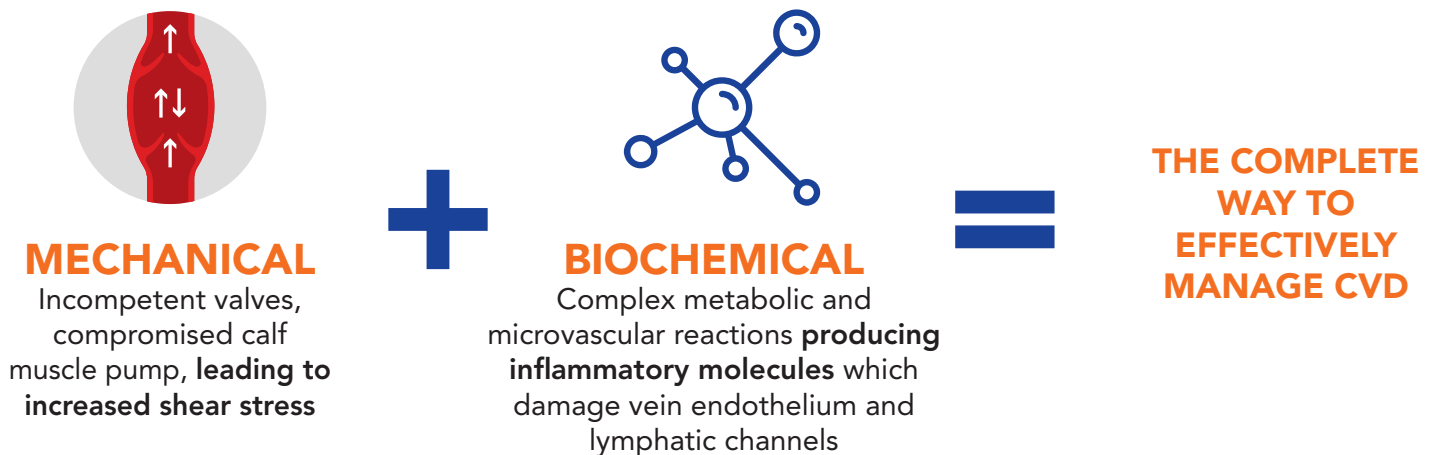


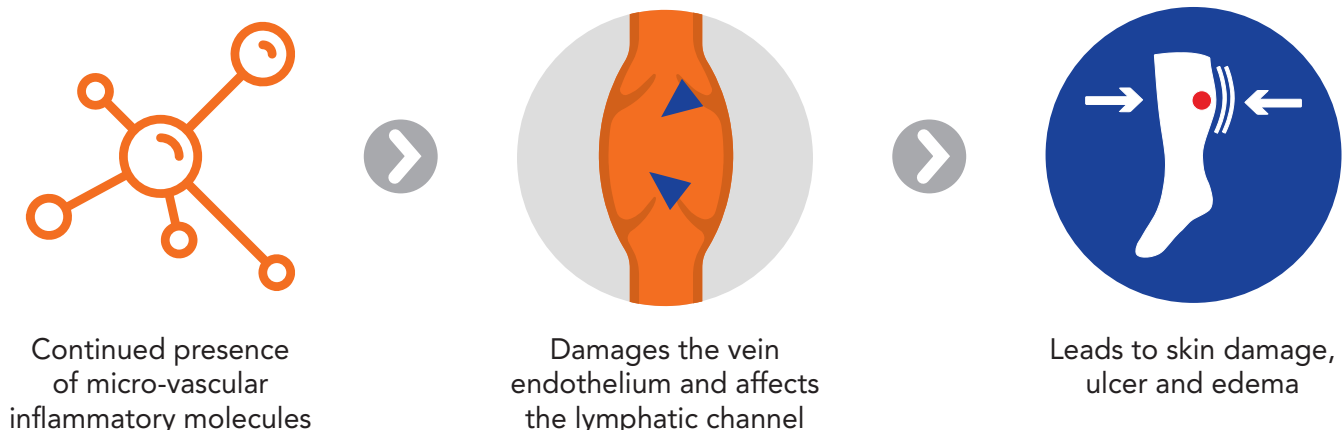
Pathophysiology of CVD: The Mechanical and Biochemical Pathways

While most treatments address the mechanical aspects of venous hypertension, only one addresses the inflammatory molecules



It's Vital to Address the Biochemical Pathway to Effectively Manage CVD

Accelerated disease progression can occur if the inflammatory molecules produced by venous hypertension are not downregulated



Vasculera is the Only Prescription Medication that Addresses the Biochemical (Inflammatory) Pathway Associated with CVD

- Contains safe, clinically-proven MPFF, with decades of use in Europe and recommended in international guidelines since 2008
- The only treatment that downregulates the inflammatory molecules produced by venous hypertension
- Unique mechanism of action affects the biochemical (inflammatory) pathway by decreasing leukocyte activation, downregulating VEGF expression and decreasing TNF- α , which results in improved symptoms of CVD and disease regression
- Randomized controlled studies have shown MPFF, an active ingredient in Vasculera, works on the signs and symptoms of CVD with improved quality of life
- Derived from hesperidin, found in citrus, and has GRAS status (Generally Recognized As Safe), the highest level of safety designated by the FDA

Vasculera is the Complete Way to Effectively Manage CVD



Vasculera®
diosmiplex 630mg



Patients are Guaranteed the
Lowest Price When You Prescribe
Through Primus Care Direct

Rx

Vasculera

Sig: $\dot{\dagger}$ QD #30

Refill x11

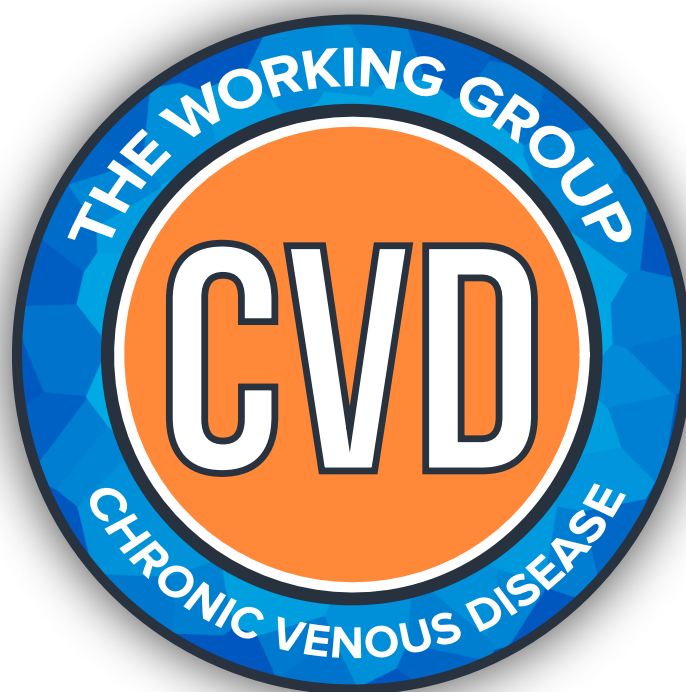
DISPENSE AS WRITTEN

Vasculera.com

Dispensed by Prescription

References: 1. Saharay M, Shields DA, Georgiannos SN, et al. Endothelial activation in patients with chronic venous disease. J Vasc Surg 1998;15:342-349. 2. Bergan J, Shortell C. Venous ulcers, Academic Press, Elsevier, 2006. 3. Wittens C, Davies AH, Baekgaard N, et al. Clinical Practice Guidelines from the ESVS, Eur J Vasc Endovasc Surg 2015;49:678-737. 4. Niccolaiades A, Allegra C, Bergan J et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Int Angiol. 2008;27:1-59. 5. O'Donnell TF, Passman MA, Marston WA, Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Society. J Vasc Surg 2014;60:1S-60S. 6. Guilhou JJ, Dereure O, Marzin L et al. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients. Angiology 1997;48(1):77-85. 7. Glinski W. The beneficial augmentative effect of micronized purified flavonoid fraction (MPFF) on the healing of leg ulcers: An open, multicenter, controlled, randomized study. Phlebology 1999;4(4):151-8. 8. Roztocil K, Stvrtnova V, Strejcek J. Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. Int Angiol 2003;22(1):24-31. 9. Feroso J, Legido AG, Del Pino J, et al. Therapeutic value of diosmin in the treatment of venous disorders of the lower limbs. Curr Ther Res 1992;52(1):124-34. 10. Gilly R, Pillion G, Frileux C. Evaluation of a New Venoactive Micronized Flavonoid Fraction (S 5682) in Symptomatic Disturbances of the Venolymphatic Circulation of the Lower Limb: A Double-Blind, Placebo-Controlled Study. Phlebology 1994; 9(2):67-70. 11. Laurent R, Gilly R, Frileux C. Clinical evaluation of a venotropic drug in man. Example of Daflon 500 mg. Int Angiol 1988;7(2S):S1-43. 12. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM et al. Phlebotonics for venous insufficiency. Cochrane Database of Systematic Reviews 2016;(4). 13. Jantet G, and the RELIEF Study Group. Chronic Venous Insufficiency: Worldwide results of the RELIEF Study. Angiology 53:245-256, 2002

***Recommended in European and
U.S. Clinical-Practice Guidelines***



***Supported by World-Renowned
Vascular Experts***

Vasculera[®]
diosmiplex 630mg

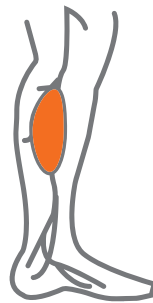
Without Treatment, Chronic Venous Disease (CVD) Can Lead to Life-Threatening Consequences

Edema
Varicose Veins



25 MILLION
Most Common

Trophic Changes
Lipodermatosclerosis
Ulceration



6 MILLION
More Severe

Deep Vein
Thrombosis (DVT)

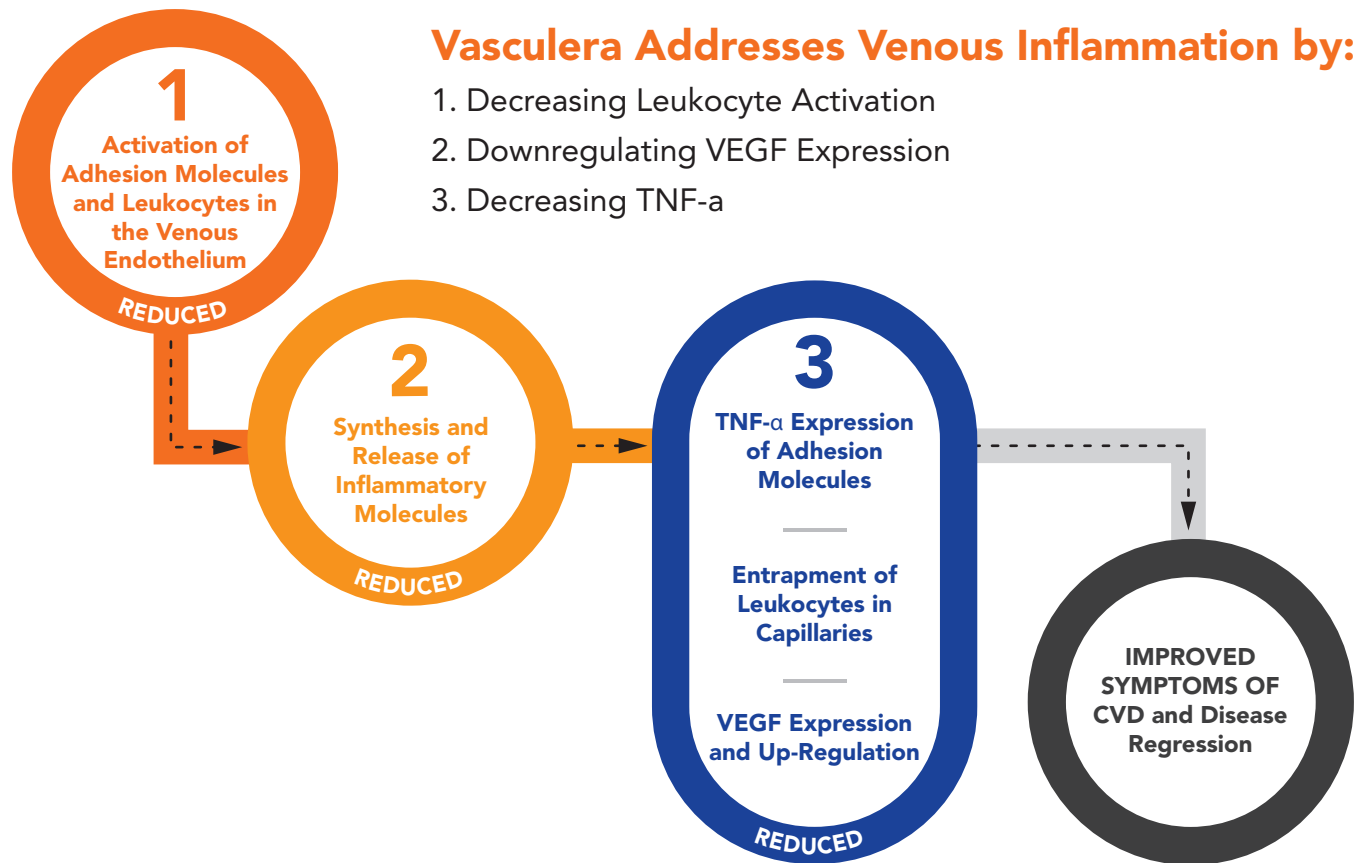


100K DIE PER YEAR
Life Threatening

CEAP: A Comprehensive Classification System of Chronic Venous Disease (Classes 0-6)

0	1	2	3	4	5	6
No visual or palpable signs of CVD	Telangiectases or reticular veins	Varicose veins	Edema	Pigmentation: Skin changes assigned to venous disease	Skin changes with healed ulceration	Skin changes with active ulceration
						

Vasculera Downregulates the Inflammatory Molecules Associated with Venous Hypertension



Vasculera is Recommended in Peer-Reviewed Clinical-Practice Guidelines and Supported by a Body of Evidence

2008

FOR HEALING OF VENOUS ULCERS AND THE SYMPTOMS OF CVD

International Angiography

American Academy of Chest Physicians: Antithrombotic and Thrombotic Therapy



2014

FOR LONG-STANDING OR LARGE VENOUS ULCERS, WITH COMPRESSION

Clinical Practice Guidelines of the Society of Vascular Society and the American Venous Forum: Management of Venous Leg Ulcers



2015

REDUCES EDEMA AND RESTLESS LEGS, USEFUL IN CRAMPS AND TO HEAL VENOUS ULCERS

Clinical Practice Guidelines for the European Society for Vascular Surgery (ESVS)



2016

REDUCES SYMPTOMS OF CVD AND HEALS VENOUS ULCERS

Recommendations of the Working Group in CVD (Phlebology, 2017)

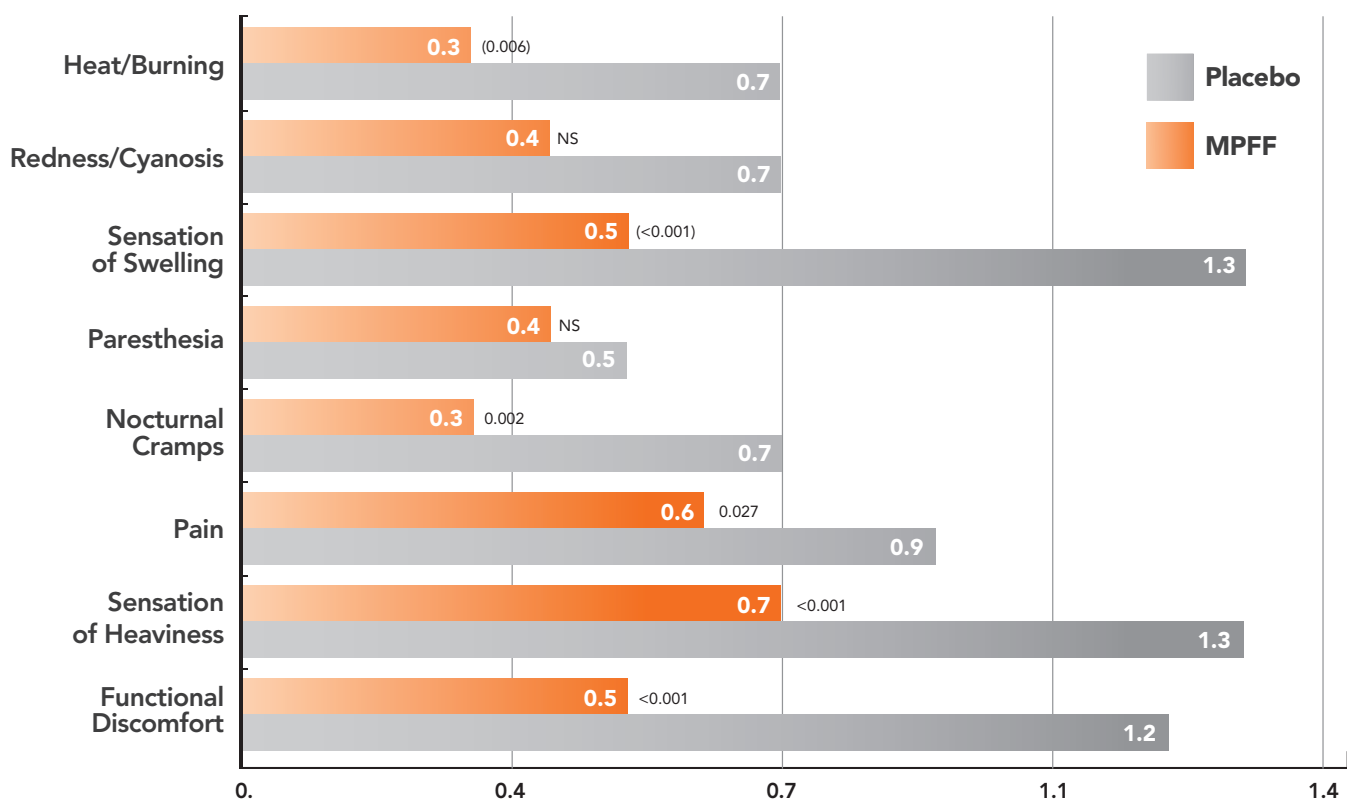
Recommended by



Patients Taking MPFF, An Active Ingredient Found in Vasculera, Showed Greater Improvement in CVD Symptoms Over 8 Weeks

- N=150: 76 MPFF, 74 placebo
- 500mg of MPFF BID for 8 weeks vs placebo
- Symptoms were assessed at weeks 0, 4 and 8
- At week 4, there were significant improvements in functional discomfort, nocturnal cramps, and sensation of swelling and heaviness

SYMPTOM IMPROVEMENT SCALE AFTER 8 WEEKS: MPFF VS PLACBEQ



SYMPTOM SCALE

0	1	2	3
No symptom	Moderate without impact on daily activities	"Appreciable" but permitting ADLs	Severe symptom, causing discomfort or hampering daily activities

The RELIEF* Study is a Prospective, Multicenter Study of 4,527 Patients with CVD in CEAP Classes 0-4 Treated with MPFF for 6 Months

- N=3174: 43% reflux, 57% no reflux
- 500mg of MPFF BID for 6 months
- Symptoms were assessed at day 60, 120 and 180

*RELIEF (Reflux assEssment and quality of lIfe improvEment with micronized Flavonoids)

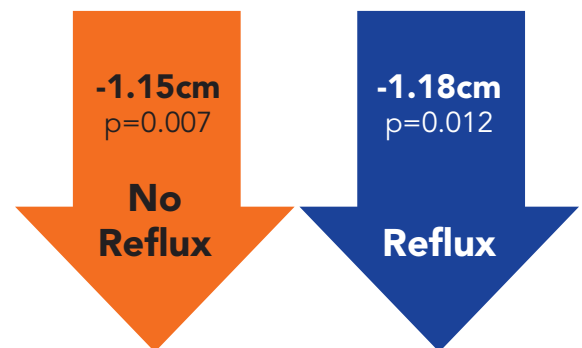
MPFF Provided Significant Improvements in CVD Symptoms and Quality of Life

PERCENTAGE OF PATIENTS WITH REDUCTION IN SYMPTOMS

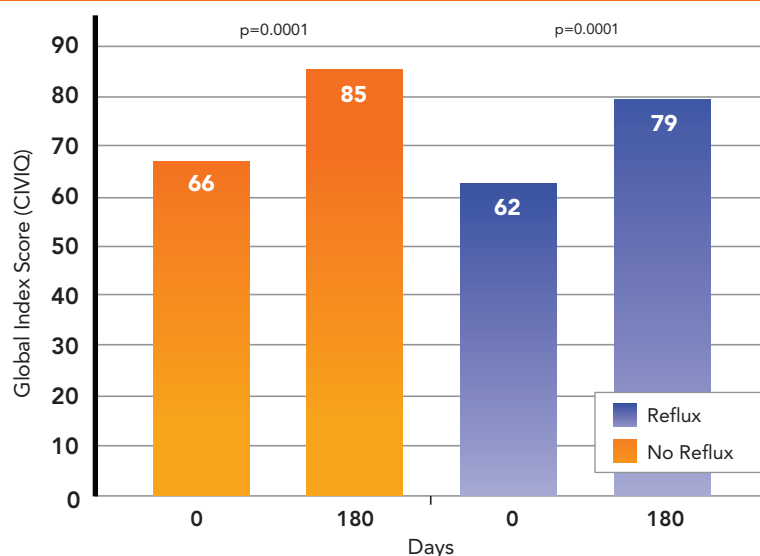
	SWELLING SENSATION (<0.001)	HEAVINESS (<0.001)	CRAMPS (<0.001)
No Reflux	▼ 48%	▼ 55%	▼ 57%
Reflux	▼ 36%	▼ 39%	▼ 48%

The reduction in the clinical scores between Day 0 and the last observation was highly significant for each group and the whole population ($p = 0.0001$).

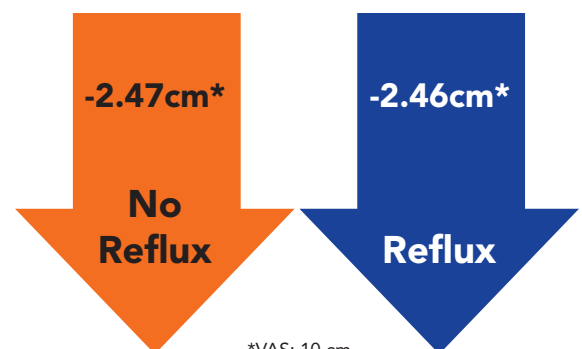
REDUCTION IN ANKLE SIZE



IMPROVED QUALITY OF LIFE



REDUCTION IN PAIN



*VAS: 10 cm

Vasculera is Proven Clinically-Effective in Patients

STASIS DERMATITIS



➤ Previous Rx: Compression stockings, topical steroid 2x/day

➤ Rx: Topical steroid 2x/day, **PLUS Vasculera QD**

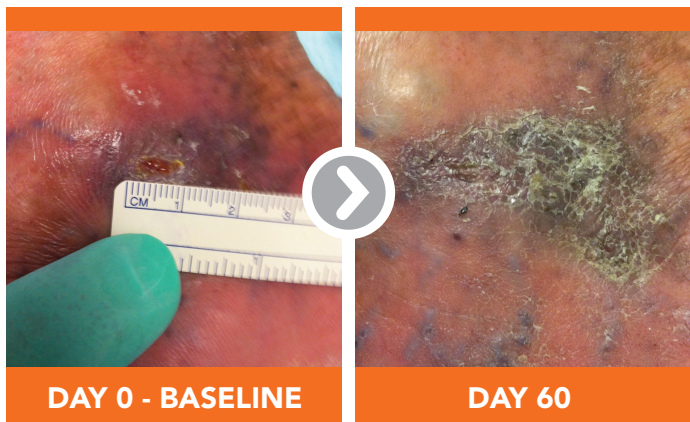
EDEMA



➤ Compression stockings, **Vasculera QD** (right ankle circumference: 26cm)

➤ Compression stockings, **Vasculera QD** (right ankle circumference: 21.25cm)

VENOUS STASIS ULCER



➤ Diagnosis: CVI, venous stasis ulcer to right medial ankle. Prior Rx: Unchanged for 6 months despite standard of care Oasis Current Rx: **Vasculera QD**

STASIS DERMATITIS



➤ 72 year-old male: Stasis Dermatitis for 15 years

MPFF, the Active Ingredient in Vasculera, Works on the Signs and Symptoms of CVD

- Benefits ulcer healing and reducing ulcer healing time
- Demonstrated significant benefit in healing trophic changes
- Demonstrated a decrease in ankle edema