American Vein and Lymphatic Society
formerly the American College of Phlebology

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**Position Statement**
**Non-Compounded Foam Sclerotherapy**
**Healthcare Policy Committee**

***Revised: January 8, 2019***

## Introduction

Historically, treatment options for patients with venous insufficiency and varicose veins primarily consisted of high ligation and stripping of the great saphenous vein (GSV) in association with phlebectomy of individual varicosities. During the past 18 years, such painful interventions, which required general anesthesia along with several days in the hospital and weeks of recuperation, have been supplanted by outpatient office-based endovascular ablation techniques with conscious sedation and/or local anesthesia and an almost immediate return to normal activities of daily living. Such endovascular treatment of venous disease has been primarily performed with thermally-based radiofrequency or laser ablation that require percutaneous, perivenous tumescent anesthesia. They are superior to high ligation and stripping and are recommended by published multi-society guidelines for the treatment of the incompetent superficial axial incompetent veins (GSV, SS, AASV etc.) [Gloviczki P et al. ***The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum***. *J Vasc Surg.* 2011;53(5 suppl):2S-48S] With these approaches, patients achieve excellent vein occlusion rates and more importantly improved quality of life for years after intervention. Newer approaches seek to improve upon these currently available methods by achieving similar clinical outcomes without thermal energy and thus obviate the need for tumescent anesthesia. Elimination of tumescent anesthesia results in less intraoperative pain, no risk of nerve injury and minimal skin damage. The opportunity for physicians to have a choice of treatment options in order to choose the one that is optimal for an individual patient will result in the best outcomes in the treatment of venous insufficiency and varicose veins.

## Non-Compounded Foam Sclerotherapy: Varithena

With over 30,000 patients treated since launch and a comprehensive clinical development program in C2-C6 patients, Varithena® has proven itself to be an effective and safe option for medically necessary treatment for varicose vein disease. Since 2018, Varithena is described by an active category I CPT code (36465/36466) when used in truncal veins, and is now included in a majority of regional and national payer policies and local coverage decisions. Varithena affords physicians treatment flexibility with clinical data for treatment of venous insufficiency in any vein shape and a wide variety of diameters up to 25.9 mm above and below the knee(1, 4), including tortuous veins and for patients with recurrent symptoms after previous treatments, as well as veins that may not be accessible with other modalities. Varithena delivers proven outcomes and improvements related to how a patient feels, functions, and survives (1-4) with comparable closure rates (94%) (5) to endovenous procedures, including RFA or Laser Ablation (5). Since Varithena is relatively new, longer term data on vein closure with Varithena, e.g., 24-36 months, is subject to further trials and research. With Varithena, clinicians can treat the great saphenous vein and tributary branches in one visit. The Varithena procedure is a straightforward, minimally invasive procedure, eliminating the need to use potentially painful tumescent injections, which allows

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treatment of patients with as few as one or two access sites per treatment. Patient quality of life is an important outcome for all clinicians, and Varithena has a robust dataset to support its impact on patient reported outcomes (1-4). In the VANISH clinical trials, patients reported improved symptoms including heaviness, achiness, swelling, throbbing and itching (HASTI) following treatment with Varithena. In addition, patients with comorbidities and a history of prior vein procedures that have failed treatment or have advanced venous disease with significant symptoms, including ulceration will also benefit from Varithena. Varithena delivers a safe and effective option to comprehensively treat patients with chronic venous insufficiency suffering with C2-C6 disease.

**Conclusion**

The current published evidence, and FDA approval, support Varithena as a safe, effective and clinically meaningful option for the treatment of superficial venous disease when it is deemed to be medically necessary. The American Vein and Lymphatic Society, on behalf of our members and their patients, request that carriers cover Varithena for all FDA-approved indications with reimbursement commensurate with CMS valuation, or by contract with private payers. Attached are the clinical data and references to substantiate our recommendations.

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**References**

1. King JT, O'Byrne M, Vasquez M, Wright D, and Group V-I. Treatment of Truncal Incompetence and Varicose Veins with a Single Administration of a New Polidocanol Endovenous Microfoam Preparation Improves Symptoms and Appearance. Eur J Vasc Endovasc Surg 50: 784-793, 2015.
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**Number of peer-reviewed articles**

Currently, there are 11 peer-reviewed articles that have been published regarding the product and its safety and/or efficacy.

**Varithena Bibliography**

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11. Wright DD, Gibson KD, Barclay J, Razumovsky A, Rush J, and McCollum CN. High prevalence of right-to-left shunt in patients with symptomatic great saphenous incompetence and varicose veins. J Vasc Surg 51: 104-107, 2010.

**Year of FDA Approval**
Varithena® was approved by the FDA in November of 2013

**Date for First in Human Use**

The current FDA-approved formulation of Varithena® (<0.8% Nitrogen, 65%O2:35% CO2, 1:7 liquid to gas) was first administered to humans in August 2001 in a number of clinical studies (VAP.COM001 and VV005) with additional studies starting some months later (VV001).

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The first use in the post-approval setting was on the 11th of August 2014.

The period between the early use and the acquisition of a Marketing Authorization highlights the extensive clinical trial program that was developed and implemented in the US.

**Number of Units/Patients treated with technology**
More than 30,000 patients have been treated with Varithena® to date.

**Summary of pivotal studies**

Two pivotal Phase III studies were completed, VANISH-1 (King et al. 2015) and VANISH-2 (Todd et al. 2014).

VANISH-1

This multicenter, parallel group study was designed to determine if a single administration of 15 mL of pharmaceutical-grade polidocanol endovenous microfoam (PEM, Varithena®) could alleviate symptoms and improve appearance of varicose veins in a typical population of patients with moderate to very severe symptoms of superficial venous incompetence and visible varicosities of the great saphenous vein (GSV) system.

The primary endpoint was patient-reported venous symptom improvement measured by change from baseline to Week 8 in 7-day average VVSymQ score (Patient reported outcomes of Heaviness, Achiness, Swelling, Throbbing and Itching or HASTI).

Co-secondary endpoints measured improvement in appearance of visible varicose veins from baseline to Week 8, as measured by the Independent Photography Review of Visible Varicose Veins (IPR-V3) and Patient Self-assessment of Visible Varicose Veins (PA-V3) scores. Patients (N=284) were randomized to five groups: PEM 0.125% (control), 0.5%, 1%, 2%, or placebo. Adverse events (AEs) were recorded at each study visit.

Tertiary endpoints measured duplex ultrasound response, changes in venous clinical severity score (VCSS), and the modified Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VIENES-QoL). At Week 8, VVSymQ scores for the pooled PEM group (0.5%, 1%, 2%; $p < .0001$) and individual dose concentrations ($p < .001$) were significantly superior to placebo. Mean changes from baseline to Week 8 in IPR-V3 and PA-V3 scores were significantly greater for pooled PEM than for placebo ($p < .0001$). In this patient population treated with PEM, vein diameters ranged from 1.5 – 25.9 mm.

Most AEs were mild and resolved without sequelae. No pulmonary emboli were reported. This study demonstrated that a single administration of up to 15 mL of PEM is a safe, effective, and convenient treatment for the symptoms of superficial venous incompetence and the appearance of visible varicosities of the GSV system.

VANISH-2

The purpose of this Phase III pivotal study was to determine the efficacy and safety of polidocanol endovenous microfoam (Varithena®) in the treatment of symptoms and appearance in 230 patients with saphenofemoral junction incompetence due to reflux of the great saphenous vein or major

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accessory veins. Patients (N=235) were randomized equally to receive polidocanol endovenous microfoam 0.5%, 1.0% or placebo.

The primary efficacy endpoint was patient-reported improvement in symptoms, as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ score.

The co-secondary endpoints were the improvement in appearance of visible varicosities from baseline to Week 8, as measured by patients and by an independent physician review panel. In 232 treated patients, polidocanol endovenous microfoam 0.5% and polidocanol endovenous microfoam 1.0% were superior to placebo, with a larger improvement in symptoms (VVSymQ (-6.01 and -5.06, respectively, versus - 2.00; $P<0.0001$) and greater improvements in physician (IPR-V3) and patient (PA-V) assessments of appearance ($P<0.0001$). These findings were supported by the results of duplex ultrasound and other clinical measures.

Of the 230 polidocanol endovenous microfoam-treated patients (including open-label patients who received PEM after placebo), 60% had an adverse event compared with 39% of placebo; 95% were mild or moderate. No pulmonary emboli were detected and no clinically important neurologic or visual adverse events were reported. The most common adverse events in patients treated with polidocanol endovenous microfoam were retained coagulum, leg pain and superficial thrombophlebitis; most were related to treatment and resolved without sequelae.

Polidocanol endovenous microfoam provided clinically meaningful benefit in treating symptoms and appearance in patients with varicose veins. Polidocanol endovenous microfoam was an effective and comprehensive minimally invasive treatment for patients with a broad spectrum of vein disease (clinical, etiology, anatomy, pathophysiology clinical class C2 to C6) and great saphenous vein diameters ranging from 3.1 to 19.4 mm. Treatment with polidocanol endovenous microfoam was associated with mild or moderate manageable side effects. VVSymQ is an important new and validated instrument for symptom assessment in patients with varicose veins.