

# EVIDENCE BASED STATEMENT

## DOMAIN 8, Statement 1

TOPIC: “CERTIFIED AND VALIDATED VENOUS ACTIVE DRUGS”

### SEARCH TERMS & SOURCES

((venous insufficiency[MeSH Terms]) AND (active drug OR phlebotonic)) NOT (thrombo\*[MeSH Terms]) NOT (ischemia)  
//PubMed, Embase and Cochrane Library

### INCLUSION CRITERIA

Indexed Journal, English Language.

Reviews

<10 y

### SEARCH RESULT BEFORE - AFTER SELECTION

118 (before) - 6 (after selection)

### PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Pharmacological treatment for chronic venous disease: an umbrella review of systematic reviews. *Int Ang* 2022 in press
2. Cacciatore MA. Misinformation and public opinion of science and health: Approaches, findings, and future directions. *Proc Natl Acad Sci U S A*. 2021 Apr 13;118(15):e1912437117
3. De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, et al. European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg* (2022) 63, 184-267.
4. Pompilio G, Nicolaidis A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. *Phlebology*. 2021 Oct;36(9):695-709
5. Giancesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease: Narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics. *Phlebology*. 2019, Vol. 34(15) 4–66
6. Pray WS. Ethical, scientific, and educational concerns with unproven medications. *Am J Pharm Educ*. 2006;70(6):141.

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### IDENTIFIED REFERENCES

1. Martinez-Zapata MJ, Vernooij RW, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev.* 2020 Nov 3;11(11):CD003229.
2. Lichota A, Gwozdziński L, Gwozdziński K. Therapeutic potential of natural compounds in inflammation and chronic venous insufficiency. *Eur J Med Chem.* 2019 Aug 15;176:68-91.
3. Stücker M, Rabe E, Meyer K, et al. Therapeutic approach to chronic venous insufficiency - clinical benefits of red-vine-leaf-extract AS 195 (Antistax<sup>®</sup>). *Pharmazie.* 2019 Apr 1;74(4):193-200.
4. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev.* 2016 Apr 6;4(4):CD003229.
5. Mannello F, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide modulates inflammatory pathways in chronic venous disease. *Int Angiol.* 2014 Jun;33(3):236-42.
6. Carpentier P, Allaert FA, Chudek J, Mosti G. Phlebotonic and compression stocking therapy in venous edema management: an overview of recent advances with a focus on Cyclo 3 Fort<sup>®</sup> and progressive compression stockings. *Womens Health (Lond).* 2013 Jul;9(4):325-33.
7. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev.* 2012 Nov 14;11(11):CD003230.

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### TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 1, TOPIC: "CERTIFIED AND VALIDATED VENOUS ACTIVE DRUGS"

"Quackery" is a term indicating "promotion of products that do not work or have not been proven to work". The large diffusion of dietary supplements has exposed the public to the risk of false claims in terms of the related health benefit associated with different components assumption.

[Pray WS. Ethical, scientific, and educational concerns with unproven medications. *Am J Pharm Educ.* 2006;70(6):141].

Scientific organizations should be the first line of opposition toward such issue, promoting proper research and avoidance of confounding commercials.

[Cacciatore MA. Misinformation and public opinion of science and health: Approaches, findings, and future directions. *Proc Natl Acad Sci U S A.* 2021 Apr 13;118(15):e1912437117]

A validated venous active drug (VAD) could be defined as a group of natural or synthetic substances counteracting the inflammation and vessel dilation associated with venous reflux, leading to a potential clinical benefit, in an evidence-based context.

Among the natural ones, four main categories can be identified:

BENZOPYRONES (ALPHA, like coumarin and dicumarol, or GAMMA, also known as "flavonoids", like miconized purified flavonoid fraction, diosmine, kaempferol, diosmetin, quercetin, rutin, rutosides, hesperidin, oxerutine)

GLYCOSAMINOGLYCANS (sulodexide)

SAPONINS (like escin, also known as horse-chestnut, ruscus, centella asiatica)

OTHER PLANT EXTRACTS

Anthocyanosides: blueberry extract, protoescigenin, barringtogenol, cryptoescin

Proanthocyanidins (maritime pine tree extract), grape seed extracts

Ginkgo biloba

The natural or synthetic origin does not implicate differences in safety or efficacy.

Among the main synthetic ones, calcium dobesilate, benzarone and naftazone.

The safety profile of these products has been documented as high, with mainly gastro-intestinal side effects. Insomnia, drowsiness and headaches have been reported as well, together with transient aganulocytosis (the latter for calcium dobesilate use).

[Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. *Int J Mol Sci.* 2018; 19: 1669].

Proper specialist customized prescription is of fundamental importance.

Analysis of the available literature and guidelines pointed out the importance of not grouping the different drugs all together in a single recommendation category in order to avoid evidence-based findings dilution: different drugs demonstrated different clinical benefit by means of different scientific works. Also for this reason, a scientifically aware prescription and use must be promoted.

\*[Gianesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease. *Phlebology.* 2019, Vol. 34(1S) 4–66]

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### STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 1

**“An excess of products in the market are claiming activities on the venous –lymphatic system that are not properly scientifically demonstrated. Relying on the available evidence and research as well as expert physicians advise is mandatory ”**

### 4 SELECTED REFERENCES

1. Pray WS. Ethical, scientific, and educational concerns with unproven medications. Am J Pharm Educ. 2006;70(6):141
2. Cacciatore MA. Misinformation and public opinion of science and health: Approaches, findings, and future directions. Proc Natl Acad Sci U S A. 2021 Apr 13;118(15):e1912437117
3. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018; 19: 1669
4. Gianesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease. Phlebology. 2019, Vol. 34(1S) 4–66

### identified LITERATURE BIAS

Lack of correlation between objective haemodynamic and quality of life parameters

### SUGGESTED NEXT LINES OF RESEARCH

Evidence based data production on supplements  
Quality of life and cost-effectiveness in VAD use