National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	LEO Pharma	The topic is appropriate to be referred to NICE	Comment noted. No action required.
	Clinical Leaders of Thrombosis (CLOT)	Yes	Comment noted. No action required.
	Daiichi Sankyo	It is appropriate to refer this topic to NICE. Warfarin is still the most commonly prescribed anticoagulant in the UK, and while it is an effective, suitable means of treatment and secondary prevention for patients with VTE, it has a number of recognised limitations, including a variable and unpredictable effect requiring regular INR monitoring and dose adjustment, a narrow therapeutic window, slow onset and offset of action and numerous food/drug interactions.	Comment noted. Vitamin K antagonists were included as comparators in the draft scope. No action required.
	Pfizer	No comment.	No action required.
Wording	LEO Pharma	The wording is appropriate	Comment noted. No action required.
	Clinical Leaders	No issues	Comment noted. No

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	of Thrombosis (CLOT)		action required.
	Daiichi Sankyo	The wording of the remit reflects the issues of clinical and cost-effectiveness that should be considered.	Comment noted. No action required.
	Pfizer	No comment.	No action required.
Timing Issues	LEO Pharma	The STA timing framework is appropriate	Comment noted. No action required.
	Clinical Leaders of Thrombosis (CLOT)	Not urgent as existing treatments are in place	Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
	Daiichi Sankyo	Edoxaban tosylate addresses currently unmet clinical need (as described above), and therefore guidance to the NHS on its use should not be delayed.	Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
	Pfizer	No comment.	No action required.

Section	Consultee/ Commentator	Comments	Action
Additional comments on the draft remit		No comments received.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	LEO Pharma	The Information is adequate	Comment noted. No action required.
	Clinical Leaders of Thrombosis (CLOT)	There is an error in paragraph one: It should reads "chronic thromboembolic pulmonary hypertension is a rare but potentially treatable cause of pulmonary hypertension" this should be amended to "chronic thromboembolic pulmonary hypertension is a rare but potentially treatable consequence of pulmonary embolism"	Thank you for your comment. The scope has been amended.
	Daiichi Sankyo	No Comment	No action required.
	Pfizer	No comment.	No action required.
The technology/ intervention	LEO Pharma	No Comment	No action required.
	Clinical Leaders of Thrombosis (CLOT)	Yes	No action required.
	Daiichi Sankyo	It should be made clear that the heparin received by patients in the trial was as initial treatment only.	Thank you for your comment. The scope

Section	Consultee/ Commentator	Comments	Action
			has been amended.
	Daiichi Sankyo	[redacted] is the brand name intended by Daiichi Sankyo for its active ingredient edoxaban, and has been filed for market authorisation in Europe. The mechanism of action and mode of administration are correct. It is important to add, however, that it is administered once-a-day without the need for routine clinical monitoring, and can be taken with or without food.	Comment noted. The 'technology' section is intended to provide a brief description of the technology under appraisal. No change to the scope required.
	Daiichi Sankyo	While it is correct to state that edoxaban does not currently have marketing authorisation, we would like to clarify that the pivotal trial for this indication is complete[1], and the regulatory dossier was submitted to the EMA in [redacted]. 1. The Hokusai-VTE investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369(15):1406-15.	Comment noted. No action required.
	Pfizer	No comment.	No action required.
Population	LEO Pharma	The appraisal should separate its analyses and guidance for patients with cancer and patients without cancer, not just because of the difference in comparators but also because of the difference in healthcare costs, causes of death, health-related utility, and baseline mortality risk.	Comment noted. The final scope states that, if the evidence allows, the analysis should consider separately people with active cancer.
	Clinical Leaders of Thrombosis	Possibly to stratify by age.	Comment noted. Attendees at the

Section	Consultee/ Commentator	Comments	Action
	(CLOT)		scoping workshop advised there was no compelling reason to consider subgroups stratified by age. No action required.
	Daiichi Sankyo	The population is defined appropriately.	Comment noted. No action required.
	Pfizer	No comment.	No action required.
Comparators	LEO Pharma	With respect to rivaroxaban, this product is not recommended by NICE for use in the subgroup of patients with cancer (See TA 261: "Rivaroxaban for treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism" - July 2012 and TA 287: "Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism" - June 2013), nor is it regularly used in clinical practice in this subgroup.	Comment noted. In TA 261, the Committee concluded that rivaroxaban should not be excluded as a treatment option for preventing venous thromboembolism in people with cancer. In TA 287, the Committee concluded that without direct evidence of the relative efficacy of rivaroxaban compared with LMWH alone, it would be inappropriate to make a recommendation for this group. Therefore,

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			rivaroxaban remains as a potential comparator in the subgroup of patients with cancer. No action required.
	LEO Pharma	With respect to the "Low molecular weight heparins" (LMWHs) please note: LMWHs have a variety of licenses for the management of DVT/PE, in particular there are differences with respect to using LMWHs in cancer patients. The differences are driven not only by the available efficacy data but also by differences in pharmacokinetic and biological activity. In the UK, many LMWHs are used off-label in cancer patients. For example, enoxaparin is not licensed for use in cancer patients in the UK although it is used. Tinazparin is expected to gain a UK license for the treatment of cancer patients in 2014. The LMWHs have different packaging and strengths/sizes, meaning that the calculation of an 'average' treatment cost for LMWHs may require extra consultation to accurately establish current UK usage patterns and a representative dose.	Comment noted. The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation for the indication defined in the scope, when they are considered to be part of established clinical practice for the indication in the NHS (see section 6.2.4 of the NICE guide to the methods of technology appraisal). No action required.
	Clinical Leaders of Thrombosis (CLOT)	Standard comparative therapies are all covered	Comment noted. No action required.
	Daiichi Sankyo	The proposed comparators for the full population are appropriate. However, we are aware that both dabigatran etexilate and apixaban are currently being	Comment noted. The final scope includes

Section	Consultee/ Commentator	Comments	Action
		scoped for similar indications. Supposing that both topics are referred to NICE for appraisal prior to a future appraisal of edoxaban beginning, can you please provide clarity on how these would be dealt with as possible comparators?	dabigatran etexilate as a comparator.
	Daiichi Sankyo	With regard to the 'for people with cancer' sub-group: Is this intended to mean for people with active cancer, or for people with a history of cancer?	Comment noted. The revised scope specifies active cancer.
	Daiichi Sankyo	Firstly, we understand from clinical expert advice that it is not uncommon for patients with active cancer to be treated with initial heparin and continued warfarin (LMWH/VKA), especially patients who don't want the added burden of having to regularly administer subcutaneous injections. This suggests that standard practice may be different to that suggested in clinical guideline. For patients with cancer, a comparison against LMWH/VKA may therefore be appropriate.	Comment noted. Consultees at the scoping workshop agreed that some patients with active cancer are treated with initial heparin and continued warfarin. Accordingly, consultees agreed that the comparators for the subgroup of people with active cancer should be the same as the comparators for the overall population.
	Daiichi Sankyo	Secondly, it is more appropriate to list this subgroup with the conditional clause "if evidence allows", as the presence of active cancer was an exclusion criterion in Hokusai-VTE if long term treatment with LMWH was planned.	Comment noted. The final scope specifies 'if the evidence allows'.

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	Pfizer	Pfizer welcomes the inclusion of LMWH as a comparator in the cancer associated thrombosis (CAT) sub-population. NICE CG144 specifically advises that CAT patients should be treated with a licenced LMWH.	Comment noted. No action required.
Outcomes	LEO Pharma	The outcomes are appropriate	Comment noted. No action required.
	Clinical Leaders of Thrombosis (CLOT)	Yes	No action required.
	Daiichi Sankyo	[redacted]	Comment noted. No action required.
	Pfizer	Pfizer welcomes the inclusion of bleeding as a key outcome. Due to the severity of this outcome, it is essential to properly consider it in any clinical review or economic modelling.	Comment noted. Bleeding was included in the draft scope. No action required.
Economic analysis	LEO Pharma	The optimal time horizon for analysing cancer patients may be different to that required to analyse the general population. The most appropriate time horizon for analysing the cost-effectiveness of longer-term treatment with apixaban could be different to the time horizon required to assess shorter-term treatment. Several models may thus be required.	Comment noted. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the

Section	Consultee/ Commentator	Comments	Action
			technologies being compared (see section 5.1.15 of the NICE guide to the methods of technology appraisal). No action required.
	Clinical Leaders of Thrombosis (CLOT)	No comments	No action required.
	Daiichi Sankyo	No comment.	No action required.
	Pfizer	CAT patients are a very specific sub-population with particular predisposition towards developing thrombi. In addition, a parenteral route of administration can be of benefit in patients experiencing nausea & vomiting. The specific requirements of CAT patients should be carefully captured and modelled. For CAT patients a key issue will be the availability of comparative evidence in order to generate robust cost-effectiveness results.	Comment noted. The final scope states that, if the evidence allows, the analysis should consider separately people with active cancer.
Equality and Diversity	LEO Pharma	No Comment	No action required.
	Clinical Leaders of Thrombosis (CLOT)	No issues	No action required.
	Daiichi Sankyo	No comment.	No action required.
	Pfizer	No comment.	No action required.

Section	Consultee/ Commentator	Comments	Action
Innovation	LEO Pharma	No Comment	No action required.
	Clinical Leaders of Thrombosis (CLOT)	Innovative in the reducing the need for repeated blood tests as required with Vitamin K antagonists	Comment noted. The company is invited to provide evidence on the innovative nature of the technology in its submission.
	Daiichi Sankyo	Edoxaban is the first of the NOACs to have **both** a once-daily dosing regimen and to have the same dose for both of its intended indications (VTE and AF).[1,2] 1. The Hokusai-VTE investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369(15):1406-15. 2. Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093-104	Comment noted. The company is invited to provide evidence on the innovative nature of the technology in its submission.
	Pfizer	No comment.	No action required.
Other considerations	LEO Pharma	No Comment	No action required.
	Clinical Leaders of Thrombosis (CLOT)	No issues	No action required.
	Daiichi Sankyo	The proposed sub-groups are appropriate, and data are available from the trial to support the required analyses.	Comment noted. No action required.

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	Pfizer	No comment.	No action required.
Questions for consultation	LEO Pharma	No Comment	No action required.
	Clinical Leaders of Thrombosis (CLOT)	No comment	No action required.
	Daiichi Sankyo	Warfarin is the most widely used VKA, and therefore should be included as a comparator. Other VKAs are not sufficiently different from warfarin that they should be considered separately.	Comment noted. Vitamin K antagonists were included as comparators in the draft scope. No action required.
	Pfizer	No comment.	No action required.
Additional comments on the draft scope		None received.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health, Healthcare Improvement Scotland, Royal College of Nursing, Vascular Society of Great Britain and Ireland

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Amdipharm Mercury Pharmaceuticals (phenindione), (warfarin)	NICE Secretariat		Amended	This organisation is not the maker of warfarin, therefore an amendment has been made and is listed on the matrix as Amdipharm Mercury Pharmaceuticals (phenindione) under 'comparator manufacturer'.

2.	Boehringer Ingelheim (dabigatran)	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Boehringer Ingelheim (dabigatran)has been added to the matrix of consultees and commentators under 'comparator manufacturer'.
3.	National Centre for Anticoagulation Training	Boehringer Ingelheim Ltd		Added	This organisation's interests is directly related to the appraisal topic as per our inclusion criteria. National Centre for Anticoagulation Training has been included in the matrix of consultees and commentators. under 'research groups'.

4.	National Centre for Cardiovascular Prevention and Outcomes	NICE Secretariat		Added	This organisation's interests are is directly related to the appraisal topic and as per our inclusion criteria. National Centre for Cardiovascular Prevention and Outcomes has been included in the matrix of consultees and commentators. under 'research groups'.
5.	Research Institute for the Care of People	NICE Secretariat		Removed	This organisation does not have an interest related to the appraisal topic and as per our inclusion criteria. Research Institute for the Care of People has been removed from the matrix of consultees and commentators under 'research groups'.