

# EVIDENCE BASED STATEMENT

## DOMAIN 8, Statement 3

TOPIC: “SULODEXIDE EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT”

### SEARCH TERMS & SOURCES

(sulodexide) AND ((vein) OR (venous))  
PubMed, Embase and Cochrane Library

### INCLUSION CRITERIA

Indexed Journal, English Language, lower limb  
Reviews, <10 y.

### SEARCH RESULT BEFORE - AFTER SELECTION

21 (before) - 18 (after selection)

### PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Asimwe IG, Pushpakom SP, Turner RM, et al. Cardiovascular drugs and COVID-19 clinical outcomes: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol*. 2022 Mar 24
2. Gonzalez-Ochoa AJ, Raffetto JD, Hernández Ag et al. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial. *Thromb Haemost*. 2021 Jul;121(7):944-954.
3. Gonzalez Ochoa AJ, Carrillo J, Manríquez D, et al. Reducing hyperpigmentation after sclerotherapy: A randomized clinical trial. *J Vasc Surg Venous Lymphat Disord*. 2021 Jan;9(1):154-162
4. Giancesini 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
5. Andreozzi GM, Bignamini AA, Davì G, et al. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study. *Circulation*. 2015;17;132(20):1891-7.

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### IDENTIFIED REFERENCES

(from the most recent down)

1. Chaitidis N, Kokkinidis DG, Papadopoulou Z, et al. Management of Post-thrombotic Syndrome: A Comprehensive Review. *Curr Pharm Des.* 2022;28(7):550-559.
2. Pompilio G, Nicolaides 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.
3. Raffetto JD, Ligi D, Maniscalco R, et al. Why Venous Leg Ulcers Have Difficulty Healing: Overview on Pathophysiology, Clinical Consequences, and Treatment. *J Clin Med.* 2020 Dec 24;10(1):29.
4. Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. *Wounds.* 2020 Jul;32(7):195-207.
5. Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis. *Adv Ther.* 2020 Mar;37(3):1013-1033.
6. Nicolaides AN. The Most Severe Stage of Chronic Venous Disease: An Update on the Management of Patients with Venous Leg Ulcers. *Adv Ther.* 2020 Feb;37(Suppl 1):19-24.
7. Mansilha A, Sousa J. Benefits of venoactive drug therapy in surgical or endovenous treatment for varicose veins: a systematic review. *Int Angiol.* 2019 Aug;38(4):291-298.
8. Carroll BJ, Piazza G, Goldhaber SZ. Sulodexide in venous disease. *J Thromb Haemost.* 2019 Jan;17(1):31-38.
9. Jiang QJ, Bai J, Jin J, et al. Sulodexide for Secondary Prevention of Recurrent Venous Thromboembolism: A Systematic Review and Meta-Analysis. *Front Pharmacol.* 2018 Aug 8;9:876.
10. Elmi G, Pizzini AM, Silingardi M. The secondary prevention of venous thromboembolism: Towards an individual therapeutic strategy. *Vascular.* 2018 Dec;26(6):670-682.
11. Cosmi B. Management of idiopathic venous thromboembolism. *Expert Rev Cardiovasc Ther.* 2016 Dec;14(12):1371-1384.
12. Wu B, Lu J, Yang M, Xu T. Sulodexide for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2016 Jun 2;(6):CD010694.
13. Varatharajan L, Thapar A, Lane T, et al. Pharmacological adjuncts for chronic venous ulcer healing: a systematic review. *Phlebology.* 2016 Jun;31(5):356-65.
14. Andreozzi GM. Role of sulodexide in the treatment of CVD. *Int Angiol.* 2014 Jun;33(3):255-62.
15. Mannello F, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide modulates inflammatory pathways in chronic venous disease. *Int Angiol.* 2014 Jun;33(3):236-42.
16. Hoppensteadt DA, Fareed J. Pharmacological profile of sulodexide. *Int Angiol.* 2014 Jun;33(3):229-35.
17. Coccheri S. Biological and clinical effects of sulodexide in arterial disorders and diseases. *Int Angiol.* 2014 Jun;33(3):263-74.
18. Coccheri S, Mannello F. Development and use of sulodexide in vascular diseases: implications for treatment. *Drug Des Devel Ther.* 2013 Dec 24;8:49-65.

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### TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 3, TOPIC: "SULODEXIDE EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT"

Sulodexide is a drug made by a fast moving heparin fraction and by a dermatan sulphate fraction.

It demonstrated an anti-inflammatory effect providing endothelium protection and permeability regulation, coagulation balance and vasal tone action.

Clinical trials demonstrates its potential benefits in peripheral arterial disease, , diabetic nephropathy and rethinopathy, post-myocardial infarction, recurrent deep venous thrombosis, post-thrombotic syndrome and chronic venous disease (CVD).

A recent review on sulodexide demonstrated its capability to decrease the intensity of pain, cramps, heaviness, oedema, together with a reduction in inflammatory mediators in patients with CVD

**[Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis. Adv Ther. 2020 Mar;37(3):1013-1033].**

Another literature revision concluded the drug is at least as effective as pentoxifylline and MPFF in venous ulcer healing.

Randomized comparative and head to head studies are needed to provide solid recommendations all along the CVD spectrum.

**\*[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].**

Sulodexide demonstrated to reduce the risk of unprovoked venous thromboembolism recurrence, with no increase of bleeding risk. Future studies are encouraged to assess the value of the drug in the periprocedural thromboprophylaxis context.

**[Chaitidis N, Kokkinidis DG, Papadopoulou Z, et al. Management of Post-thrombotic Syndrome: A Comprehensive Review. Curr Pharm Des. 2022;28(7):550-559].**

Preliminary data showed the possibility of reducing post-sclerotherapy pigmentation following the use of sulodexide.

**[Gonzalez Ochoa AJ, Carrillo J, Manríquez D, et al. Reducing hyperpigmentation after sclerotherapy: A randomized clinical trial. J Vasc Surg Venous Lymphat Disord. 2021 Jan;9(1):154-162]**

This drug vasculoprotective action was shown also in COVID induced endotheliopathy, leading to a reduced need of hospital admission and oxygen administration.

Patients undergoing sulodexide treatment showed no differences in thrombo-embolic events, major bleeding or mortality.

**[Gonzalez-Ochoa AJ, Raffetto JD, Hernández Ag et al. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial. Thromb Haemost. 2021 Jul;121(7):944-954].**

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### STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 3

“Sulodexide demonstrated to significantly control chronic venous disease signs and symptoms, to favor venous ulcer healing, to reduce the risk of thrombotic recurrence in specific context, to potentially reduce the impact of COVID-induced inflammation.”

### 4 SELECTED REFERENCES

1. Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis. *Adv Ther.* 2020 Mar;37(3):1013-1033
2. \*Pompilio G, Nicolaides 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
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5. Gonzalez Ochoa AJ, Carrillo J, Manríquez D, et al. Reducing hyperpigmentation after sclerotherapy: A randomized clinical trial. *J Vasc Surg Venous Lymphat Disord.* 2021 Jan;9(1):154-162
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### identified LITERATURE BIAS

Head to head studies on sulodexide impact on CVD signs and symptoms

### SUGGESTED NEXT LINES OF RESEARCH

Sulodexide features in venous periprocedural thromboprophylaxis  
RCT on CVD related signs and symptoms