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

Supported by World-Renowned Vascular Experts
Without Treatment, Chronic Venous Disease (CVD) Can Lead to Life-Threatening Consequences

- 25 MILLION Most Common
- 6 MILLION More Severe
- 100K DIE PER YEAR Life Threatening

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

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No visual or palpable signs of CVD</td>
<td>Telangiectases or reticular veins</td>
<td>Varicose veins</td>
<td>Edema</td>
<td>Pigmentation: Skin changes assigned to venous disease</td>
<td>Skin changes with healed ulceration</td>
<td>Skin changes with active ulceration</td>
</tr>
</tbody>
</table>
Pathophysiology of CVD: The Mechanical and Biochemical Pathways

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

Even if the mechanical pathway is addressed, the continued presence of inflammatory molecules can lead to disease progression

Continued presence of micro-vascular inflammatory molecules 

Damages the vein endothelium and affects the lymphatic channel

Leads to skin damage, ulcer and edema
Vasculera® Downregulates the Inflammatory Molecules Associated with Venous Hypertension

Vasculera Addresses Venous Inflammation by:
1. Decreasing Leukocyte Activation
2. Downregulating VEGF Expression
3. Decreasing TNF-α

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 Surgery 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
MPFF, An Active Ingredient in Vasculera is Proven to Work on All 8 Symptoms of CVD

- 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

*The data in the bar chart above is based on the analysis of mean improvement in symptom score between MPFF and placebo by the CVD Working Group published in “Recommendations of the Working Group in CVD” (Phlebology, 2017)
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

<table>
<thead>
<tr>
<th>PERCENTAGE OF PATIENTS WITH REDUCTION IN SYMPTOMS</th>
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<tbody>
<tr>
<td>SWELLING SENSATION (&lt;=0.001)</td>
</tr>
<tr>
<td>No Reflux</td>
</tr>
<tr>
<td>Reflux</td>
</tr>
</tbody>
</table>

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 PAIN

-2.47cm*  
-2.46cm*  
*VAS: 10 cm
Vasculera is Proven Clinically-Effective in Patients

MPFF Improves the Signs of CVD

• Benefits ulcer healing and reducing ulcer healing time
• Demonstrated significant benefit in healing trophic changes
• Demonstrated a decrease in ankle edema
Vasculera® is the Only Prescription Medication that Addresses the Biochemical Pathway Associated with CVD

Recommendations for the Use of MPFF in the Management of Chronic Venous Disease

- Hemodynamic pathophysiology leads to major cellular and enzymatic pathologic mechanisms
- Inflammation is central to symptoms/signs of CVD
- Pharmacologic treatment with Micronized Purified Flavonoid Fracture—MPFF
  - Reduces microvascular inflammation
  - Improves pain and edema in patients with C2-C4 disease
  - Improves ulcer healing and reduces ulcer healing time in patients with C5-C6 disease
- Only available MPFF in US formulation of 95% purified flavonoid is diosmiplex
  - Dosed once daily
  - Addition of Alka-4 complex may address GI upset with the high dose of diosmin and potentially as a buffer for the acidic environment

References: