) and IFU, under separate cover. Unlike DMEPA, CDRH, Human Factors Team stated:

"...this consultant does not have any outstanding concerns regarding the study results and their implication on device design and IFU."

3.3.3 Sponsor verification of physician credentials

The appropriate medical credentials proposed by the Sponsor are:

- a degree from an accredited college of medicine,
- a full unrestricted license to practice medicine in the United States; and
- minimum experience managing vein disease of at least 100 cases treated within the last two years.

3.3.4 Restricted distribution of Varithena to trained and credentialed physicians

Physicians who are appropriately credentialed and have successfully completed the training and knowledge assessments will be entered into a commercial distribution database allowing them access to Varithena. Distributors will be required to verify the ordering physician in the database prior to shipping Varithena. The Sponsor will also make medical liaisons available to schedule in-office support visits following completion of the training program to re-enforce training and confirm understanding of the IFU, facility and procedure set-up, Varithena administration, and post-procedure patient management.

4 DISCUSSION

The benefits of treatment with Varithena as seen in the pivotal studies include the following:

- Statistically significant improvement in the symptoms of chronic venous insufficiency, as measured by the patient-completed Varicose Vein Symptoms Questionnaire (VVSymQ).
- Statistically significant improvement in the appearance of visible varicosities, as evaluated by both patients using a questionnaire (PA-V³) and an independent panel of clinicians using photographs (IPR-V³).

There are other benefits of Varithena to be considered such as:

- Reasonable costs of therapy compared with surgical alternatives (costs reduced by almost 50%) (Murad, 2011)

- Less invasive and shorter recovery times than surgical alternatives (2 vs 8 days to return to normal activities) (Murad, 2011)
- Availability of an approved polidocanol foam which is safer than the current hand-made foams. In addition, it will provide clinically proven dosing and administration recommendations which are not available for currently utilized hand-made foams.

The serious risks of concern with Varithena are DVTs, which have the potential to lead to pulmonary embolism (PE), and ischemic cerebrovascular conditions such as stroke or transient ischemic attack. To mitigate these risks the Sponsor has proposed labeling and additional risk minimization activities including a Sponsor mandated physician training program and restricted distribution.

DVT with the potential to result in PE

Regarding the concern of DVT which may lead to PE, DVT occurs no more frequently with the use of Varithena than with the use of other treatment modalities for varicose veins (i.e. surgery, laser ablation); thus, the targeted prescribers are knowledgeable of the occurrence, prevention, and management of this risk in this patient population.

Demonstrated actions that can mitigate the risk of DVT, specific to this product, are to stop injection of the microfoam 3 to 5 cm distal to the SFJ and use only the recommended amount of microfoam (<5 mL per injection and <15 mL per treatment session). The Sponsor has proposed extensive labeling to instruct providers on product specific risk mitigation strategies in the *Dosage and Administration* section and further addresses general DVT risk mitigation strategies in *Contraindications, Warnings and Precautions, Adverse Reactions*, and *Patient Counseling Information* (see Section 3.3.1, Table 1).

For the above reasons, the IFU and professional labeling proposed by the Sponsor are sufficient to mitigate the risk of DVT among the prescribers who are expected to utilize this product after approval. A REMS is not necessary to ensure the benefit of this product exceeds the risk of DVT that has the potential to result in PE.

Ischemic Cerebrovascular Events

The Sponsor has not included CNS AE's in the *Warnings and Precautions* section of the label. In the *Adverse Reactions* section, the Sponsor describes the clinical trial experience where none of the 1333 patients treated with Varithena experienced clinically important neurological or visual adverse events. Though the clinical studies showed no greater risk with Varithena than placebo, patients with right to left cardiac shunt are at a high risk to have bubbles reach their arterial circulation and there have been multiple literature reports of CNS side effects from polidocanol foam injections. After discussion with DCRP, information regarding the potential for neurological effects associated with the use of foam sclerotherapy products will be added to Section 6.1 (Clinical Trials) of the prescribing information.

Regarding the concern of ischemic cerebrovascular conditions, the formation of a consistent size bubble with low nitrogen content in the foam is the primary way to mitigate this risk. The sponsor has established that the proper use of the Varithena device generates consistently small bubbles with low nitrogen content when activated. The secondary step to prevent CNS AEs, due to large bubbles, is to inject the foam within

75 seconds of generating it. After generating the microfoam, over time, the microfoam will begin to coalesce back into a liquid, which will also impact the effectiveness of the product. The 75 second limit proposed by the Sponsor is conservative and provides a reasonable safety margin. The rationale for selection of the 75 second time limit is explained in a response to an IR submitted by DRISK and is as follows:

How did the Sponsor identify 75 seconds as the appropriate time limit to place on injection of PEM from time of foam generation?

Response

For the original PEM formulation (b) (4) the limit for time to injection from time of microfoam generation was set at (b) (4) seconds, which was half of the (b) (4) -second half separation time typical for this formulation ... Half separation time is defined as the time for half the microfoam volume to coalesce to liquid after generation of microfoam. (b) (4) seconds was selected to allow for sufficient safety margin between the time limit and the half separation time. The new, low nitrogen formulation has a specification of (b) (4) seconds...with a typical half separation time of 150 seconds...Accordingly, the time limit was amended to 75 seconds...

Lastly, to mitigate this risk, HCPs are instructed to inspect the manometer tubing for bubbles as the product is being injected and to stop administration if larger bubbles are detected. This step is standard of care when injecting any medication IV and does not need additional risk mitigation beyond labeling.

In conclusion, there are multiple ways CNS side effects can be mitigated in the administration process. DRISK believes that the labeling will sufficiently provide the administration recommendations to HCPs expected to utilize this product after approval.

Sponsor-mandated training program for physicians

The Sponsor has proposed (b) (4)

While a practical demonstration is a useful tool for physicians, it does not rise to the level of requiring a REMS for Varithena. This prescribing population is already familiar with treating varicosities, the use of duplex ultrasound, and post-procedure patient care. And for these reasons Varithena can be safely used by the intended prescribers with labeling and the IFU. (b) (4), DRISK does not believe the training is necessary to ensure the benefits outweigh the risks.

Usability Study

Though DMEPA does not believe that the usability of Varithena has been demonstrated, the errors that they point to in their review are related to the difficulty with gas transfer, removal of the oxygen canister or MTU attachment, failure to write the first use date on the canister, and errors that occurred during priming, flushing/filling the syringe. These failures, while concerning, were primarily attributed to an assistant who would be preparing the microfoam for a physician and not to actions performed by the physician

while injecting the microfoam. In addition, the errors identified would not result in an increased risk of DVT or CNS AE.

DMEPA provides recommendations to improve the proposed labels, labeling, and IFU to add clarity and bring prominence to specific information that will further minimize the risk for use errors.

CDRH, Human Factors Team, does not have any outstanding concerns regarding the usability of Varithena and has no additional recommendations.

In the absence of a REMS, the labeling and IFU alone must be sufficient to mitigate the serious risks of the product. I believe, like DMEPA, improvements to the labeling and IFU to add clarity and bring prominence to specific information should be made to further minimize risks.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Varithena (polidocanol endovenous microfoam). Varithena microfoam has proven efficacy in improving patient symptoms and improving the appearance of varicosities. The serious risks of concern with Varithena treatment include DVT which may lead to PE and ischemic cerebrovascular conditions. There were no patients with PE diagnosed or significant neurological or ischemic cerebrovascular events in the Varithena studies. Thus, benefit-risk profile for Varithena is favorable and the risks can be mitigated through the professional labeling.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product, please contact DRISK.

6 REFERENCES

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