



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Sulodexide 250 LSU softgel capsule Sulodexide 300 LSU/mL, 2mL ampule solution for injection
Indication:	<ol style="list-style-type: none">1. For the treatment of peripheral vascular insufficiency; for patients at risk of thrombosis like peripheral vascular insufficiencies, myocardial infarction and cerebral transient ischemic attack or strokes; diabetic retinopathy.2. Vascular pathologies with thrombotic risk, transient ischemic attacks and cerebrovascular disease, peripheral vascular insufficiency, diabetic retinopathy, myocardial infarction, retinal vasal thrombosis.
Date of deliberation:	01 July 2015 26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>Based on the evidence presented, the Council noted that there is no significant difference between sulodexide and acenocoumarol in terms of effect. An available study which compared sulodexide and warfarin showed that the former is as effective as the latter in terms of recanalization (45% and 47.5%; p=0.77). As for the safety of the drug, SEs and complications also did not significantly differ between sulodexide and warfarin (7.3% vs. 8.9%).</p> <p>It was noted that sulodexide is as effective and safe as heparin or warfarin in the treatment of deep vein thrombosis, however, it is more expensive.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>

Cost data:

The cost comparison showed that with regard to the cost of monthly treatment, sulodexide is more expensive (Php 1,926 for the capsule and Php 8,400 for the injection) compared to warfarin even if the cost of prothrombin time analysis is included.

The Council acknowledged the cost of treatment presented in the report of the Evidence Review Group (*See Attachment*).

Remarks:

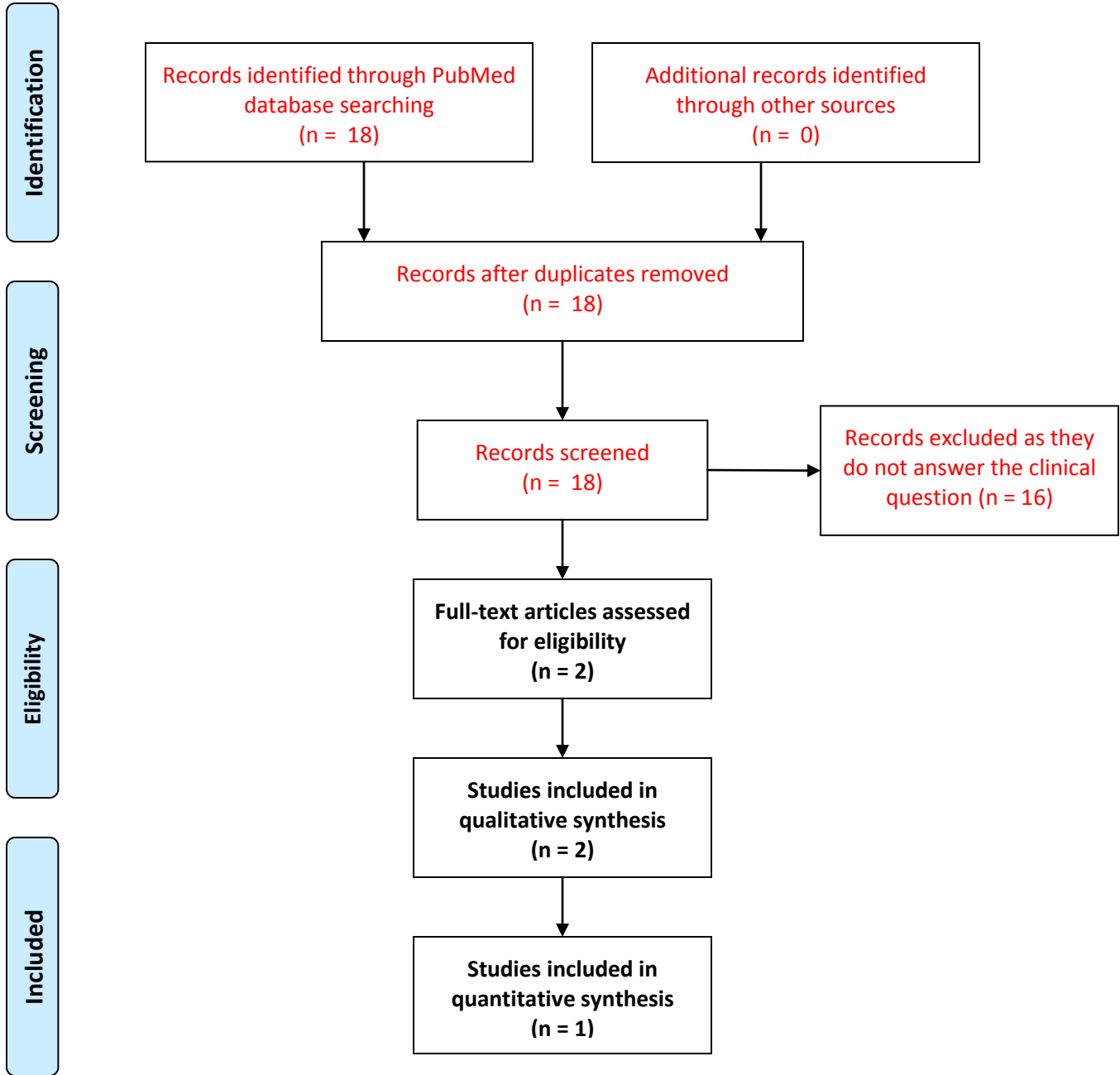
The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that the articles were mostly placebo-controlled trials and do not answer the question of comparing sulodexide with LMWH or other anticoagulants. Hence, the ERG maintains its recommendation that:

“Overall, we found sulodexide to be as effective and safe as heparin or warfarin for the treatment of deep vein thrombosis. However it is 3-4 times the cost.”

Likewise, given that the product has prohibitive cost and the proponent did not give a lower price offer, the Council recommended for its disapproval.

The Secretary of Health has officially disapproved the proposal to include sulodexide in the PNF.

PRISMA Table



1) What is the comparative clinical effectiveness of Sulodexide 250mg capsule/2ml ampule and low-molecular-weight heparin (LMWH) acting as anticoagulant in the prevention and treatment of acute venous thromboembolism (VTE)? 2) How is Sulodexide compared with the low-molecular-weight heparin (LMWH) in terms of safety?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Sulodexide		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Cirujeda and Granado. Angiology. 2006	Parallel controlled study	150 patients with deep vein thrombosis of lower limbs	Sulodexide vs. acenocoumarol	Recanalization by Doppler after 6 months Recurrence cases Hemorrhagic complications Adverse reactions Death rates Total cost of treatment in Euro (drugs, hematology, vascular surgery, pro-time)	45% 3 (4.4%) 0 1 4 109.98	68 	47.5% 4 (5.9%) 1 2 3 593.79	67 	High	p=0.77 NS NS NS NS
	Pinto et al. Angiology. 1997	RCT	30 adult patient with deep vein thrombosis	Sulodexide vs. heparin	venous pressures in the affected legs, reducing clinical symptoms	No available data		No available data		Abstract only	improvement with the same efficacy

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				Importance
							No. of patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD	
No appropriate meta-analysis for sulodexide											

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<p>PARAMETER (Indicate information for intended recipient)* <i><u>INTENDED RECIPIENT:</u></i></p>	<p>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p>REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP)</p> <p>a. Proposed list price to the government</p> <p>b. Current prevailing market price</p>	<p>Sulodexide¹ (Vessel Due) cap 250 LSU Php 32.10</p> <p>Sulodexide (Vessel Due) inj 300 LSU/mL x 2ml amps Php 280</p>	<p>Warfarin²</p> <p>1 mg tab- Php 8.80</p> <p>2.5 mg tab- Php 10.54</p> <p>5 mg tab-Php 10</p>	<p>¹Company submission</p> <p>²DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>40 (250 LSU caps)/month</p> <p>10 (300 LSU 2 mL inj)/month</p> <p>*Sulodexide parenteral is only given once daily for 5 - 10 days. The patient is shifted to the Sulodexide capsule for continuation of treatment.</p>	<p>60 (5 mg tab)/month</p>	<p>Recommended dose based on RCT</p> <p>*Based on company appeal</p>
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>2800+1,284</p> <p>Php 4,084 per month</p>	<p>Php 600</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP)</p> <p>a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)</p>		<p>500 (laboratory)</p> <p>750 (15% probability of hospital care for bleeding)</p>	
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 4,084 per month</p>	<p>Php 1,850 per month</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>			
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We conducted PubMed search using the terms “sulodexide” and “randomized controlled trial” last February 2015. The yield was 18 articles. We reviewed the abstract of the articles and considered only 2 articles for full text retrieval. Only one full text is available, the abstract was still included for the qualitative review. The included articles are:
 - Cirujeda JL (1), Granado PC. A study on the safety, efficacy, and efficiency of sulodexide compared with acenocoumarol in secondary prophylaxis in patients with deep venous thrombosis. *Angiology*. 2006 Jan-Feb;57(1):53-64.
 - Pinto A(1), Corrao S, Galati D, Arnone S, Licata A, Parrinello G, Maniscalchi T, Licata G. Sulodexide versus calcium heparin in the medium-term treatment of deep vein thrombosis of the lower limbs. *Angiology*. 1997 Sep;48(9):805-11.

Effectiveness/Efficacy

- In terms of successful recanalization, sulodexide is as effective as warfarin (45% and 47.5%; $p=0.77$).
- One article was included for qualitative analysis because of the absence of full text which also showed similar efficacy between sulodexide and heparin.

Safety

- Recurrence rates and complications also did not significantly differ between sulodexide and warfarin (please refer to evidence table).

Summary of Review

- There are few available studies on sulodexide. Of the available studies, the results showed that sulodexide is as effective as heparin or warfarin for the treatment/prevention of deep vein thrombosis.

Cost Data

- The cost comparison table showed that with regards to the cost of monthly treatment, sulodexide has higher cost compared to warfarin even if we include the cost of laboratory pro-time analysis.

Overall Recommendation

- Overall, we found sulodexide to be as effective and safe as heparin or warfarin for the treatment of deep vein thrombosis. However it is more expensive than warfarin.
- Thus there is not enough evidence and justification for the inclusion of sulodexide in the PNDP.

References

1. Goldhaber SZ(1). Venous thromboembolism: epidemiology and magnitude of the problem. *Best Pract Res Clin Haematol*. 2012 Sep;25(3):235-42. doi: 10.1016/j.beha.2012.06.007. Epub 2012 Aug 9.
2. Cirujeda JL(1), Granado PC. A study on the safety, efficacy, and efficiency of sulodexide compared with acenocoumarol in secondary prophylaxis in patients with deep venous thrombosis. *Angiology*. 2006 Jan-Feb;57(1):53-64.
3. Pinto A(1), Corrao S, Galati D, Arnone S, Licata A, Parrinello G, Maniscalchi T, Licata G. Sulodexide versus calcium heparin in the medium-term treatment of deep vein thrombosis of the lower limbs. *Angiology*. 1997 Sep;48(9):805-11.

Response to appeal on the reviewers' recommendation on Sulodexide

The articles submitted to support the appeal were mostly placebo-controlled trials and do not answer the question of comparing sulodexide with LMWH or other anticoagulants. The ERG maintains its recommendation that:

“Overall, we found sulodexide to be as effective and safe as heparin or warfarin for the treatment of deep vein thrombosis. However it is 3-4 times the cost.”

Because cost is significant issue, it is recommended that the manufacturer decrease the cost of sulodexide comparable to the comparator drugs for it to be reconsidered for inclusion in the PNF.