

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrVARITHENA™

Polidocanol injectable foam

1.3 mg polidocanol /mL foam
(generated from polidocanol solution, 1.0% w/v)

Sclerosing Agent

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Varithena™

Polidocanol injectable foam

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection	<p>Polidocanol Solution, 180 mg/18 mL (10 mg/mL) must be activated before use.</p> <p>Once activated, Varithena™ is a white, injectable foam delivering a 1% polidocanol solution combined 1:7 with a gas solution of Carbon Dioxide: Oxygen in a 35:65 ratio with <0.8% Nitrogen. Each mL of Varithena™ injectable foam contains 1.3 mg of polidocanol.</p>	<p>Ethanol Water for Injection</p> <p><i>For a complete listing see Dosage Forms, Composition and Packaging section.</i></p>

INDICATIONS AND CLINICAL USE

Varithena™ is indicated 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. Varithena™ is intended for use in adults with clinically significant venous reflux as diagnosed by duplex ultrasound.

Physicians administering Varithena™ must be experienced with venous procedures, possess a detailed working knowledge of the use of the duplex ultrasound in venous disease, and be trained in the administration of the product.

CONTRAINDICATIONS

The use of Varithena™ is contraindicated in patients with:

- Known allergy to polidocanol or any ingredient in the formulation
- Acute thromboembolic disease
- Thrombophilia
- Pregnancy

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Anaphylaxis**

Severe allergic reactions have been reported following administration of liquid polidocanol, including anaphylactic reactions, some of them fatal. Observe patients for at least 10 minutes following injection and be prepared to treat anaphylaxis appropriately.

- **Tissue Ischemia and Necrosis**

Intra-arterial injection or extravasation of polidocanol can cause severe necrosis, ischemia or gangrene. Patients with underlying arterial disease may be at increased risk for tissue ischemia. If intra-arterial injection of polidocanol occurs, consult a vascular surgeon immediately.

- **Venous Thrombosis**

Varithena™ can cause venous thrombosis (See **ADVERSE REACTIONS**). Follow administration instructions closely and monitor for signs of venous thrombosis after treatment. Patients with risk factors such as reduced mobility, history of deep vein thrombosis or pulmonary embolism, recent (within 3 months) major surgery, prolonged hospitalization, malignancy, use of hormonal contraceptives, use of hormone replacement therapy, obesity or smoking are at increased risk for developing thrombosis. Benefit-risk needs to be carefully considered in these patients, the same consideration should be applied to those patients who are contraindicated for anticoagulation.

- **Ischemic cerebrovascular events**

Ischemic cerebrovascular events such transient ischemic attack (TIA) or stroke have been reported rarely for sclerosing agents minutes or days after sclerotherapy. These events have not been reported to date with Varithena™. Factors that may increase the risk of these events after physician-compounded foam sclerotherapy include the use of room air instead of carbon dioxide to prepare the foam, large bubbles size, a presence of patent foramen ovale (PFO), failure to elevate the limb during and after therapy, and any excessive amount of foam used during one session. Because of the potential for arterial gas-emboli to occur, patients with known PFO should be appropriately counselled about this risk with Varithena™ treatment and the risk –benefit of treating these patients with Varithena™ should be carefully considered (See **WARNING AND PRECAUTION, Special populations, Patent foramen ovale**).

Post-Procedural Period

Physician should monitor patients for signs suggestive of hypersensitivity (redness of the skin and conjunctiva, pruritus, cough) and neurological signs (scotomas, amaurosis, or focal sensory and /or motor deficits).

Advise the patient to keep post-treatment bandages dry and in place for 48 hours and to wear compression stockings on the treated legs continuously for 2 weeks (see DOSAGE AND ADMINISTRATION).

Cardiovascular

Benefit-risk needs to be carefully considered in patients with significant cardiovascular disease, such as recent myocardial infarction, uncontrolled hypertension and heart failure (NYHA Class III or IV), and those with a history of TIA/Stroke because these patients have not been studied in clinical trials.

Special Populations

Patent foramen ovale (PFO): Ischemic adverse events have been reported in clinical trials and in the medical literature a few minutes after injection of polidocanol in liquid or physician-compounded room air-based foam. Physicians should advise patients to avoid any Valsalva manoeuvre or similar activities (such as bending to put on stockings or coughing, etc.) immediately following foam sclerotherapy. The potential for Varithena™-derived bubbles to cause cerebrovascular events was investigated in one study², patients with proven PFO and varicose veins were treated with Varithena™; patients with bubbles demonstrated in the middle cerebral artery were carefully monitored including serial MRI. No significant clinical neurological events or MRI changes were demonstrated (See **ACTION AND CLINICAL PHARMACOLOGY**).

Pregnant Women: There are no adequate and well-controlled studies of Varithena™ in pregnant women; therefore, use of Varithena™ is contraindicated.

Developmental reproductive toxicity testing was performed in rats and rabbits using intravenous administration of polidocanol solution. In rabbits, dose levels up to 10 mg/kg/day (approximately 12 times the maximum human dose of 15 mL of 1.0% polidocanol injectable foam based on body surface area) did not produce any indication of adverse effects on embryo-fetal mortality, fetal weight, or the incidences of fetal abnormalities and variants. In rats, at dose levels up to 27 mg/kg/day of polidocanol solution (approximately 13.5 times the maximum human dose of 15 mL of 1.0% polidocanol injectable foam based on body surface area), there were no adverse effects on pregnancy performance but there was an increased incidence of supernumerary ribs in fetuses at ≥ 3 mg/kg/day of polidocanol solution (approximately 1.5 times the maximum human dose of 15 mL of 1.0% polidocanol injectable foam based on body surface area) which slightly exceeded the historic control groups. In a peri-natal and post-natal study in rats, dose levels of polidocanol up to 9 mg/kg/day (approximately 4.5 times the human dose based on body surface area) were without adverse effects on the development of the conceptus and offspring, and at a dose level of 27 mg/kg/day of polidocanol solution (approximately 13.5 times the human dose based on body surface area), adverse effects were confined to an equivocal reduction in body weights of first-generation males, and an associated equivocal delay in the age of preputial separation.

Nursing Women: It is not known whether polidocanol is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, avoid administering Varithena™ to a nursing woman.

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established. Therefore Varithena™ is not recommended.

Geriatrics (> 65 years of age): Of the 1333 subjects treated with Varithena™ in clinical studies, 9.1% (n=121) of subjects were ≥65 years of age. No clinically important differences in safety or efficacy were observed between older and younger patients.

Hepatic and Renal Impairment: The safety and efficacy of Varithena™ treatment in patients with known hepatic impairment, renal impairment or clinically significant proteinuria has not been established and therefore caution is advised with the use of Varithena™ in these patients.

There is no clinical experience in patients undergoing renal dialysis. Use in patients on renal dialysis is not recommended.

Monitoring and Laboratory Tests:

Patients should be monitored during the administration of Varithena™ and for confirmation of venospasm.

No specific laboratory tests are required. Since Varithena™ induces thrombosis in the treated superficial veins, D-dimer is commonly elevated post-treatment and is not useful diagnostically to assess patients for venous thrombus following treatment with Varithena™.

ADVERSE REACTIONS

The Adverse Reactions reported in the clinical trial population are discussed in the section below. Based upon the clinical trial data, the most serious Adverse Reactions that may influence prescribing decisions or that could result in clinical intervention are outlined below and discussed in greater detail in the *Warnings and Precautions* section.

- Anaphylaxis
- Tissue Ischemia and Necrosis
- Venous Thrombosis

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug or procedure. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A total of 1333 patients in 12 clinical trials were evaluated for safety when treated with Varithena™ at dose concentrations of 0.125%, 0.5%, 1.0%, or 2.0%; these include 437 patients treated with polidocanol injectable foam in placebo-controlled clinical trials.

In patients treated with Varithena™ 1%, 16 patients experienced 20 serious adverse events: 3 patients died (traffic accident, heart failure, hepatic cirrhosis/acute on chronic renal failure) and 13 patients experienced non-fatal serious adverse events, including facial injury, venous thrombosis limb (2 cases), appendicitis, angina pectoris, grand mal convulsion, spinal osteoarthritis, tracheobronchitis, bronchitis, influenza, bronchopneumopathy, cellulitis, sick sinus syndrome, gastric obstruction, diverticulitis and pneumonia.

The most common (>10%) adverse events in patients treated with Varithena™ 1% include contusion, pain in extremity, headache and skin discoloration.

In patients treated with Varithena™ 1%, excluding the 3 patients who died, 9 patients were discontinued due to adverse events, including venous thrombosis limb (3 cases; 2 were SAEs, see [Table 2](#) footnote), spinal osteoarthritis (SAE), extravasation (2 cases), superficial thrombophlebitis, foam entering the deep venous system and injection site pain.

Adverse Reactions that occurred in 2% of patients receiving polidocanol injectable foam 1% or in 1% more than in patients receiving placebo are shown in [Table 1](#). All adverse reactions that occurred in the treatment arms were common or very common in terms of frequency. The event terms venous thrombosis limb and deep vein thrombosis occurred only in the treatment arms of the studies, not in patients who received placebo.

Table 1: Treatment-Emergent Adverse Reactions (2% on Varithena™ [polidocanol injectable foam] or 1% more than on Placebo) Through Week 8

Adverse Reaction by SOC & Frequency	Placebo (N=151)	Varithena™ 1.0% (N=149)
General Disorders and Administration Site Conditions		
Infusion site thrombosis ^a	0	16.1%
Contusion/injection site hematoma	6.0%	15.4%
Tenderness/injection site pain	3.3%	10.7%
Oedema Peripheral	2.0%	4.0%
Extravasation	0.7%	3.4%
Inflammation	0	2.0%
Chest Discomfort	0	1.3%
Chest Pain	0	1.3%
Infections and Infestations		
Nasopharyngitis	2.0%	3.4%
Bronchitis	0	1.3%
Influenza	0	1.3%
Musculoskeletal and connective tissue disorders		
Pain in extremity	9.3%	16.8%
Limb discomfort	3.3%	12.1%
Arthralgia	0.7%	2.7%
Muscle Spasms	0.7%	2.0%
Nervous System Disorders		
Headache	2.6%	5.4%

Adverse Reaction by SOC & Frequency	Placebo (N=151)	Varithena™ 1.0% (N=149)
Skin and Subcutaneous Tissue Disorders		
Pruritus	6.0%	4.0%
Rash	2.0%	4.0%
Erythema	0	2.0%
Surgical and Medical Procedures		
Haematoma Evacuation	0	1.3%
Vascular Disorders		
Venous thrombosis limb ^b	0	8.1%
Thrombophlebitis superficial	1.3%	5.4%
Deep vein thrombosis ^c	0	4.7%
Thrombosis ^d	0	2.0%

MedDRA preferred terms most appropriate to the condition were selected to identify different thrombotic adverse events

- Infusion site thrombosis = retained coagulum in treated vein
- Venous thrombosis limb = Common femoral vein thrombus extension
- Deep vein thrombosis = thrombosis in the axial deep veins of the leg
- Thrombosis = thrombosis in small calf veins (gastrocnemius or soleal veins)

In Varithena™-treated patients, 80% of pain events in the treated extremity resolved within 1 week.

In the 1333 patients treated with polidocanol injectable foam, the following venous thrombus adverse events occurred: common femoral vein thrombus extension (2.9%), proximal deep vein thrombosis (DVT) (1.7%), distal DVT (1.1%), and isolated gastrocnemius and soleal vein thrombosis (1.4%) [Table 2](#).

Proximal symptomatic venous thrombi occurred in <1% of patients treated with polidocanol injectable foam. Approximately half (49%) of patients with thrombi received treatment with anticoagulants.

All thrombi that were detected in the deep and muscular calf veins were reported as were all extensions of thrombus from the SFJ into the common femoral vein (common femoral vein thrombus extension; CFVTE). If a thrombus AE was identified:

- Patients underwent an additional duplex scan 1 and 2 weeks later and then monthly until the thrombi stabilized or resolved.
- The patient was evaluated for the presence of symptoms of venous thrombus and of pulmonary embolism.
- Management of the identified thrombi was according to clinical presentation and usual clinical practice.

Table 2: Venous Thrombus Adverse Events (Main Treatment Period, N=1192)

	Placebo (N=151)	Varithena™ 1.0% (N=837)
Venous Thrombus AEs	0 (0)	49 (5.9%)
Pulmonary Embolism	0 (0)	0
Proximal		
Symptomatic	0 (0)	10 (1.2%)

	Placebo (N=151)	Varithena™ 1.0% (N=837)
Asymptomatic	0 (0)	24 (2.9%) ^a
Distal		
Symptomatic	0 (0)	3 (0.4%)
Asymptomatic	0 (0)	12 (1.4%)
	0 (0)	
Proximal		
Common Femoral	0 (0)	24 (2.9%)
Femoral	0 (0)	6 (0.7%)
Popliteal	0 (0)	4 (0.5%)
Distal		
Posterior Tibial	0 (0)	2 (0.2%)
Anterior Tibial	0 (0)	1 (0.1%)
Peroneal	0 (0)	1 (0.1%)
Soleus	0 (0)	1 (0.1%)
Gastrocnemius	0 (0)	10 (1.2%)

In addition, 1 patient (2.6%) treated with ETA + Placebo had a posterior tibial, asymptomatic venous thrombus AE, and 1 patient (0.8%) treated with non-Varithena™ sclerotherapy had a gastrocnemius, symptomatic venous thrombus AE.

^a 2 patients had serious venous thrombus AEs. In both cases, the event was serious because the investigator, per institutional policy, was required to hospitalize the patient in order to begin treatment with intravenous unfractionated heparin.

None of the 1333 patients treated with polidocanol injectable foam in clinical trials experienced clinically important neurological or visual adverse events suggestive of cerebral gas embolism. In the early clinical trials of Varithena™, product containing up to 10% nitrogen was used. In Study 001, six patients had transient treatment-emergent AEs that might have been attributed to cerebral gas embolism. All of these events were brief; the longest event, which had features of a transient ischemic attack, lasted 20 minutes. The product was subsequently modified to remove all but a trace of nitrogen (<0.8%, 100 times less than room air) and is the current marketed product. As gas emboli occur immediately or shortly after administration, adverse neurological events related to gas embolization would be reported within 1 day.

In all studies, the incidence of possible neurologic adverse events within 1 day of treatment with Varithena™ 1% was 81/837 (9.7%). In contrast, studies using the formulation with up to 10% nitrogen was 13.5% (n=532) compared with 3.4% (n=265) in Varithena™ 1% (current formulation <0.8% nitrogen,) and 4.0% (n=151) in the placebo group.

Less Common Clinical Trial Adverse Reactions

The following additional adverse reactions were reported at incidence of less than 2% and greater than placebo, regardless of causality.

Blood and Lymphatic System Disorders: Anaemia, Microcytic Anaemia

Cardiac Disorders: Arrhythmia, Cardiomegaly, Palpitations, Sick Sinus Syndrome, Ventricular Extrasystoles

Ear and Labyrinth Disorders: Ear Pain, Tympanic Membrane Perforation, Vertigo

Endocrine Disorders: Hyperthyroidism, Hypothyroidism

Eye Disorders: Blindness, Conjunctival Haemorrhage, Conjunctivitis, Eye Pain, Eye Swelling, Vision Blurred, Visual Acuity Reduced, Visual Impairment

Gastrointestinal Disorders: Abdominal Discomfort, Abdominal Distension, Abdominal Pain, Abdominal Pain Upper, Constipation, Dry Mouth, Dyspepsia, Flatulence, Gastrointestinal Disorder, Gastroesophageal Reflux Disease, Haematemesis, Haemorrhoids, Lip Ulceration, Oral Discomfort, Oral Pain, Sensitivity of Teeth, Tongue Ulceration, Toothache, Vomiting

Immune System Disorders: Allergy to Arthropod Sting, Hypersensitivity, Seasonal Allergy

Injury, Poisoning and Procedural Complications: Animal Bite, Arthropod Sting, Clavicle Fracture, Corneal Abrasion, Face Injury, Injury, Meniscus Lesion, Mountain Sickness Acute, Procedural Complication, Procedural Pain, Road Traffic Accident, Sunburn, Therapeutic Agent Toxicity, Thermal Burn, Wrist Fracture

Investigations: Alanine Aminotransferase Abnormal, Alanine Aminotransferase Increased, Arthroscopy, Aspartate Aminotransferase Increased, Blood Alkaline Phosphatase Increased, Blood Cholesterol Abnormal, Blood Cholesterol Increased, Blood Creatine Phosphokinase Increased, Blood Pressure Increased, Blood Pressure Systolic Increased, End-Tidal Co2 Abnormal, End-Tidal Co2 Decreased, Gamma-Glutamyltransferase Abnormal, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Abnormal, Progesterone Decreased, Prothrombin Time Abnormal, Prothrombin Time Prolonged, Ultrasound Doppler Abnormal

Metabolism and Nutrition Disorders: Hypercholesterolaemia

Neoplasms Benign, Malignant and Unspecified (Cysts and Polyps): Skin Papilloma

Nervous System Disorders: Burning Sensation, Lethargy, Sciatica, Sensory Disturbance, Somnolence, Speech Disorder, Visual Field Defect

Pregnancy, Puerperium and Perinatal Conditions: Abortion Spontaneous

Psychiatric Disorders: Anxiety Disorder, Depression

Renal and Urinary Disorders: Glycosuria, Haematuria, Renal Colic

Reproductive System and Breast Disorders: Dysmenorrhoea, Menopausal Symptoms, Menorrhagia

Respiratory, Thoracic and Mediastinal Disorders: Cough, Dry Throat, Dysphonia, Dyspnoea, Epistaxis, Oropharyngeal Pain, Rhinitis Allergic, Rhinorrhoea

Skin and Subcutaneous Tissue Disorders: Acne, Alopecia, Blister, Blood Blister, Dermatitis, Dermatitis Allergic, Dermatitis Contact, Drug Eruption, Dry Skin, Ecchymosis, Eczema, Erythema, Night Sweats, Pigmentation Disorder, Skin Discomfort, Skin Tightness, Skin Ulcer, Stasis Dermatitis, Swelling Face, Urticaria

Surgical and Medical Procedures: Dermabrasion, Haematoma Evacuation, Inguinal Hernia Repair, Thrombectomy

In all studies, the incidence of skin discolouration adverse events in patients treated with Varithena™ 1% was 32.1%. When excluding Study 001 in which events were solicited rather

than spontaneously reported, skin discolouration was reported in 12.3% of patients treated with Varithena™ 1% compared to 0.7% of patients treated with placebo in placebo-controlled studies.

No anaphylaxis or life-threatening hypersensitivity reactions were reported in any of the 1333 patients treated with polidocanol injectable foam in clinical trials.

Post-Market Adverse Drug Reactions

As of 19 June 2015, approximately 1581 patients have been treated with Varithena™, and a small number of adverse events have been received from the market place. Adverse events are very rare with the product (reported in less than 1% of the treatment population) and all of the adverse events received with Varithena™ to date have been non-serious. The Adverse Events that have been reported with post-market use of Varithena™ are as follows:

General disorders and administration site conditions: Injection site erythema, Injection site vesicles, Medical device site irritation, Medical device site vesicles, Pyrexia, Injection site pain, Infusion site thrombosis.

Immune system disorders: Device allergy.

Infections and infestations: Cellulitis.

Vascular disorders: Deep vein thrombosis, Thrombophlebitis, Thrombophlebitis Superficial, Venous thrombosis, Phlebitis, Venous thrombosis limb.

Musculoskeletal and connective tissue disorders: Pain in extremity.

Skin and Subcutaneous Tissue Disorders: Dermatitis Contact.

DRUG INTERACTIONS

No specific drug interaction studies have been performed. There are no known drug interactions with polidocanol injectable foam.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food interactions

Interactions with food have not been established.

Drug-Herb interactions

Interactions with herbal products have not been established.

Drug-laboratory test interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Varithena™ is intended for intravenous injection only, as the activated foam, using ultrasound guidance and is administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities.

See the attached Instruction of Use leaflet for detailed instructions on activation and preparation of the product.

Maintain the sterile bi-canister assembly within the Tyvek pouch until immediately prior to activation

Recommended Dose and Dosage Adjustment

Use no more than 15 mL per patient treatment session administered in aliquots of 5 mL or less. Depending on the extent and diameter of the varicose veins to be treated, additional treatment sessions may be needed. Separate each treatment session by a minimum of 5 days.

Administration

Physicians administering Varithena™ must be experienced with venous procedures, possess a detailed working knowledge of the use of the duplex ultrasound in venous disease and be trained in the administration of Varithena™.

Local anesthetic may be administered prior to cannula insertion but neither tumescent anesthesia nor patient sedation is required. Cannulate the vein to be treated using ultrasound guidance to confirm venous access.

Occlude the treated vein distal to the cannula using finger pressure and inject freshly-generated Varithena™ injectable foam slowly (approximately 1 mL/second in the GSV and 0.5 mL/second in accessory veins or varicosities) while monitoring using ultrasound. Confirm venospasm of the treated vein using ultrasound. Special care must be employed if a perforator is present, to minimize the risk of foam entering the deep venous system.

When treating the proximal GSV, stop the injection when Varithena™ (polidocanol injectable foam) is 3-5 cm distal to the saphenofemoral junction (SFJ).

Apply compression bandaging and stockings and have the patient walk for at least 10 minutes following treatment. Maintain compression for 2 weeks after treatment. Following treatment, advise the patient to avoid heavy exercise for 1 week and extended periods of inactivity for 1 month.

Retained coagulum may be removed by aspiration (microthrombectomy) to improve comfort and reduce skin staining.

Generation of Foam

Activate Varithena™ using the Varithena™ oxygen canister and polidocanol canister [*see the attached Instructions for Use leaflet*]. Once a Varithena™ transfer unit is in place, foam can be

generated and transferred to a syringe. Discard the syringe contents if there are any visible bubbles.

Once activated, the canister of Varithena™ should be stored at room temperature in the upright position, and used within 30 days

Administer the injectable foam within 75 seconds of extraction from the canister to maintain injectable foam properties. If the foam has not been used within 75 seconds discard and generate new foam, as the foam quality will begin to deteriorate.

Use a new sterile syringe after each injection.

Use a new Varithena™ transfer unit for each treatment session.

See Instructions for Use

OVERDOSAGE

In clinical studies, total volumes of up to 60 mL of Varithena™ (polidocanol injectable foam) per treatment session have been administered. There are no known cases of overdosage with Varithena™.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Varithena™ (polidocanol injectable foam) is a drug/device combination product that generates injectable foam. The injectable foam is composed of a liquid and gas phase, both of which are necessary to have its therapeutic effect. Varithena™ is intended to act as follows:

- (1) the foam displaces blood from the vein to be treated, and
- (2) the foam scleroses the endothelium.

The active pharmaceutical ingredient of Varithena™ is polidocanol, a non-ionic surfactant sclerosing agent. The hydrophobic pole of the polidocanol molecule attaches to the lipid cell membrane of the venous endothelium, resulting in disruption of the osmotic barrier, destruction of the venous endothelium, and vasospasm. Following exposure to polidocanol, the interior surface of the vein becomes thrombogenic, which leads to thrombus formation and venous occlusion. The occluded vein is eventually replaced by fibrous connective tissue. Polidocanol is deactivated upon contact with blood, thus limiting the sclerosant action to the endothelium near the site of injection.

Gas absorption

Transient neurologic adverse events such as visual disturbance, migraine like-headache, dizziness or paresthesia have been reported following use of unapproved physician-compounded room air foam sclerotherapy, as a result of presumed passage of bubbles through a patent foramen ovale and temporary occlusion of the cerebral microvasculature.

Blood at ambient pressure is saturated with nitrogen and has no capacity to absorb gaseous nitrogen (similar to the Bends). For this reason Varithena™ excludes all but a trace of nitrogen (<0.8%), and is made of readily absorbable gasses carbon dioxide and oxygen (injected into venous blood containing desaturated hemoglobin). Absorption of Varithena™ gases into human blood is complete within 2 minutes, in contrast foam made with nitrogen does not absorb (80% in air). In another study air based foam was shown to completely occlude the microvasculature of the rat whereas Varithena™ even at 8x the dose did not¹.

In one study investigating the safety of Varithena™, 82 patients with varicose veins were enrolled, including 61 screened for presence of patent foramen ovale². Patients were treated with up to 20 mL Varithena™ 1% (current product with <0.8% nitrogen). Patients were monitored by transcranial Doppler ultrasound for bubbles in the middle cerebral artery (MCA) during and up to one hour post treatment; 60 patients had at least one MCA bubble (mean=22; maximum=382). Patients were hospitalized and monitored for 24 hours, including pulse oximetry); patients with MCA bubbles had neurological examinations, visual field testing, Troponin and ECG, and serial diffusion-weighted MRI within 6 hours and again at 24 hours, 7 days and 28 days. One patient complained of ‘twinkly lights’ which lasted for 20 seconds; ophthalmologic and neurological examinations, visual field assessments and diffusion-weighted MRI performed immediately after this incident were normal.

No patient had any clinical or subclinical neurological signs or symptoms; in particular, there were no changes in the 24 hour MRI diffusion weighted sequence, which would have demonstrated changes in edema in small volumes of cerebral tissue^{2,3}.

Pharmacodynamics

Polidocanol had a concentration dependent sclerosant effect when injected either as a foam or solution in the marginal ear vein of the rabbit.

Pharmacokinetics

The pharmacokinetics of polidocanol injectable foam (as a weighted sum of 4 oligomers: E5, E9, E12 and E14) were evaluated at two concentrations (1.0% and 2.0%) randomly assigned within gender in 20 patients with GSV incompetence.

When administered as an intravenous injectable foam as 2 fixed 5 mL doses separated by 10 minutes, polidocanol was rapidly detected in plasma, reaching maximum concentration of drug in the body after dosing (C_{max}) within 15 minutes of the first injection and within 5 minutes of receiving the second injection of polidocanol injectable foam 1.0% or polidocanol injectable foam 2.0%. The mean volume of distribution (V_d) of polidocanol ranged from 35 to 82 L.

Mean systemic clearance (CL) of polidocanol ranged from 0.2 to 0.4 L/min. The clearance of E5 was significantly greater than that of longer oligomers. Mean terminal elimination half-life ($t_{1/2}$) ranged from 102 to 153 minutes, with most plasma samples below the limit of quantitation (BLQ) at the end of the 8-hour collection period. The increase in plasma polidocanol concentrations was less than proportional with increasing polidocanol injectable foam

concentration. Weight-normalized data demonstrated no consistent differences in C_{\max} or area under the concentration-time curve (AUC) between males and females.

Table 3: Summary of Pharmacokinetic Parameters of Polidocanol following Administration of Polidocanol Injectable Foam 1.0% in Patients with Incompetence of the SFJ Associated with Incompetence of the GSV or Other Major Accessory Veins

Parameter		Varithena™ 1.0 %	
		Male (n=3)	Female * (n=6)
C_{\max} (ng/mL)	Mean	454.8	798.7
	SD	118.2	359.3
$C_{\max 1}$ (after 1 st injection; ng/mL)	Mean	388.4	600.0
	SD	115.2	262.9
$C_{\max 2}$ (after 2 nd injection; ng/mL)	Mean	452.9	750.5
	SD	121.1	378.0
T_{\max} (min)	Median	14.0	14.0
$T_{\max 1}$ (after 1 st injection; min)	Median	5.0	4.0
$T_{\max 2}$ (after 2 nd injection; min)	Median	5.0	4.5
AUC _{0-∞} (ng.min/mL)	Mean	48405.7	60777.8
	SD	15256.3	22073.1
AUC _{0-∞} (ng.min/mL) Weight-Normalized	Mean	62784.7	62374.6
	SD	22482.6	19481.4
AUC _[0-t] (ng.min/mL)	Mean	41414.7	53262.4
	SD	11814.7	16416.9
AUC _[0-t] (ng.min/mL) Weight Normalized	Mean	53629.5	54921.7
	SD	17316.4	15517.8
AUC _[0-t] (ng.min/mL) Dose-Normalized	Mean	3185.7	4097.1
	SD	908.8	1262.8
AUC ₀₋₁₀ (ng.min/mL)	Mean	2474.5	3593.9
	SD	753.1	1168.5
Terminal elimination half-life ($t_{1/2}$; min)	Mean	102.0	105.5
	SD	10.5	21.5
CL (L/min)	Mean	0.288	0.236
	SD	0.095	0.078
Vd (L)	Mean	41.8	34.9
	SD	11.9	9.8
Ae _[0-4 hrs] (ng)	Mean	NC	2394.8
	SD		2252.3
Ae (% dose)	Mean	NC	0.018
	SD		0.017
Renal Clearance (mL/min)	Mean	NC	0.053
	SD		0.057

* n = 4 females for Ae and Ae% following Varithena™ 1.0%.

AUC_[0-t] where t = 300 min

Ae: amount excreted in urine; Ae% percent excreted in urine;

ng = nanogram; min = minute; mL = milliliter; L = Liter; NC = Not calculable, no polidocanol detected in urine; SD = standard deviation

Absorption: Total polidocanol was rapidly detected in plasma following injection into the incompetent GSV (or major accessory). For Varithena™ 1.0%, C_{\max} was reached within 14 min

and increased with dose (along with AUC) in a less than proportional manner. Overall exposure (C_{\max} and AUC) was higher in females when compared to males; this was accounted for by differences in body weight.

Distribution: Vd ranged from 34.9 L to 82.4 L and was considered similar between males (41.8 L) and females (34.9 L) following administration of Varithena™ 1.0% and between males (82.4 L) and females (48.0 L) following administration of Varithena™ 2.0%.

Metabolism: The data suggest that, since there is no significant renal excretion of intact polidocanol oligomers E5, E9, E12, and E14, metabolism is likely the major route of elimination of polidocanol. *In-vitro* metabolism studies have demonstrated a time-dependent metabolism of [^{14}C]-polidocanol following incubation with rat, dog and human liver microsomal and S9 fractions. Qualitative analysis suggested metabolism to be more extensive in human than animal species, and microsomal metabolism was greater than S9 for each species. In rat and dog *in-vivo* studies, following intravenous administration, [^{14}C]-polidocanol was mainly metabolised to polar metabolites that were rapidly eliminated, predominantly via the renal route and to a lesser extent via the biliary route and in expired air.

Excretion: Terminal $t_{1/2}$ ranged from 102.0-153.4 min and was considered similar between males (102.0 min) and females (105.5 min) administered Varithena™ 1.0% and males (153.4 min) and females (114.1 min) administered Varithena™ 2.0 %. CL ranged from 0.236 L/min to 0.351 L/min and was considered similar between males (0.288 L/min) and females (0.236 L/min) administered Varithena™ 1.0 % and males (0.351 L/min) and females (0.291 L/min) administered Varithena™ 2.0 %. Approximately 0.02% of total polidocanol was excreted in the urine following Varithena™ 1.0% and approximately 0.01% of total polidocanol was excreted in the urine following Varithena™ 2.0%, with low renal clearance (\leq approximately 0.05 mL/min), suggesting metabolism is likely the major route of elimination of polidocanol.

Visual inspection of polidocanol injectable foam AUC and C_{\max} values suggests that the increase in AUC and C_{\max} values was modestly less than proportional to increasing dose. The lack of a consistent dose-dependent change in half-life, CL, and Vd suggests that polidocanol injectable foam pharmacokinetics are linear over the dose range studied.

STORAGE AND STABILITY

Contains gas under pressure: May explode if heated. Store in a well-ventilated place. Store the canisters away from sources of heat, including strong light conditions.

Pressurized Oxygen: May cause or intensify fire; oxidiser. Store away from combustible materials.

Maintain the sterile bi-canister assembly within the Tyvek pouch until immediately prior to activation.

Once activated, the canister of Varithena™ must be used within thirty (30) days. The activated Varithena™ canister should always be stored with a Varithena™ transfer unit in place in the upright position at 20-25°C with excursions permitted to 15 and 30°C.

Discard aerosol canisters after use in accordance with local requirements.

SPECIAL HANDLING INSTRUCTIONS

Always write the activation date and time on the canister and verify that the product has not expired prior to use. Do not shake Varithena™ canisters. Avoid contact with eyes.

As the foam fills the syringe and before injecting, inspect the syringe full of foam for any visible bubbles. If visible bubbles are present, the foam should be emptied into the Varithena™ transfer unit waste chamber and the syringe refilled.

A new Varithena™ transfer unit must be used for each treatment session. Use a new sterile syringe after each injection. Do not fill a syringe until just before the foam is required for administration.

For more information, please refer to the Instruction for Use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Varithena™ is a sterile, injectable foam of an aqueous polidocanol solution (1%) combined with carbon dioxide and oxygen, containing the following inactive ingredients: ethanol (4.2% w/w), disodium hydrogen phosphate dihydrate (0.24% w/w), and potassium dihydrogen phosphate (0.085% w/w) with pH in the range 6.0-7.5.

Polidocanol solution, 180 mg/ 18 mL (10mg/mL) must be activated before use. Once activated, Varithena™ injectable foam delivers a 1% polidocanol solution. Each 1 mL of Varithena™ injectable foam contains 1.3 mg of polidocanol (0.13%). One canister of Varithena™ generates 90 mL of foam, which following purging instructions in the Instructions for Use, is sufficient to yield 45 mL of usable foam for injection.

Varithena™ is supplied as two connecting sterile canisters in a Tyvek® pouch containing:

- Canister 1- Polidocanol solution, 180 mg/18 mL (10 mg/mL) in carbon dioxide atmosphere
- Canister 2 – Oxygen

The two canisters must be connected and the oxygen added to the polidocanol solution. The foam is then generated after activation [see Product Monograph *Administration Section* and *Instructions For Use*].

The injectable foam generated after activation of the polidocanol canister with oxygen from a second aluminum canister, results in a final gas mixture of oxygen:carbon dioxide in a ratio of 65:35 with low (<0.8%) nitrogen content.

The foam is then transferred to a syringe through the Varithena™ transfer unit.

The injectable foam thus generated presents controlled density and bubble size and a liquid-to-gas ratio of approximately 1:7 by volume. The median bubble diameter is less than 100 µm and no bubbles are greater than 500 µm.

Varithena™ (polidocanol injectable foam) product is supplied as two commercial presentations:

- Varithena™ Bi-Canister
 - o A Tyvek® pouch containing two sterile, connected 303 mL aluminum alloy canisters: one containing polidocanol solution, 180 mg/18 mL (10 mg/mL) (1% polidocanol), under a carbon dioxide atmosphere, the second containing pressurized oxygen at approximately 5.4 bar absolute pressure. The connector joins the two canisters and allows activation of the product.
 - o Product Monograph
 - o Patient Medication Information
 - o Instructions for Use
- Varithena™ Administration Pack
 - o One Varithena™ transfer unit to generate and dispense foam
 - o Instructions for Use
 - o Patient ancillary components:
 - Three 10 mL silicone-free Luer syringes
 - One 51 cm manometer tube
 - Two compression pads

Varithena™ is also supplied in a **Convenience Box** that contains:

- A Tyvek® pouch containing two sterile, connected 303 mL aluminum alloy canisters, as above:
- Product Monograph
- Patient Medication Information
- Instructions for Use
- Three Varithena™ transfer units to dispense injectable foam;
- Three Ancillary Packs each containing:
 - o Three 10 mL silicone-free Luer syringes
 - o One 51 cm manometer tube
 - o Two compression pads

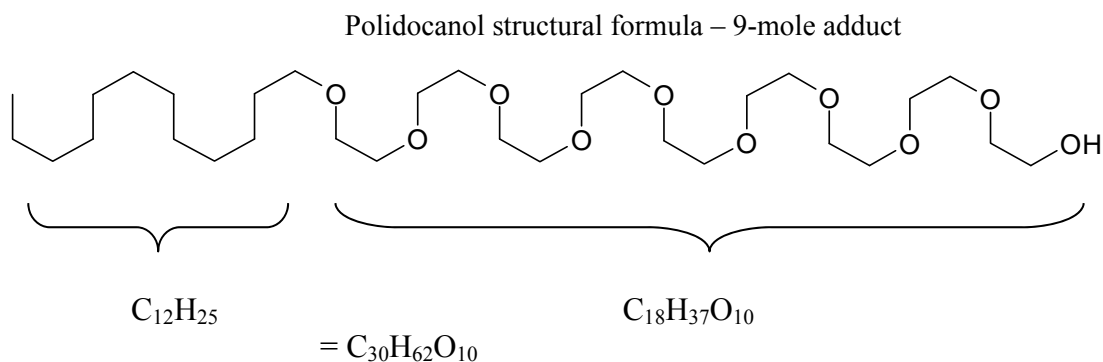
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance Proper name: polidocanol, macrogol lauryl ether, BP/Ph.Eur., polyoxyl lauryl ether, USP

Chemical name: α -dodecyl- ω -hydroxypoly(oxyethylene), oxypolyethoxydodecane, macrogol lauryl ether, polyoxyl lauryl ether, polyethylene glycol monolauryl ether

Molecular formula and molecular mass:



Foam Liquid Phase 1.0% solution of $(\text{CH}_3(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_n\text{OH})_x$ where n = an average of nine (9)

Foam Gas Phase $(\text{CO}_2)_y.(\text{O}_2)_z$ where Y:Z = 35:65; Nitrogen content <0.8%

Liquid Phase: Gas Phase = 1:7

Physicochemical properties:

(a) Physical description (e.g., appearance, colour, physical state):

Polidocanol is a white/almost white waxy solid at 15-20°C, as referenced in the Ph.Eur monograph on Macrogol Lauryl Ether (Ph.Eur 01/2008:1124)

(b) Physical form (e.g., polymorphic form, solvate, hydrate):

Polidocanol is a heterogeneous controlled oligomeric compound which has an average polymer length of 9 ethoxy units. It is a waxy solid in appearance and texture, which does not melt at a specific single point due to its heterogeneous nature. The drug substance exhibits no crystallinity and therefore there is no potential for polymorphism.

(c) Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):

Polidocanol is hygroscopic, soluble in water and alcohol, and practically insoluble in light petroleum.

(d) pH and pKa values:

To obtain an accurate and meaningful value for pKa or log P the compound needs to be a single homogenous entity. As polidocanol is a mixture of oligomers, values for pKa and log P are not useful or meaningful measurements.

(e) Other (e.g., partition coefficients, melting or boiling points, optical rotation, refractive index (for a liquid), hygroscopicity, UV absorption maxima and molar absorptivity):

Table 4: Additional Properties of Polidocanol

Property	Value
Density at 45°C	0.987 g/cm ³
pH (solution at 3% w/v)	4.0 - 7.5
Refractive Index at 25°C	1.44 - 1.46
Melting point Range as determined by DSC ^a	21 - 27°C
Surface tension at 25°C in PBS ^b of 1.0 % w/v solution	31.8 mNm ⁻¹

^a Differential scanning calorimetry

^b Phosphate-buffered saline

CLINICAL TRIALS

Study demographics and trial design: Varithena™ was evaluated in two randomized, blinded, multicenter clinical trials designed to assess the efficacy and safety of Varithena™ 0.5%, 1.0%, and 2.0% (VANISH-1) and Varithena™ 0.5% and 1.0% (VANISH-2) compared with placebo in the treatment of both symptoms and appearance. These trials were conducted in patients with saphenofemoral junction (SFJ) incompetence as evidenced by reflux of the GSV or major accessory veins. In both studies, a Varithena™ 0.125% treatment group was included as a control for blinding of the duplex ultrasound assessment. Patients with history of deep vein thrombosis or pulmonary embolism; inability to comply with post-treatment compression due to severe peripheral arterial disease or leg obesity; incompetence of the small saphenous vein or deep venous reflux as a major source of reflux; or reduced mobility, major surgery, pregnancy, or prolonged hospitalization within 3 months were excluded. Patients were randomized in an equal distribution to each treatment group; the primary time point for analyses of the primary, secondary, and tertiary efficacy endpoints was Week 8.

In these clinical trials, the maximum volume of injectable foam or placebo to be administered per treatment session was 15 mL.

In VANISH-1, patients received one blinded treatment and in VANISH-2, patients received one blinded treatment with an option for a second blinded treatment 1 week later. In VANISH-2, patients in the Varithena™ 1.0% treatment group received an average of 1.4 blinded treatments. All patients received post-procedure compression therapy for 14 days following treatment.

At each study visit after the initial treatment, AEs, concomitant medications and procedures were recorded. One week after each study treatment (initial or optional additional treatment), patients had a follow-up visit for safety using duplex ultrasound.

Of the 519 patients randomized in VANISH-1 and VANISH-2, a total of 511 were treated with Varithena™ 0.5% (n=111), 1.0% (n=110), or 2.0% (n=63), Varithena™ 0.125% as control (n=114), or placebo (n=113). Ninety-nine percent of the patients in VANISH-1 and VANISH-2 completed the blinded treatment period.

In the Varithena™ 1.0% group in VANISH-2, 23 of 58 patients received an additional blinded treatment. Two of these patients had retreatment of veins treated in the initial treatment session. The remaining 21 patients received treatment for additional veins not treated in the initial treatment session.

In VANISH-1 and VANISH-2, the mean age was approximately 50 years and approximately three-fourths of the patients were women. The mean BMI was similar in VANISH-1 and VANISH-2, at 28 kg/m² (range 16 to 44 kg/m²) and 30 kg/m² (range 17 to 48 kg/m²), respectively. The mean baseline GSV diameter was also similar in VANISH-1 and VANISH-2, at 7.6 mm (range 1.5 to 25.9 mm) and 8.7 mm (range 3.1 to 19.4 mm), respectively. Overall, 22% of patients in VANISH-1 and 25% of patients in VANISH-2 reported one or more prior varicose vein procedures in the leg to be treated.

Study results: In VANISH 1 and VANISH 2, Varithena™ was demonstrated to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities. The primary efficacy endpoint in both clinical trials was improvement in patient symptoms, as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ™ score. The VVSymQ™ score is a patient-reported outcome measure based on daily patient assessment of the duration of varicose vein symptoms determined to be most important to patients: heaviness, achiness, swelling, throbbing, and itching. VVSymQ™ scores range from 0 to 25, where 0 represents no symptoms and 25 represents all 5 symptoms experienced all of the time. Results are shown in [Table 5](#).

Table 5: Improvement in Symptoms of Varicose Veins as Measured by VVSymQ™ at Week 8, VANISH-1 and VANISH-2

	VVSymQ™			
	VANISH-1		VANISH-2	
	Placebo	Varithena™ 1.0%	Placebo	Varithena™ 1.0%
n	55	50	54	57
Baseline Score, mean	8.60	8.82	9.26	7.82
Adjusted Mean Change from baseline at Week 8	-2.13	-4.87	-2.00	-5.06
Comparison vs. Placebo at Week 8, <i>P</i> -value, Adjusted Mean Change		<0.0001		<0.0001

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.

In both VANISH-1 and VANISH-2, treatment with Varithena™ 1.0% was superior to placebo in improving symptoms as measured by VVSymQ™; these findings were consistent when duration-based and intensity-based scales were used to measure patients' symptoms.

The co-secondary endpoints in VANISH-1 and VANISH-2 were the improvement in appearance of visible varicosities from baseline to Week 8 as measured by 1) patients scoring the appearance of their varicose veins in the medial view of their study leg (PA-V³ score) from “Not at all noticeable” (a score of 0) to “Extremely noticeable” (a score of 4); and 2) an independent photography review panel rating the severity of the patient's varicose vein appearance in standardized digital photographs of the medial view of each patient's study leg (IPR-V³ score) from “None” (a score of 0) to “Very severe” (a score of 4). Results are shown in [Table 6](#).

Table 6: Improvement in Appearance of Visible Varicosities as Measured by IPR-V³ and PA-V³ at Week 8, VANISH-1 and VANISH-2

	VANISH-1		VANISH-2	
	Placebo	Varithena™ 1.0%	Placebo	Varithena™ 1.0%
IPR-V^{3**}				
n	55	49	56	57
Baseline Score, mean	1.82	1.98	2.18	2.02
Adjusted mean change from baseline	-0.01	-0.76	-0.07	-0.83
Comparison vs. Placebo, <i>P</i> -value at Week 8, Adjusted Mean Change		<0.0001		<0.0001
PA-V³				
N	55	50	56	57
Baseline Score, mean	3.49	3.46	3.30	3.49
Adjusted mean change from baseline at Week 8	-0.15	-1.60	-0.32	-1.79
Comparison vs. Placebo, <i>P</i> -value at Week 8, Adjusted Mean Change		<0.0001		<0.0001

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.

**IPR-V3 assessed at Week 8 only.

Tertiary endpoints in VANISH-1 and VANISH-2 included response to treatment as determined by duplex ultrasound, by change from baseline in Venous Clinical Severity Score (VCSS), and by change from baseline in Venous Insufficiency Epidemiologic and Economic Study – Quality of Life (VEINES-QOL) score.

The physiological response to treatment, as measured by duplex ultrasound (duplex response), was defined as elimination of reflux through the SFJ and/or complete occlusion of all incompetent GSV and major accessory veins at baseline. The primary comparison for duplex response in both studies was the pooled Varithena™ groups versus the Varithena™ 0.125% (control) group. Results are shown in [Table 7](#).

Table 7: Response to Treatment as Measured by Duplex Ultrasound at Week 8, VANISH-1 and VANISH-2

Parameter	Treatment Group, %			Comparison of Pooled Varithena™* vs. Varithena™ 0.125% (control)
	Placebo	Varithena™ 0.125% (control)	Varithena™ 1.0%	P-value
Responders, VANISH-1**	5.4% (n=56)	42.1% (n=57)	80.4% (n=51)	<0.0001
Responders, VANISH-2	1.8% (n=56)	59.6% (n=57)	86.2% (n=58)	0.0002

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.

**In VANISH-1, a significant dose-response trend was evident between the percent of responders and the dose concentration of Varithena™ ($P<0.0001$).

VCSS is a clinician rating of severity of chronic venous insufficiency ranging from 0 to 30, where higher scores indicate more severe venous disease. In VANISH-1 and VANISH-2, the adjusted mean changes from baseline in VCSS at Week 8 in the Varithena™ 1.0% treatment groups were 3.70 and 5.05, respectively, compared with 0.75 and 1.52 points, respectively, in the placebo groups (Table 8). In both studies, the differences between these improvements were statistically significant ($P<0.0001$).

Table 8: Improvement in VCSS at Week 8, VANISH-1 and VANISH-2

	VCSS			
	VANISH-1		VANISH-2	
	Placebo	Varithena™ 1.0%	Placebo	Varithena™ 1.0%
n	55	49	56	55
Baseline Score, mean	7.11	7.39	8.04	8.11
Adjusted Mean Change from Baseline at Week 8	-0.75	-3.70	-1.52	-5.05
Comparison vs. Placebo at Week 8, P-value		<0.0001		<0.0001

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.

VEINES-QOL is a disease-specific quality of life instrument, with scores ranging from 0 (worst possible quality of life) to 100 (best possible quality of life). In VANISH-1 and VANISH-2, the adjusted mean changes from baseline in VEINES-QOL in the pooled Varithena™ treatment groups were 21.2 and 21.6, respectively, at Week 8 compared with 7.7 and 7.4 points in the placebo groups, respectively. For both studies, the differences between these improvements are statistically significant ($P<0.0001$).

The efficacy of Varithena™ was consistent across age, sex, BMI (up to 48 kg/m²), CEAP clinical class, GSV diameter and VCSS subgroups for each efficacy endpoint evaluated.

Treatment with Varithena™ led to clinically meaningful improvements in primary and secondary endpoints.

DETAILED PHARMACOLOGY

Animal Studies

Safety Pharmacology

An extensive package of *in vitro* and *in vivo* safety pharmacology studies has been performed with polidocanol solution and foam.

At 10 mg/kg intravenous dose of polidocanol solution, blood in the urine was noted at 6 hours after dosing in male rats but this effect was no longer evident 24 hours after dosing. The 10 mg/kg dose is approximately 5 times the maximum human dose of 15 mL of Varithena™ 1.0% polidocanol on the basis of body surface area.

Intravenous administration of polidocanol solution at 20 mg/kg in the anesthetized dog slightly increased diastolic and mean blood pressure and increased P-Q and QRS interval. The NOAEL for cardiovascular effects in this study was 15 mg/kg (approximately 25 times the maximum human dose of 15 mL of Varithena™ 1.0% polidocanol on the basis of body surface area).

In a further cardiovascular pharmacology study conducted with a once weekly, for four weeks, intravenous bolus injection of Varithena™ in the conscious dog, dose levels of up to 8.0 mL/kg (approximately 17 times the human dose of 15 mL of Varithena™ 1.0% polidocanol based on body surface area) to beagle dogs caused only a transient, but consistent, effect on respiration, evidenced by a decrease in tidal volume and RMV at 15 minutes post-dose, resolving by one hour post-dose. Histopathology of the lung at the end of the 3 month follow-up period showed no abnormalities.

Clinical Pharmacokinetics

In one dedicated pharmacokinetics study, all patients were treated with the current, low-nitrogen formulation of Varithena™ that was used in the pivotal US Phase 3 studies and is planned for marketing. The Study was a 5-week, single-center, open-label, randomly assigned within gender, parallel-group study in which a 10 mL dose of two concentrations of Varithena™ (1.0% and 2.0%) was evaluated. Patients were assigned to receive either Varithena™ 1.0% (3 males and 6 females) or Varithena™ 2.0% (6 males and 6 females).

Patients had SFJ incompetence, incompetence of the GSV or other major accessory veins, and an expected need for treatment with at least 10 mL of Varithena™ to complete treatment of the incompetent GSV and tributaries. A standardized, fixed volume of Varithena™ was administered (i.e., two 5 mL injections 10 minutes apart).

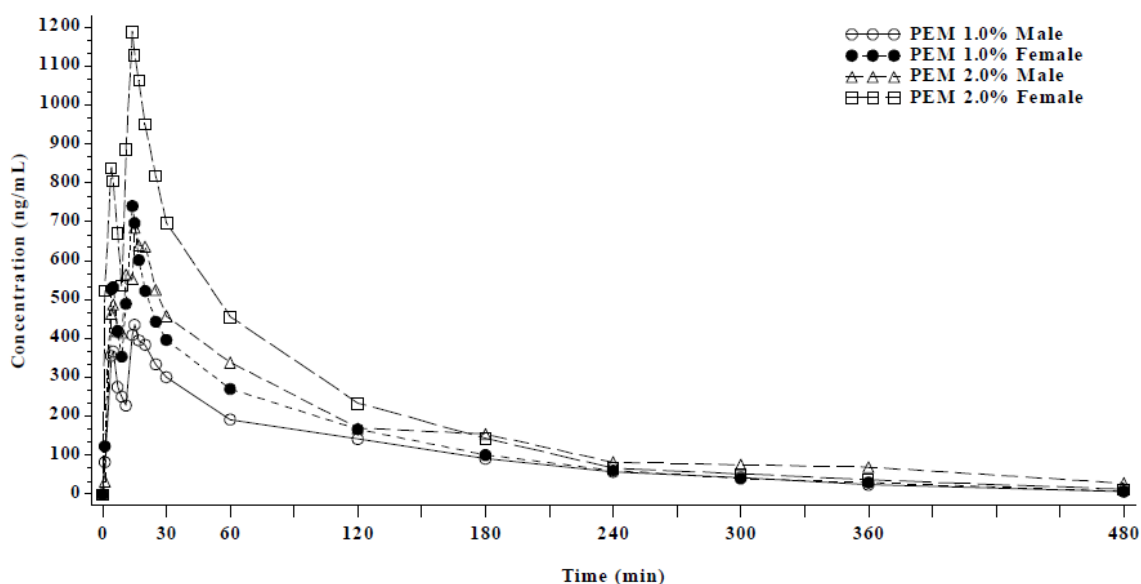
Patients randomized to receive Varithena™ 2.0% in received approximately 25% more polidocanol than is contained in the anticipated marketed maximum dose, 15 mL of Varithena™ 1.0% per treatment session.

The primary objective of this study was to determine the pharmacokinetic parameters of polidocanol, including maximum concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the concentration-time curve (AUC), clearance (CL), terminal rate constant (K_{el}),

volume of distribution (V_d) and elimination half-life ($T_{1/2}$) after administration of Varithena™ 1.0% or 2.0%. The absolute amount and percent of polidocanol eliminated unchanged in urine (A_e and $A_e\%$) were also determined.

Blood was obtained to determine the plasma concentrations of the 4 major polidocanol oligomers (E5, E9, E12 and E14 oligomers) and total polidocanol concentrations pre-dose and 1, 4, 5, 7, 9, 11, 14, 15, 17, 20, 25, 30, 60, 120, 180, 240, 300, 360 and 480 minutes following the initial injection of study drug. The mean plasma concentration-time curves for total polidocanol (linear scale) is presented by treatment and gender in Figure 1 (see also Table 3).

Figure 1: Mean Plasma Concentration-time Curves for Total Polidocanol by Treatment and Gender, Linear Scale (PK)



Polidocanol was rapidly detected in plasma following injection of Varithena™ into the incompetent GSV (or major accessory vein), reaching a peak within 4-5 minutes of the first injection, and reaching C_{max} within 15 minutes following the initial dose of Varithena™ and within 5 minutes of administration of the second injection.

Plasma polidocanol increased with increasing dose. Overall exposure following administration of Varithena™ as measured by C_{max} and AUC tended to be higher in the female patients, but weight-normalized data demonstrate no consistent gender differences.

Polidocanol appears in the plasma within 1 minute of injection and the majority was eliminated within 120 minutes, with most plasma samples below the LLOQ at the end of the 8-hour collection period. Approximately 19% of the dose was excreted in the urine in patients treated with Varithena™ 1.0%, and approximately 7% was excreted in the urine in

Serial electrocardiogram (ECG) measurements were obtained in triplicate pre-dose and at 4, 7, 9, 14, 17, 20, 25, 30, 60, 120, 240, 360 and 480 minutes following the initial injection of study drug. These ECGs were analyzed centrally for heart rate (HR) and for PR, QRS, QT, QT interval corrected according to the method of Fridericia (QTcF) and QT interval corrected according to the method of Bazett (QTcB) intervals. A pharmacokinetic/ pharmacodynamic (PK/PD) analysis using a mixed linear effects modeling approach was performed for all patients who had paired ECG and plasma concentrations of polidocanol and the 4 polidocanol oligomers.

The results of the PK/PD analysis showed a slight increase in heart rate 4-6 hours after dosing. There was no signal of any effect on atrioventricular (AV) conduction or cardiac repolarization as measured by the PR and QRS interval durations. There was no significant effect on cardiac repolarization as measured by the lack of a significant change in QTcF and the slightly positive slope for polidocanol and its constituents in the PK/PD model. This ECG analysis showed no evidence of a dose-related effect of Varithena™ on QTcF.

MICROBIOLOGY

Not applicable

TOXICOLOGY

Polidocanol solution, rather than foam, was used in a number of studies because of limitations on the volume of foam that could be injected and because of effects of the foam on the vein independent of the polidocanol. Bridging studies comparing polidocanol foam and polidocanol solution were performed, where applicable. Genotoxicity and reproductive toxicity studies were performed using polidocanol solution.

General Toxicity

Substantial multiples of the clinical dose could not be administered in repeat-dose toxicology studies due to dose-limiting local reactions at the injection site. The principal target organs for toxicity identified in the general toxicity studies were the cardiovascular and the respiratory systems. These results are presented in the **DETAILED PHARMACOLOGY** section (under **Safety Pharmacology**).

Genotoxicity

The genotoxicity of polidocanol was investigated in the standard battery of tests. Polidocanol solution was not mutagenic, clastogenic or an inducer of micronuclei in rodent hemopoietic cells. While polidocanol solution was shown to have a weak mutagenic effect in the mouse lymphoma tk mutation assay, this was only seen at highly toxic concentrations and in the presence of the metabolic activation system.

Carcinogenicity

No carcinogenicity studies were performed.

Effect on Fertility

There was no adverse effect on fertility in both male and female rats at 27 mg/kg/day. This dose level is approximately 13.5 times the maximum human dose of 15 mL of Varithena™ 1.0% based on body surface area.

Immunotoxicity

In the guinea pig study, there were no antigenic effects associated with administration of polidocanol solution up to 30 mg/kg (approximately 15 times human exposure at the maximum therapeutic dose of 15 mL of Varithena™ 1.0% based on body surface area).

Local Tolerance

The paravenous injection of 0.5 ml of 2% polidocanol and 2% polidocanol foam around the marginal ear vein of rabbits produced evidence of a local irritant effect which was less marked for polidocanol foam compared to polidocanol solution.

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PART III: PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE PATIENT MEDICATION INFORMATION

Varithena™

Polidocanol Injectable Foam

Read this carefully before you are treated with Varithena™. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment. Ask if there is any new information about Varithena™.

Serious Warnings and Precautions

- **Allergic reaction**

Varithena™ is a foam; one of the ingredients is polidocanol. Some people treated with polidocanol have had severe allergic reactions, and some of these people died. After you are treated with Varithena™, a healthcare professional will watch you for signs of an allergic reaction for at least 10 minutes.

- **Damage to skin and tissue**

Varithena™ should only be injected into veins. If it is injected into arteries or outside of the vein it can cause permanent injury to the skin or tissue. If this happens, urgent care is required. The damage may be worse if you already have artery disease.

- **Blood clots – Deep vein thrombosis**

Varithena™ can cause blood clots in the deep veins. Your healthcare professional will monitor you for signs of deep vein thrombosis, typically pain, swelling and blueness of the treated leg. If these symptoms develop after your treatment, see your doctor immediately.

Patients with the following have an increased risk of having a blood clot: difficulty walking, obesity, history of blood clots in the deep veins of the leg or in the lung, surgery in the last 3 months, long stay in the hospital, cancer, taking oral birth control or hormone replacement therapy, or smoking.

- **Mini-strokes**

Rarely, treatment of varicose veins has resulted in a mini-stroke (transient ischemic attack) or stroke. This has happened either minutes or days after treatment. These events have not been reported to date with Varithena. Your doctor will be trained to manage the factors that may increase the risk of this happening. If you know you have a hole in your heart, called a patent foramen ovale (PFO; a common birth defect of the heart that usually causes no problem) you are at greater risk and you should tell your doctor so he can carefully consider if Varithena™ is right for you.

What is Varithena™ used for?

Varithena™ (polidocanol injectable foam) is for the treatment of problems with the great saphenous vein and other saphenous veins and varicose veins of the great saphenous vein system. It is for the treatment of veins above and below the knee. It is only for use in adults with significant venous reflux that was diagnosed by a duplex ultrasound.

How does Varithena™ work?

Varithena will only be administered by a trained doctor. Varithena™ is injected directly into the failed veins and varicose veins. It pushes the blood out of the vein and the active ingredient (polidocanol) irritates the lining of the vein. This causes the vein to go into spasm destroying the lining of the vein, which is then closed. Over several months the vein is slowly resorbed by the body and eventually turns into a thin string of scar tissue.

What are the ingredients in Varithena™?

- Medicinal ingredients: The active product in Varithena™ is polidocanol, although carbon dioxide and oxygen are also required in order to generate the foam.
- Non-medicinal ingredients: ethanol, disodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate, and water for injection.

Do not use Varithena™ if you:

- Are allergic to polidocanol or any other ingredient in Varithena
- Have a blood clot in your superficial or deep veins (DVT) or have a recent clot in your lung (pulmonary embolism)
- Have blood clotting problems (thrombophilia)
- Are pregnant

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use Varithena™. Talk about any health condition or problems you may have, including if you:

- Had a stroke or mini-stroke (transient ischemic attack)
- Have blood pressure that is not controlled by your medications
- Have heart failure
- Have a hole in your heart, called patent foramen ovale (PFO; a common birth defect of the heart that does not usually cause a problem)
- Are pregnant or trying to become pregnant or are nursing
- Have problems with your liver or kidneys
- Have arterial disease (a disease of the blood vessels)
- Have chest pain or previous heart attack, or other heart disease,
- Can't walk well or for long
- Ever had a blood clot in your veins or lungs
- Had major surgery in the past 3 months
- Recently had a long hospital stay

Varithena™ is not recommended for children and adolescents under 18 years of age.

Other warnings you should know about:

Some people have pain after treatment with Varithena. This pain could make it hard to use your legs, drive or operate machines. Talk to your healthcare professional about the activities you will be able to do after you are treated with Varithena. Tell your healthcare professional about how your leg feels after it is treated with Varithena.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known relevant interactions with Varithena™.

How to use Varithena™:

- Varithena™ will be injected directly into the affected veins of your leg by a trained healthcare professional. A local anesthetic to numb the pain in your leg may be used.
- The procedure will be controlled using ultrasound scanning
- You may require several injections during one treatment session, and may require several treatment sessions to completely treat all veins. Each treatment session will be separated from the next by at least 5 days.
- After treatment, bandages and a compression stocking will be applied. These should be worn without taking them off for 48 hours. Then, only the compression stocking should be worn for the next 12 days.
- You should walk for at least 10 minutes each day after treatment.

Usual Dose

- The amount of Varithena™ injected is carefully controlled by the healthcare professional by using ultrasound to see that the foam has filled the veins being treated. When the veins are filled, the treatment is complete. This will depend on the size and extent of your varicose veins.

Overdose:

The amount of Varithena™ administered is adjusted and monitored by the doctor.

If you feel any discomfort during treatment with Varithena™ tell your doctor immediately.

What are possible side effects from using Varithena™?

These are not all the possible side effects that you may feel when using Varithena™. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects seen with Varithena™ are:

- Pain, bruising, swelling at the site of injection;
- Brown staining of the skin where the vein has been treated (skin discoloration);
- Leg pain, discomfort and/or swelling;
- Blood clot in the treated vein; removal of this clot may be required;

- Headache;
- Chest pain or discomfort;
- Skin irritation, including rash, itching and/or red patches of skin;
- Muscle spasms;
- Sore joints

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON Blood clot at injection site	X		
COMMON Deep Vein Thrombosis: significant swelling, redness or pain in your treated leg which might indicate blood clot in your deep venous system		X	
RARE Neurological disorders, such as stroke or mini-stroke (transient ischemic attack): If any of these symptoms appear suddenly: trouble speaking trouble seeing in one or both eyes, feeling confused, trouble speaking or difficulty understanding speech, trouble walking, dizziness or loss of balance, numbness or weakness of the face or leg			X
RARE Tissue Ischemia and Necrosis Your skin can be seriously damaged if your doctor accidentally injects Varithena into tissue outside of the vein or into an artery			X
UNKNOWN Severe allergic reactions (anaphylaxis): rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Varithena™ is stored by the hospital or clinic where you receive the treatment. The doctors and hospital pharmacists are responsible for this.

If you want more information about Varithena™:

- Talk to your Healthcare Professional
- Find the full Product Monograph that is prepared for Healthcare Professionals and includes this Patient Medication Information by visiting the [Health Canada website](http://www.hc-sc.gc.ca) (<http://www.hc-sc.gc.ca>). For questions or to report problems please contact BTG Customer Services by calling 1-844-282-1284 or email pharmacovigilance@btgplc.com.

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Last Revised: October 20, 2017

VarithenaTM

(polidocanol injectable foam)

VarithenaTM Delivery System

Instructions for Use

Please read the Product Monograph before using the product.

The Instructions for Use are for the entire VarithenaTM system. There are 2 packaging configurations:

- **Option A:** Bi-Canister box and Administration Pack (Varithena Transfer Unit, silicone-free syringes, manometer tubing and compression pads).*
- **Option B:** Convenience box (Bi-Canister Box + 3 Ancillary Packs + 3 VarithenaTM transfer units)*
*The components in each packaging configuration are to be used only in conjunction with each other for activation of VarithenaTM.
Administration Packs can be used for either configuration for further treatment sessions.

Important Facts

- Do not shake VarithenaTM canisters.
- A canister of VarithenaTM generates 90mL of foam which, following purging instructions contained in this IFU, is sufficient to yield 45mL of usable foam for injection. The gas mix of the foam is 65:35 O₂:CO₂.
- Always write the activation date and time on the canister and verify the product has not expired prior to use.
- Once the VarithenaTM canister has been activated, the shelf life for the product is thirty (30) days. The activated VarithenaTM canister should always be stored with a VarithenaTM transfer unit in place in the upright position at 20-25°C, with excursions permitted between 15 and 30°C

WARNINGS:

- As the foam fills the syringe and before injecting, inspect the syringe full of foam for any visible bubbles. If there are any present, the foam should be emptied into the VarithenaTM transfer unit waste chamber and the syringe refilled.
- A new VarithenaTM transfer unit must be used for each treatment session.
- Use a new sterile syringe after each injection. Only fill a syringe with foam immediately before it is required as the must be used within 75 seconds of generation or discarded and new foam generated, as the foam quality begins to deteriorate.

Unpacking Varithena™:

Option A: Bi-Canister Box and Administration Pack

Gather all the items needed for the generation of foam: the Varithena™ Bi-Canister box (Figure 1a), Administration Pack (including: Varithena™ transfer unit, silicone-free syringes, manometer tubing, and compression pads) (Figure 1b), and the following items that are not supplied: scissors, pen, sterile alcoholic wipes, timer and gloves (Figure 1c).

Open the Varithena™ Bi-Canister box and remove the Varithena™ Bi-Canister pouch. Open the Administration Pack and remove the components. Inspect the pouch and components for damage (do not use product if there are any visible signs of damage to pouch or components).

Figure 1a - Varithena™ Bi-Canister Box

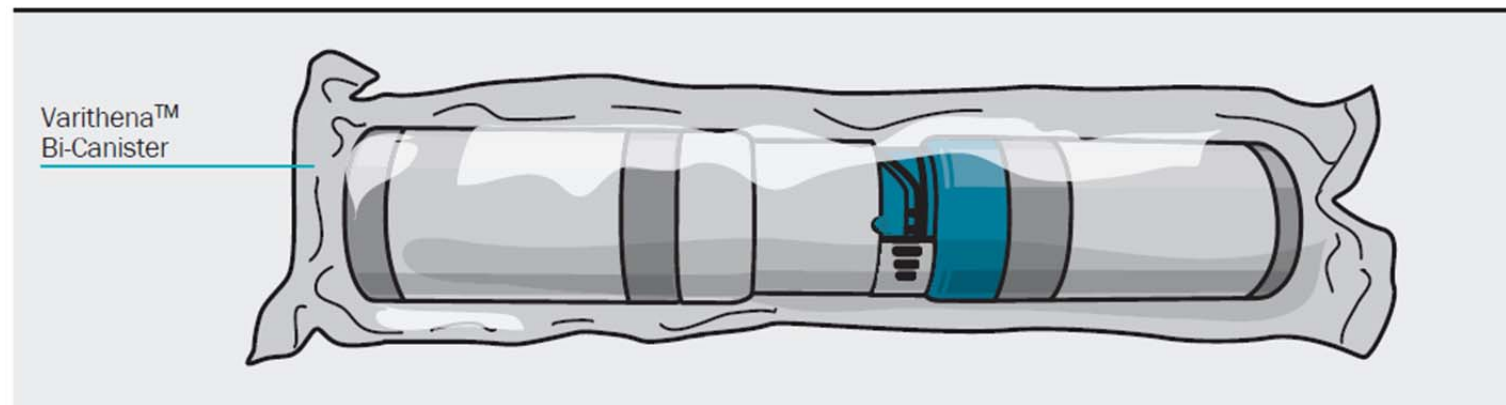


Figure 1b - Administration Pack

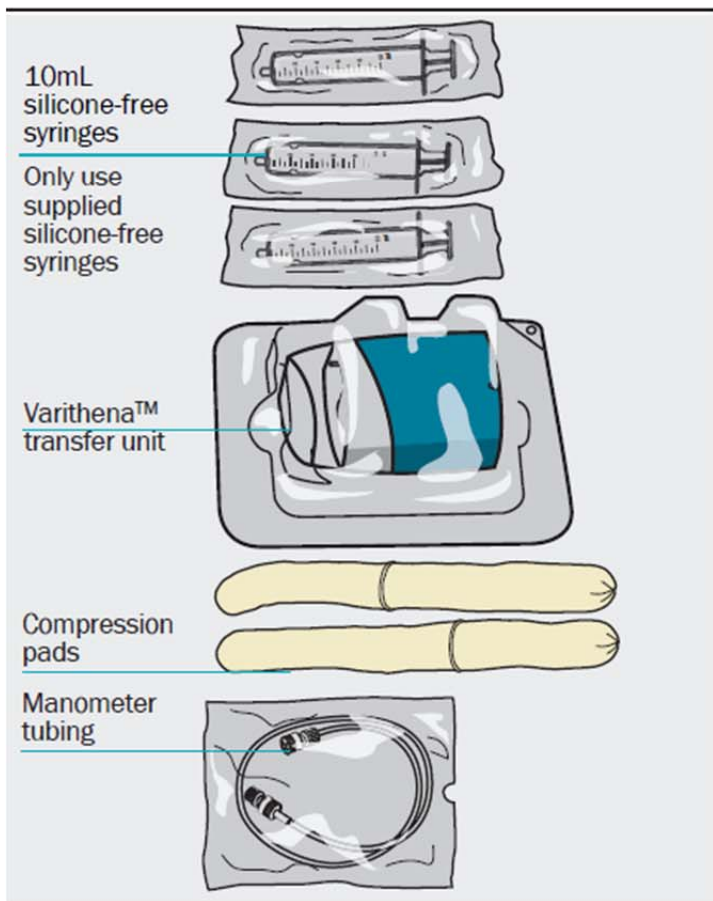
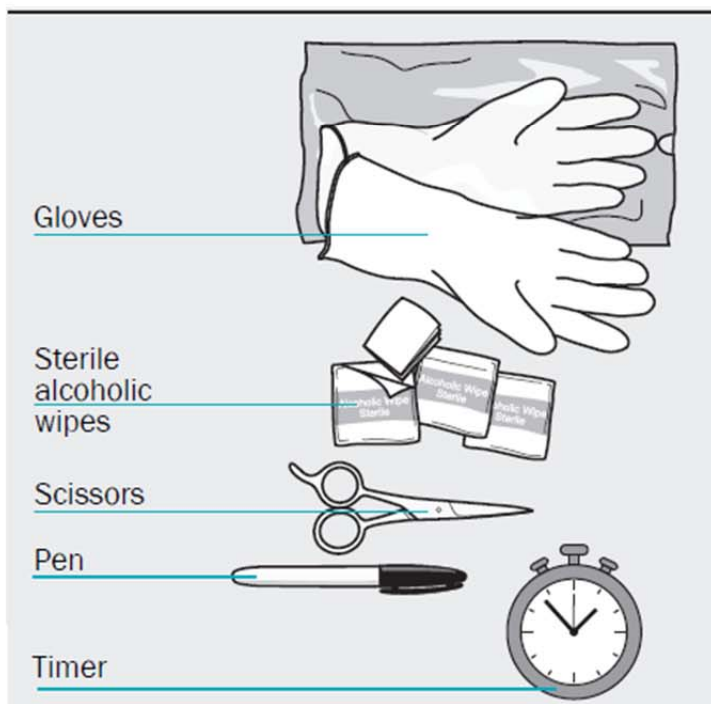


Figure 1c - Additional Procedure Items
(not supplied)



Unpacking Varithena™:

Option B: Convenience Box (Bi-Canister Box + 3 Ancillary Packs + 3 Varithena™ transfer units)

Gather all the items needed for the generation of foam: the Varithena™ Bi-Canister Box (Figure 2a), Ancillary Pack (including silicone-free syringes, manometer tubing, and compression pads (Figure 2b) and Varithena™ transfer unit (Figure 2c), and the following items that are not supplied: scissors, pen, sterile alcoholic wipes, timer and gloves (Figure 2d).

Open the Varithena™ Convenience box and remove all the components. Open the Varithena™ Bi-Canister box and remove the Varithena™ Bi-Canister pouch. Open an Ancillary Pack and remove the components. Inspect the pouch and components for damage (do not use product if there are any visible signs of damage to pouch or components).

Figure 2a - Varithena™ Bi-Canister Box

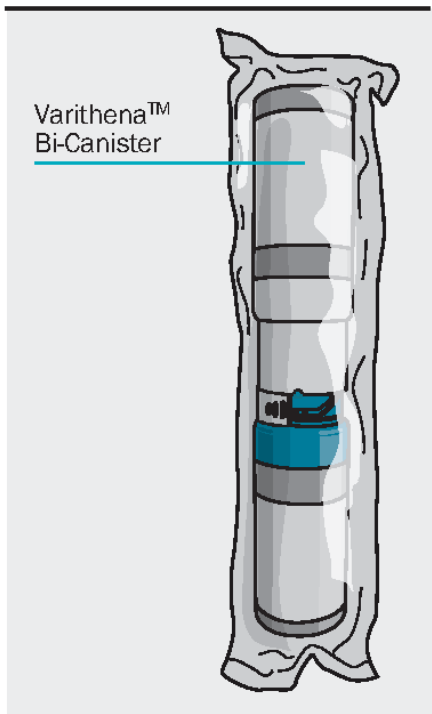


Figure 2b - Three Ancillary Packs

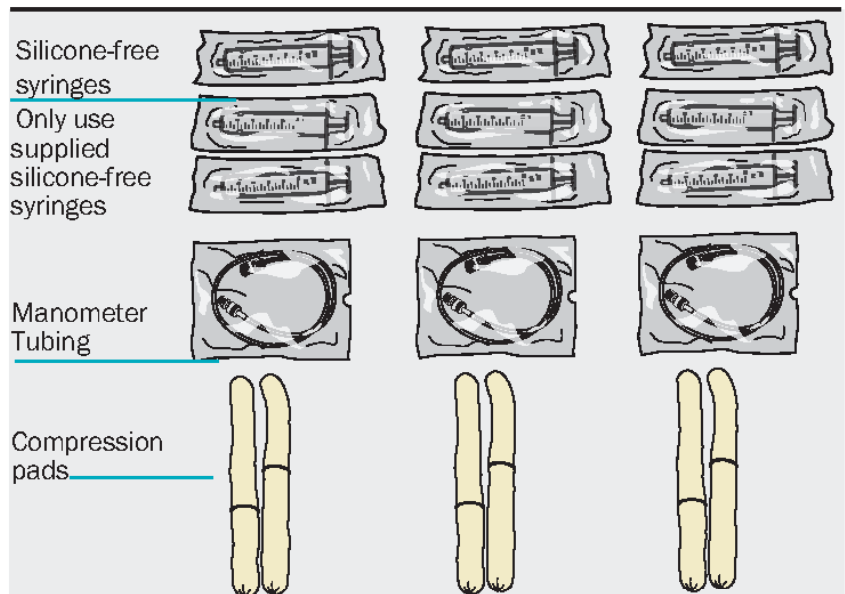


Figure 2c - Three Varithena™ transfer units

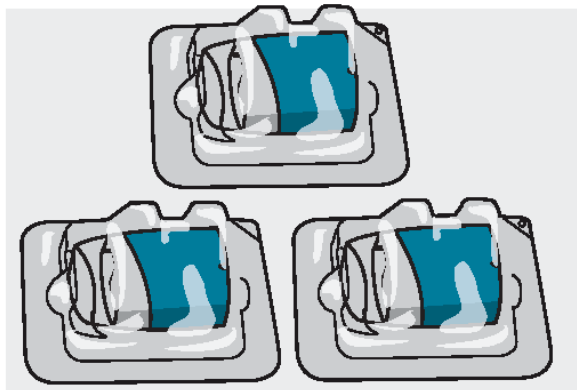
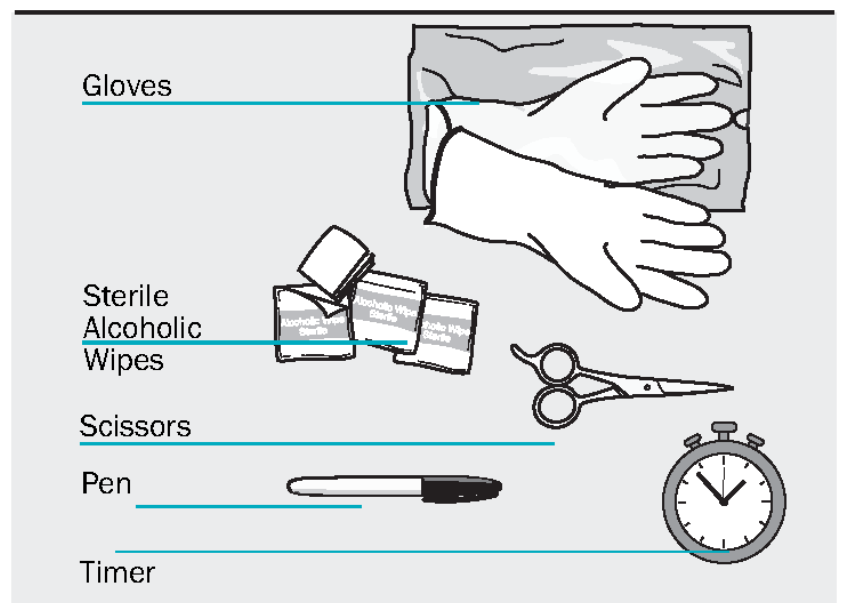


Figure 2d - Additional procedure items (not supplied)



Preparing the Patient

Preparations for treating the patient with Varithena™ should include the following steps:

- Position the patient comfortably on the treatment table in a supine position with their hip externally rotated to facilitate access to the GSV.
- Use ultrasound to find the best site for venous access.
- Using an aseptic technique, infiltrate the skin over the venous access point with local anesthetic.
- Obtain venous access under ultrasound guidance.
- IV catheters that are 16 to 22 gauge and 40 - to 50 - mm long or micropuncture sets are recommended for venous access.
- Prefill the manometer tube with sterile heparinised normal saline solution and connect to the IV catheter.
- Confirm venous access by aspirating with a syringe, blood should be dark and under low pressure.
- Flush the IV catheter and manometer tube with heparinised normal saline and secure it to the skin with adhesive tape, leave the saline syringe connected.
- With the IV catheter in place and secure, place the patient supine and elevate the leg to approximately 45 degrees.

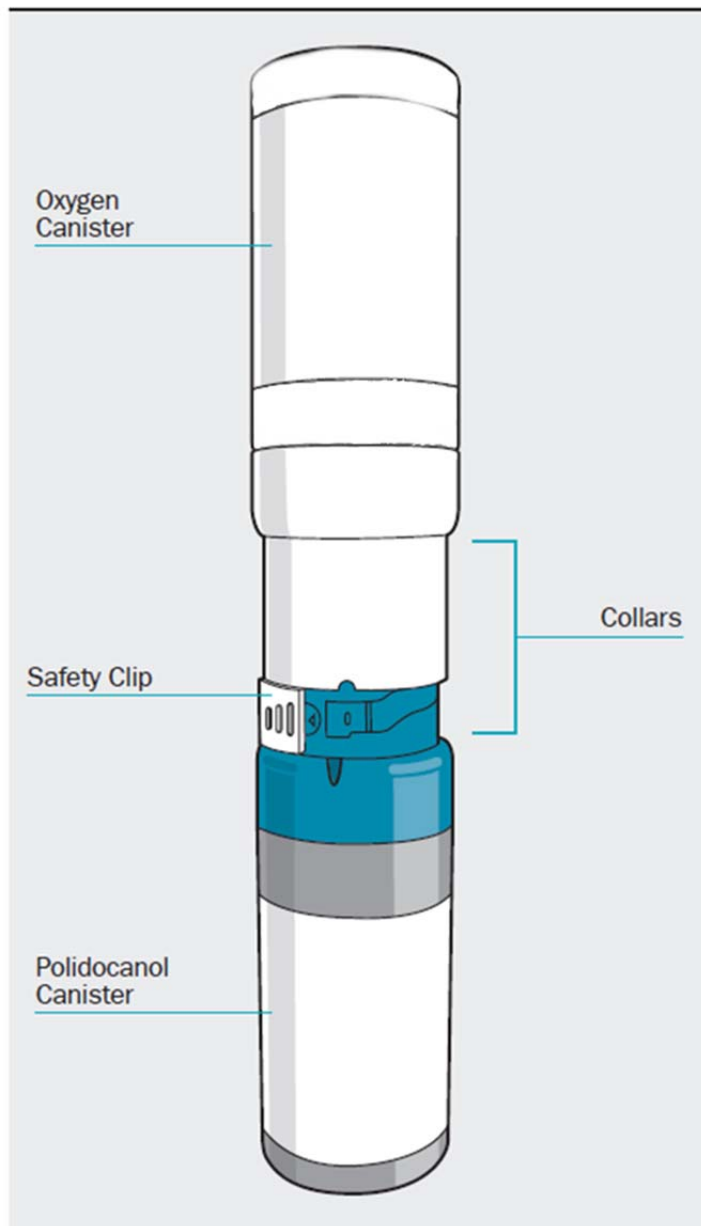
Preparation of the patient must be completed before generation of the foam.

Varithena™ Preparation

1

Open Bi-Canister pouch using a pair of scissors. Place canisters upright on a clean stable surface with the white oxygen canister on top (Figure 3). Discard empty pouch.

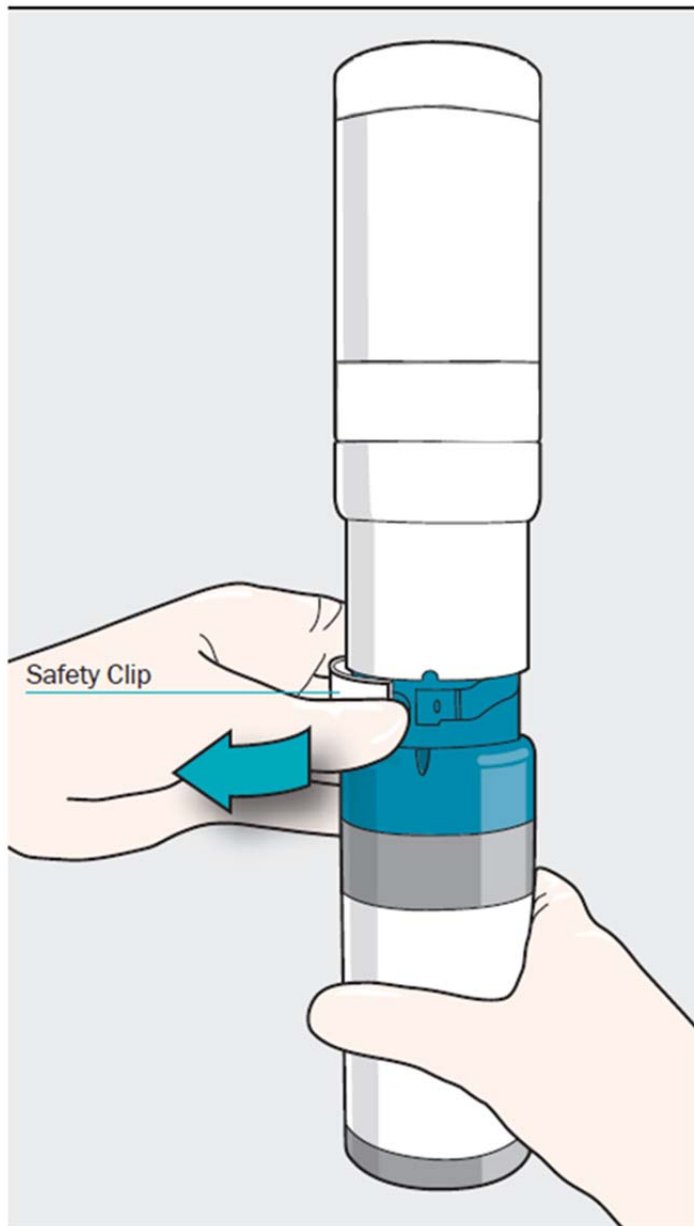
Figure 3



2

Remove the safety clip by lifting one corner of the clip out (Figure 4). Discard the safety clip.

Figure 4



Gas Activation of the Varithena™ Canister

3

To begin the gas transfer, twist the canisters together clockwise (Figure 5) until they come to a stop and the small indicators/marks on the collars are aligned (Figure 6). You may hear a bubbling sound.

While the canisters are activating, keep them upright on a clean flat surface for 1 minute. Use a timing device to keep track of the 1 minute time.

Figure 5

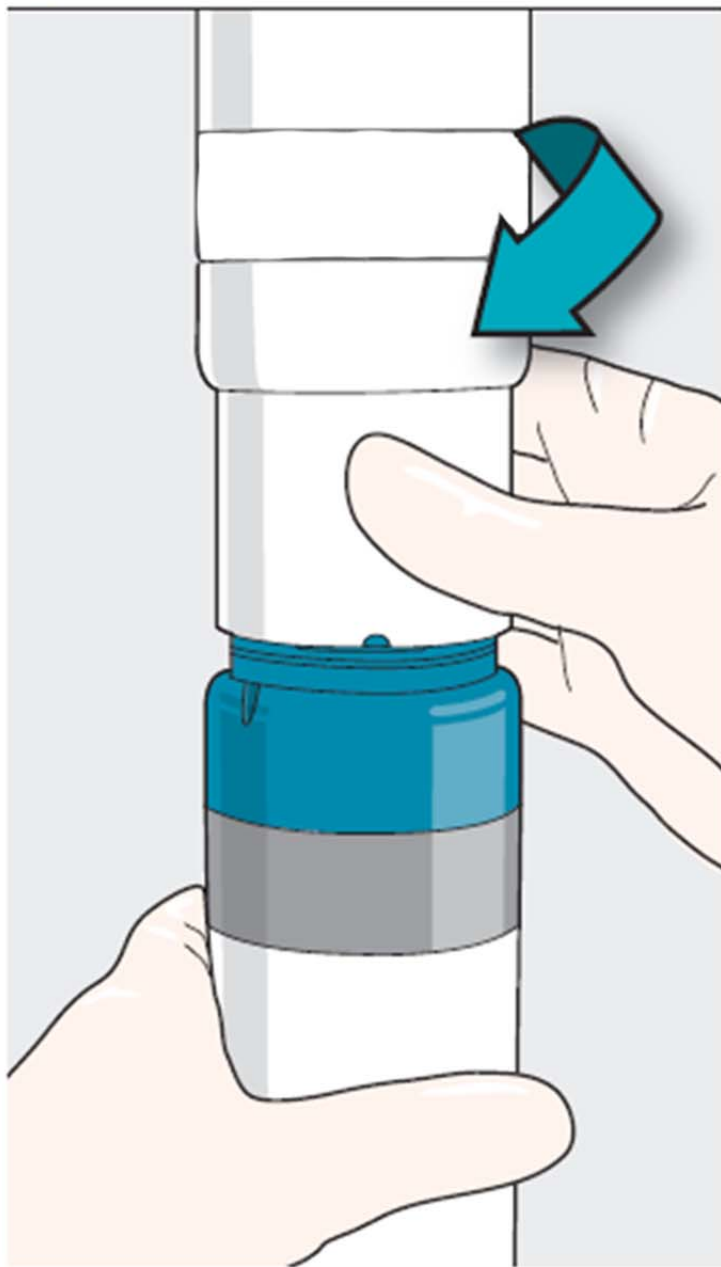
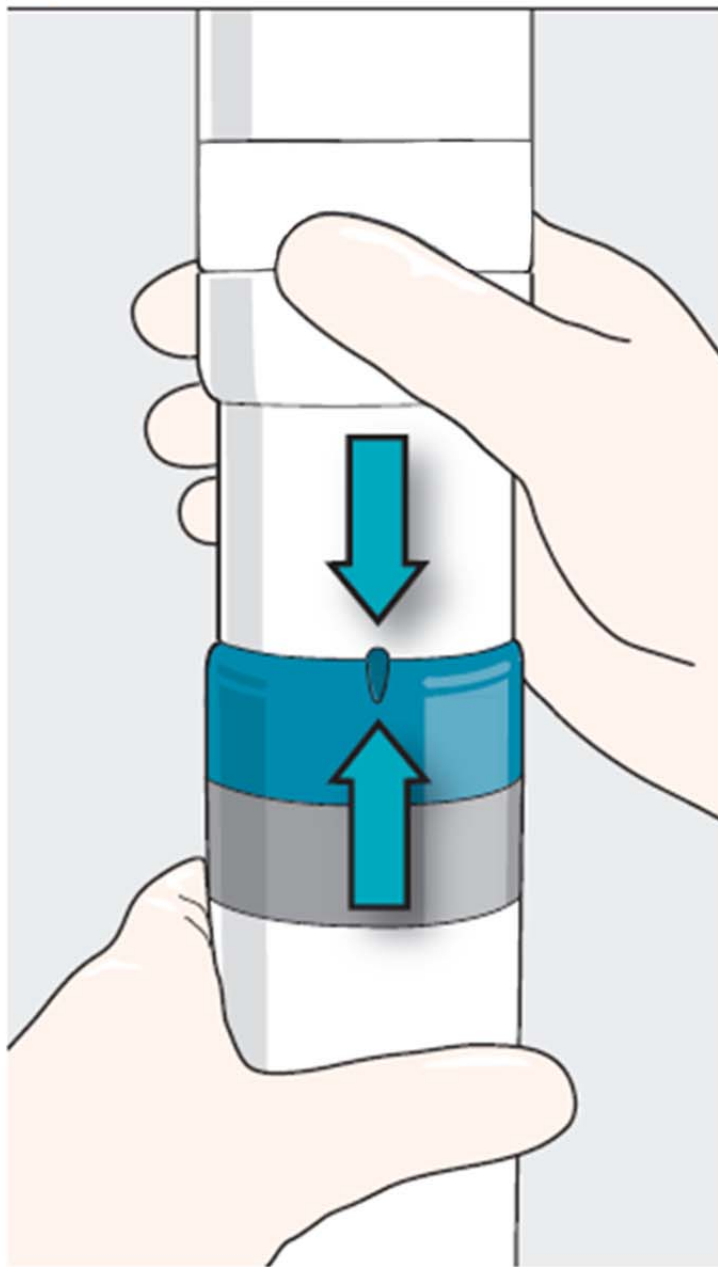


Figure 6



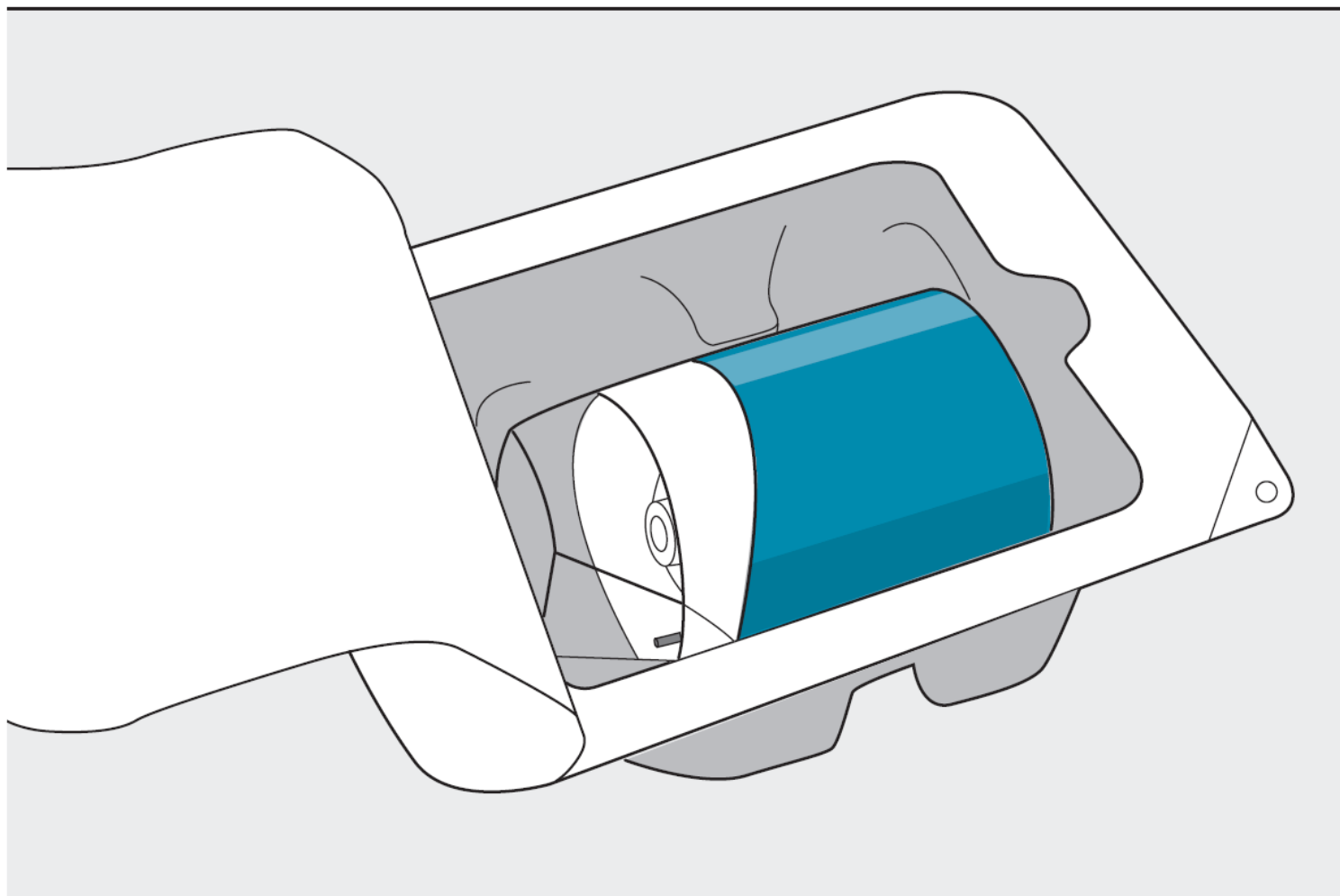
Gas Activation of the Varithena™ Canister

4

Note: In order to maintain sterility of the Varithena™ transfer unit, the following steps must be followed. While waiting 1 minute for the gas transfer, open a new Varithena™ Transfer Unit, blister pack, but leave the Varithena™ transfer unit in the package (Figure 7).

The manometer tubing should have been previously filled with sterile heparinised normal saline solution.

Figure 7



Gas Activation of the Varithena™ Canister

5

After 1 minute,

- Twist the two canisters by turning them in the opposite direction (counter clockwise) as before (Figure 8).
- Pull straight up to separate the oxygen canister from the Varithena™ canister, as shown (Figure 9). Do not separate canisters until you have a Varithena™ transfer unit ready to place onto the Varithena™ canister (As per step 4).
- Put the oxygen canister (with white collar) aside.
- The Varithena™ canister (with blue collar) should remain on a clean flat surface, in the upright position.

Figure 8

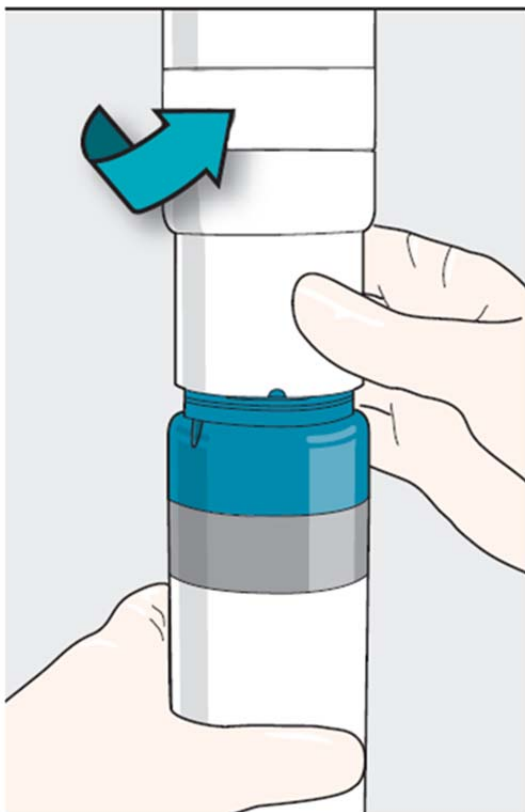
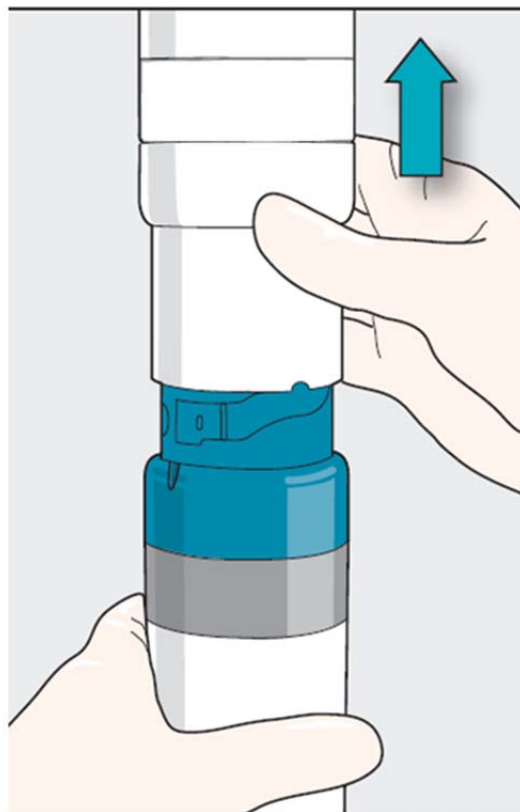


Figure 9



Write today's date and time in the "Date and Time of Activation" box on the Varithena™ canister label (Figure 10).

Figure 10



Connecting a new Varithena™ transfer unit and syringe

6

Remove the Varithena™ transfer unit from the blister pack. Make sure not to touch the sterile underside of the Varithena™ transfer unit, (discard Varithena™ transfer unit if contaminated).

Immediately place the Varithena™ transfer unit on top of the blue Varithena™ canister. Gently rotate the Varithena™ transfer unit clockwise as indicated (Figure 11) until it drops into the collar threads then twist the Varithena™ transfer unit (clockwise) until it reaches a stop (Figure 12).

Figure 11

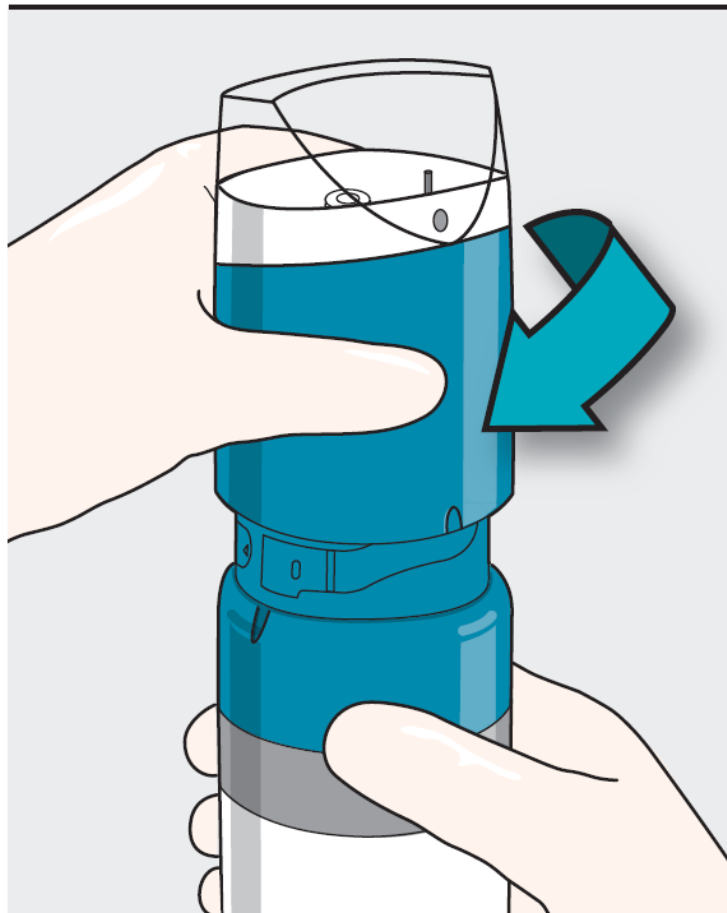
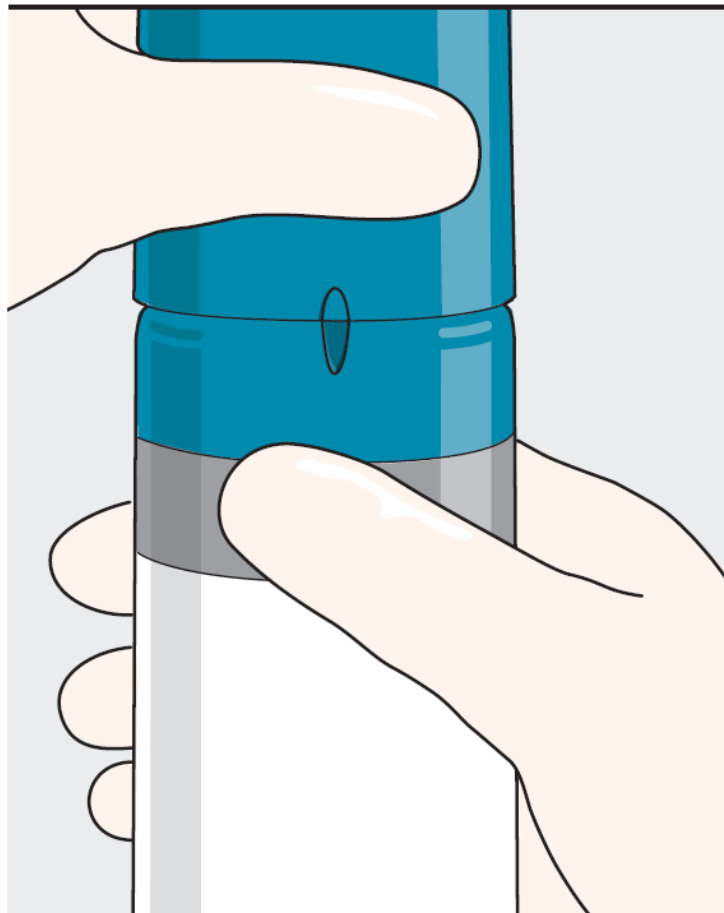


Figure 12



The system is now activated and ready for use.

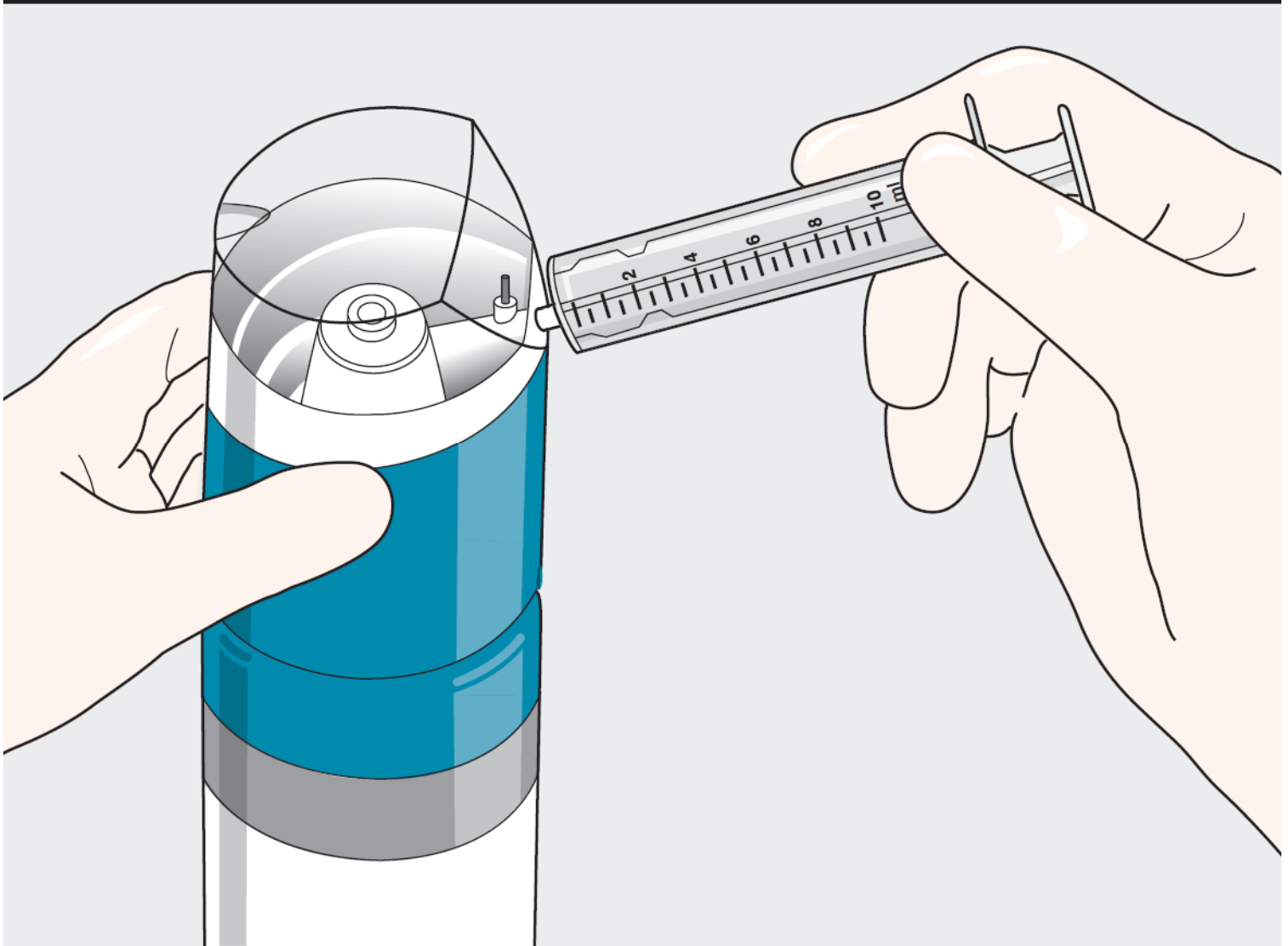
Connecting a new Varithena™ transfer unit and syringe

Once all preparations for injection are complete, i.e., cannula *in situ*, patient's leg elevated and a good ultrasound view of the saphenofemoral junction (SFJ) obtained, foam may be generated for immediate use.

7

Open a sterile 10mL silicone-free syringe package and keep it in the package until needed. Remove the syringe from the package, and connect it to the Varithena™ transfer unit as shown (Figure 13).

Figure 13



Priming a New Syringe

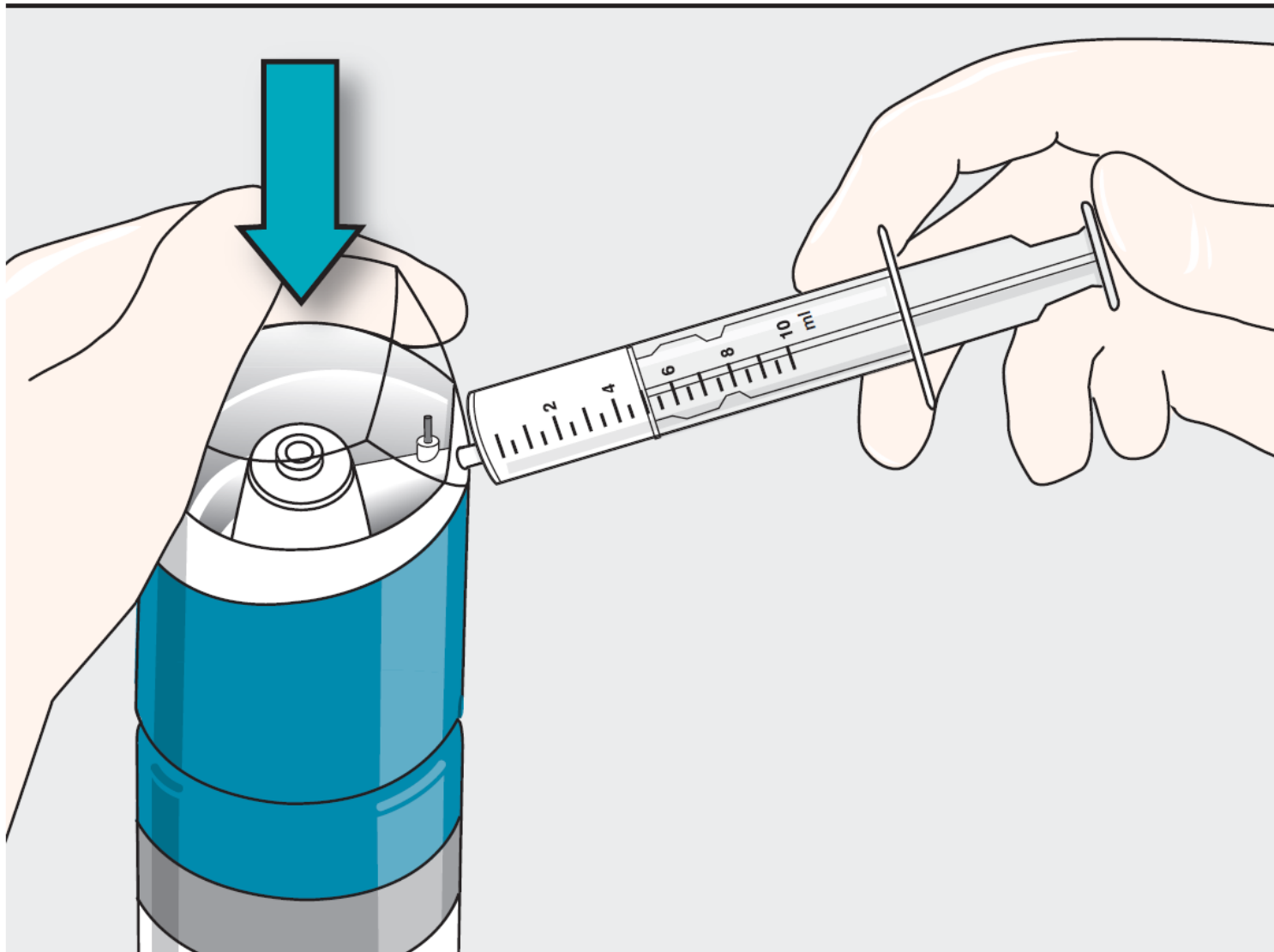
8

Gently press down the Varithena™ transfer unit to begin producing foam (Figure 14).

Using continuous pressure, allow the silicone-free syringe to fill between 3mL and 5mL.

Release the pressure on the Varithena™ transfer unit and leave the syringe connected.

Figure 14



Priming a New Syringe

9

Push the silicone-free syringe plunger in fully to discard its contents (Figure 15). Do not disconnect the syringe.

Note: The foam will automatically be diverted into the waste chamber within the Varithena™ transfer unit (Figure 16). This process eliminates the small quantity of air in the syringe and Varithena™ transfer unit.

Figure 15

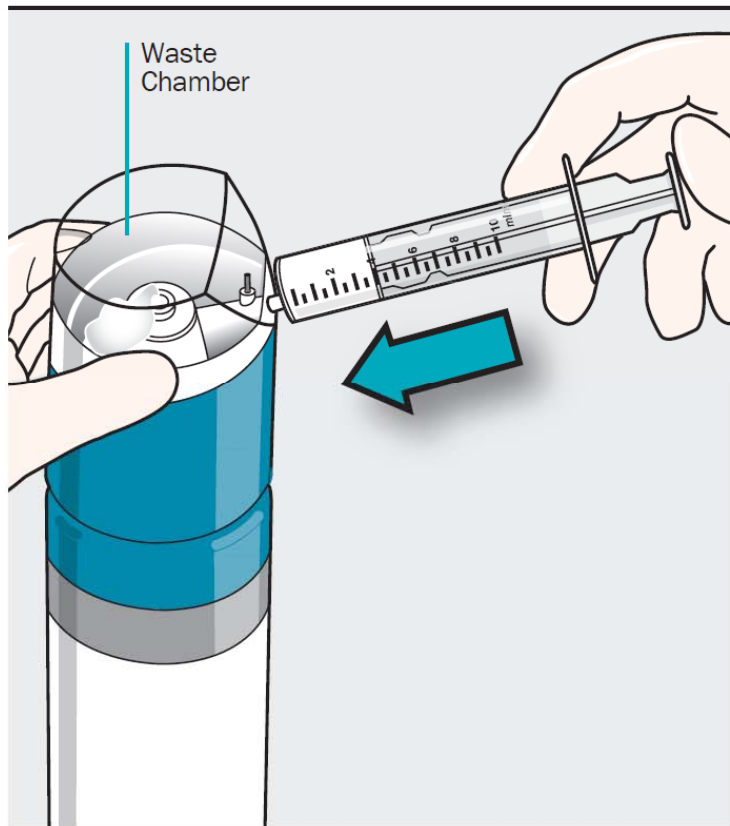
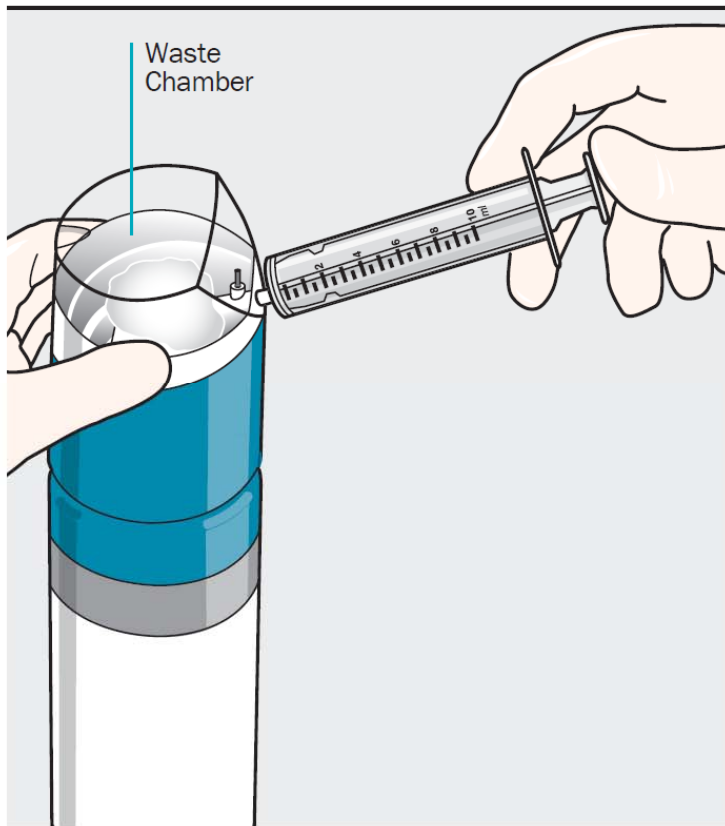


Figure 16



Generation of Foam

10

Foam Generation: The technique to produce usable foam requires a single purge cycle before filling the syringe, a process that takes less than 1 second.

Important Note: Foam must be generated by pushing down on the Varithena™ transfer unit continuously without pulling back on the plunger of the syringe (aspirating).

While holding the silicone-free syringe plunger in place, gently press down on the Varithena™ transfer unit to begin the purge cycle (Figure 17).

Visually inspect the flowing foam inside the Varithena™ transfer unit to make sure the visible air bubbles have been expelled (less than 1 second) before releasing the syringe plunger and allowing it to fill to the desired volume (Figure 18).

Draw up to 5mL of foam into the syringe.

Figure 17

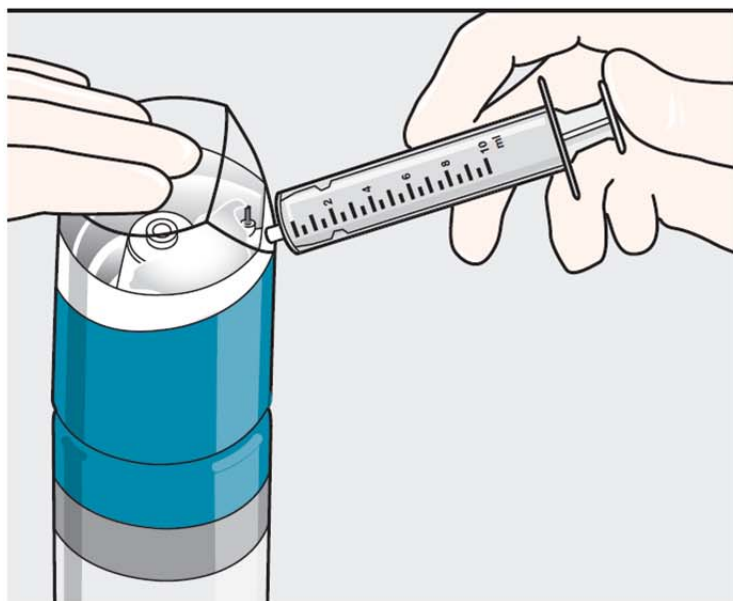
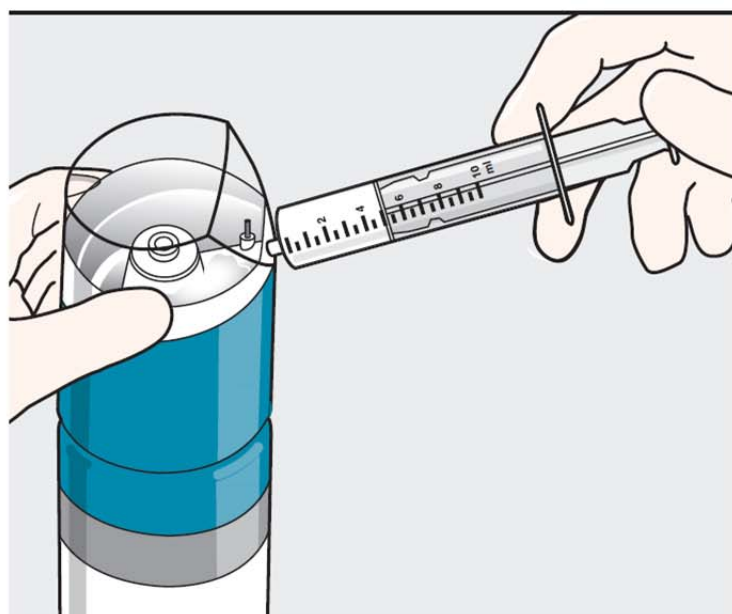


Figure 18



Inspecting and Injecting Foam

11

After the silicone-free syringe has filled to the desired volume, **wait 10 seconds** to allow the pressure to equalize before removing the syringe from the Varithena™ transfer unit (Figure 19).

WARNING: As the foam fills the syringe and before injecting, **inspect the syringe full of foam for any visible bubbles** (easily seen with the unaided eye at arm's length). If there are any present, the foam should be emptied into the Varithena™ transfer unit waste chamber and the syringe refilled.

12

Remove the syringe from the Varithena™ transfer unit and inspect it for visible bubbles (Figure 20). If no visible bubbles are present then the foam is ready for use.

Foam must be used within 75 seconds of generation or discarded and new foam generated, as the foam quality begins to deteriorate.

WARNING: The total amount of foam injected in any one treatment session must not exceed 15mL, comprised of individual injections of up to 5mL each.

After each treatment session, mark-off on the canister label the number of aliquots of up to 5mL of usable foam drawn from the canister per step 11 (Figure 21).

13

Connect a syringe of freshly generated foam to the manometer tubing, which is already connected to the cannula, in preparation for the initial injection.

The manometer tubing should have been previously filled with sterile heparinised normal saline solution

Figure 19

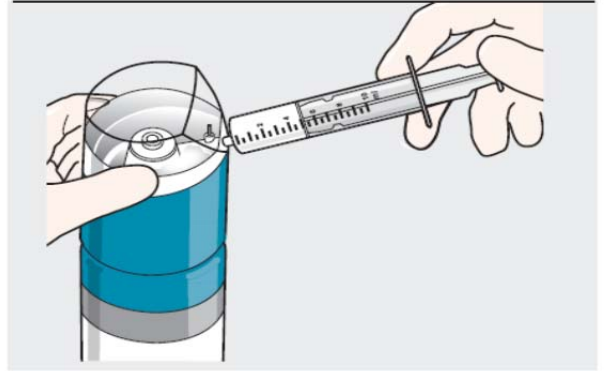


Figure 20

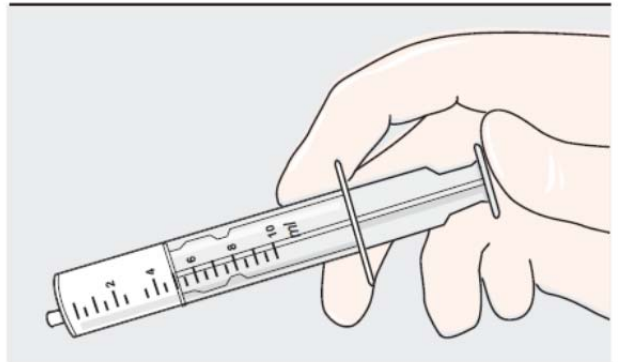


Figure 21



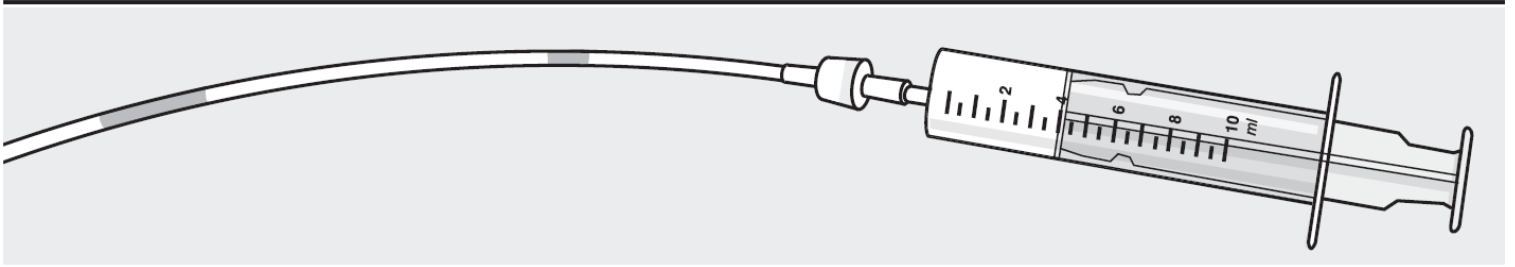
Inspecting and Injecting Foam

14

Inject the foam at approximately 0.5mL to 1.0mL per second through the manometer tubing. Five (5) mLs of foam should be injected in approximately 10 seconds. Always inspect the foam as it passes through the manometer tubing for visible bubbles (Figure 22). If any visible bubbles are seen (easily seen with the unaided eye at arm's length) they should be aspirated back into the silicone-free syringe and the syringe contents discarded back into the Varithena™ transfer unit waste chamber, and a fresh syringe of foam generated.

Notes: Use a new sterile syringe after each injection.

Figure 22



WARNING: The total amount of foam injected in any one treatment session must not exceed 15mL, comprised of individual injections of up to 5mL each

Do not remove Varithena™ transfer unit if the Varithena™ canister is to be stored (see Storage)

Compression Pads

15

Once treatment is complete, the Compression Pads should be used:

The objective of the pads is to focus the compression forces on the treated vein to keep them as free from blood as possible, thus minimizing retained thrombus.

The compression pads supplied should be placed along the course of the treated trunk vein in the thigh, and over raised treated varicose veins above and below the knee. The pads may be shaped to follow the course of the veins. The pads should be placed outside the first layer of limited stretch bandage and held in place by a second layer of bandage.

The appropriate length compression stocking is then applied.

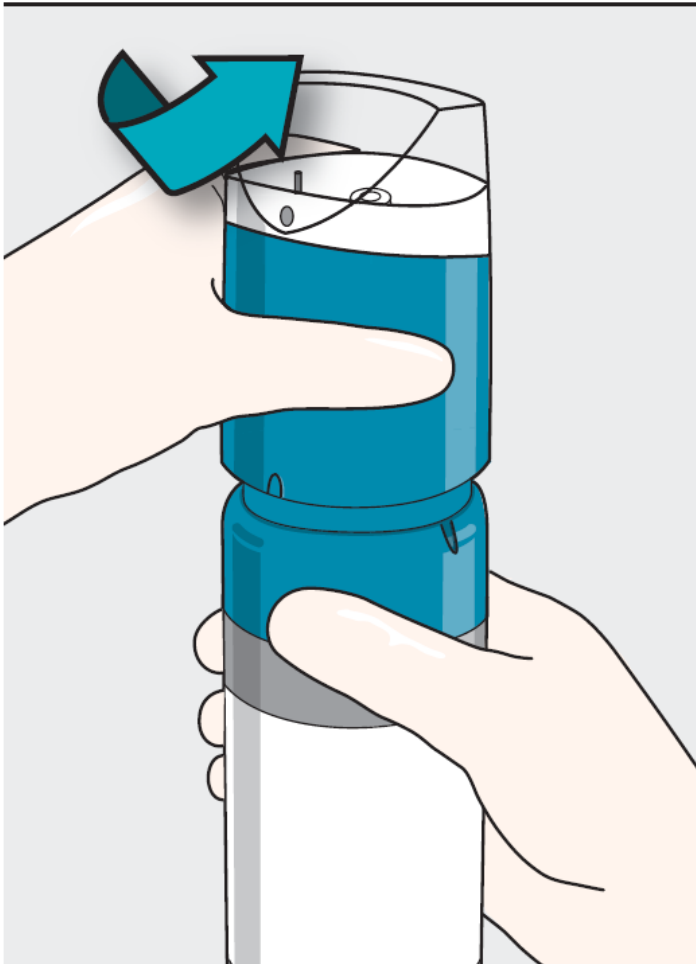
Replacing the Varithena™ transfer unit

Important Note: Do not replace the Varithena™ transfer unit if the canister is to be stored for future use. The activated Varithena™ canister should always be stored with a Varithena™ transfer unit in place in the upright position at controlled room temperature. Replace the Varithena™ transfer unit just prior to the next treatment session.

16

While holding the Varithena™ canister, twist the Varithena™ transfer unit counter clockwise then pull up to separate from the canister (Figure 23).

Figure 23



17

Discard the old Varithena™ transfer unit and open a new Varithena™ transfer unit.

Make sure not to touch the sterile underside of the Varithena™ transfer unit.

Replacing the Varithena™ transfer unit

18

Swab the uncovered shuttle of the canister with a fresh sterile alcohol wipe (Figure 24) and immediately place the Varithena™ transfer unit on top of the Varithena™ canister.

Gently rotate the Varithena™ transfer unit clockwise until it drops into the collar threads (Figure 25), then twist the Varithena™ transfer unit (clockwise) until it reaches a stop (Figure 26).

Figure 24

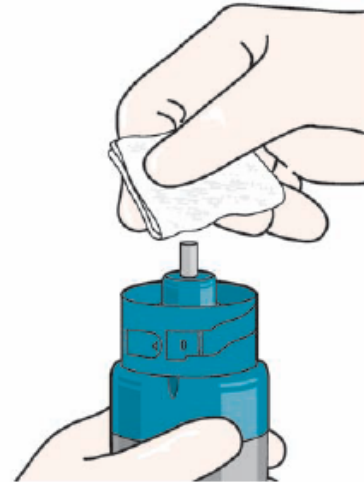


Figure 25

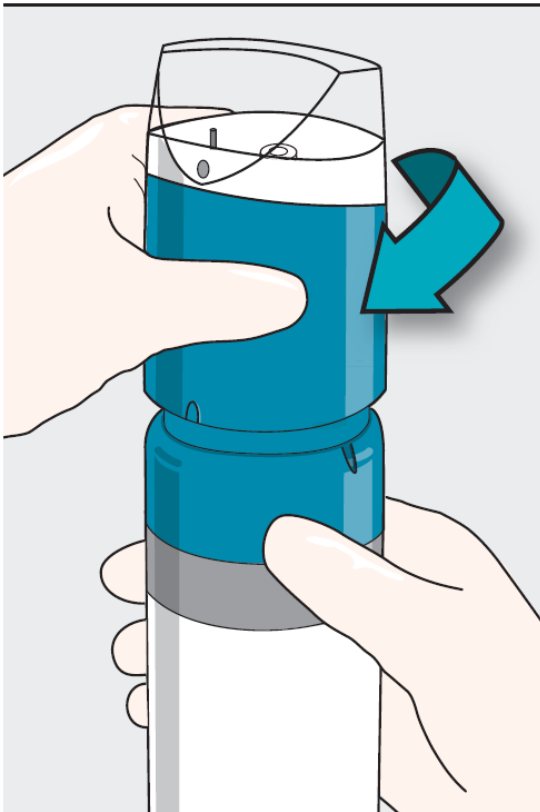
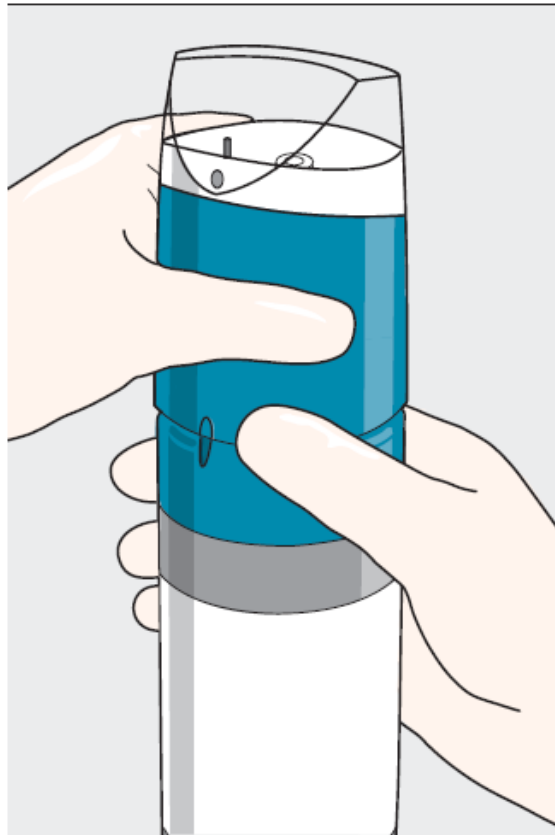


Figure 26



The Varithena™ device now ready for use for a new treatment session, following the instructions in Steps 7 to 15.

Storage and Disposal

Note: Once activated, the canister of Varithena should be stored at room temperature in the upright position, and used within 30 days.

The activated Varithena™ canister should always be stored with a Varithena™ transfer unit in place in the upright position at controlled room temperature (20-25°C). Excursions permitted 15- 30°C.

Do not refrigerate or freeze

Always write the activation date and time on the canister and verify the product has not expired prior to use.

Dispose of Varithena™ and oxygen canisters following local and national regulations for aerosol disposal.

The Varithena™ transfer unit can be disposed of as non-toxic non-clinical waste.

Net Contents: 18ml

One canister of Varithena™ contains:

180mg Polidocanol, Ethanol 756mg (96%), disodium hydrogen phosphate dihydrate 43.2mg, potassium dihydrogen phosphate 15.3mg, water for injection.

One canister of Varithena™ generates 90mL of foam which, following purging instructions contained in this IFU, is sufficient to yield 45mL of usable foam for injection.

The gas mix of the foam is 65:35 O₂:CO₂.

Manufactured for Provensis Ltd by:

Biocompatibles UK Ltd

Chapman House, Weydon Lane, Farnham, Surrey, UK , GU9 8QL

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Varithena™
(polidocanol injectable foam)

