National Institute for Health and Clinical Excellence

Single/Technology Appraisal (STA)

Rivaroxaban for the treatment pulmonary embolism and the prevention of recurrent venous thromboembolism

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

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Vascular society	Agreed	No action required
	LEO Pharma	The initial statement in the "Background" section is incorrect in our view. VTE encompasses more processes than just DVT and PE and the wording we would suggest is "*Venous thromboembolism is a term used to describe the formation of a blood clot in a vein which may break off or embolise into the venous system."* The second paragraph in this section includes a number of incidence figures but no references for these. Estimating the incidence of VTE is notoriously difficult and we feel that adequate references are essential here.	The introductory sentence has been changed to include an introduction to the process of VTE. Comment noted no action required

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	Bayer	The final sentence of paragraph 1 states that chronic thromboembolic pulmonary hypertension (CTEPH) is a cause of pulmonary hypertension (PH). In fact, CTEPH is one type of PH (Simmoneau et al 2009). CTEPH can be caused by chronic thromboembolism. Not all cases of CTEPH occur in patients with a history of clinically overt pulmonary embolism (PE) (Piazza and Goldhaber, 2011). Sentence 1 of paragraph 2 states that the annual incidence of diagnosed PE has been reported as 3-4 per 10,000 people. However, calculations based on recent published UK data indicate that the incidence may be in the region of 8-9 per 10,000 people, ie: two to three times as high (Martinez et al, 2011). Martinez C, Rietbrock S, Bamber L, Cohen AT. Incidence of venous thromboembolism (VTE) in the general population - VTE Epidemiology Group study. XXIII Conference of The International Society on Thrombosis and Haematosis (ISTH); 11 Jul; 2011. Piazza GP and Goldhaber Sz. N Engl J Med 2011; 364: 351-60. Simmoneau G et al. J Am Coll Cardiol 2009; 54: Suppl: S43-S54	Comment noted this has been changed from 'cause' to 'type' The epidemiology data has been updated accordingly.
	The Royal College of Pathologists and The British Society for Haematology.	The background information given is concise but adequate.	No action required
	NHS Somerset	None at present	No action required
	British Society of Haemostasis and Thrombosis	The quoted incidence of venous thromboembolism is probably too low; the accepted figure is nearer 1 in 1000 per year.	Comment noted, and the incidence figures have been updated

Section	Consultees	Comments	Action
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
The technology/ intervention	Vascular society	Agreed	No action required
	LEO Pharma	Yes. We would suggest that the third paragraph of the technology section includes a reference to the EINSTEIN PE study.	No action required
	Bayer	We assume that the two clinical trials referred to in paragraph 3 are EINSTEIN-PE and EINSTEIN-Ext. EINSTEIN investigators, Bauersachs R et al. N Engl J Med 2010; 363(26): 2499-510. EINSTEIN-PE investigators, Buller HR et al. N Engl J Med 2012; 366(14):1287-97.	No action required
	The Royal College of Pathologists and The British Society for Haematology.	Yes.	No action required
	NHS Somerset	None at present	No action required
	British Society of Haemostasis and Thrombosis	The description of the technology appears accurate.	No action required
	Clinical leaders of thrombosis	Yes	No action required

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	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Vascular society	Agreed	No action required
	LEO Pharma	Yes. Populations that we would suggest that are considered separately are: Patients with renal impairment - this is particularly important because the study used creatinine clearance < 30ml/min as an exclusion criteria but the SPC for treatment of recurrent DVT and PE recommends dose reduction at creatinine clearance below 30ml/min. This needs to be addressed – is this drug safe in severe renal impairment even with reduced dosing. Obese patients – is efficacy demonstrated in this group? Elderly patients – is efficacy and safety demonstrated in this group? Patients with cancer – is efficacy and safety demonstrated in this group?	Renal impairment has been added as a sub group to the other considerations section of the scope. The summary of product characteristics does not indicate a dose adjustment for elderly or obese patients; these were therefore not added as a sub group for consideration. Patient with cancer were already included as a subgroup within the other considerations section of the scope, therefore no action required.

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	Bayer	The words `acute' and `symptomatic' should be deleted so as to fit the wording of the indication. The population would then be: `People with pulmonary embolism, with or without deep vein thrombosis'; or more simply `People with pulmonary embolism'. Please see also comment in the box below in relation to comparators.	Comment noted, and the population has been updated accordingly
	The Royal College of Pathologists and The British Society for Haematology.	The population is described appropriately. Subgroups that require separate consideration are correctly identified on screen 5 of the draft scope, as having an underlying risk of bleeding, or active cancer. On the other hand, whether the episode of pulmonary embolism was provoked or unprovoked would not seem to have significant bearing on the choice of initial treatment	Comments noted, no action required
	NHS Somerset	None at present	No action required

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	British Society of Haemostasis and Thrombosis	Patients who suffer a pulmonary embolism (with/without a deep vein thrombosis) are a heterogeneous population, the following groups should be considered separately: • Pregnancy related pulmonary embolism • Cancer associated pulmonary embolism Patients who have a recurrent pulmonary embolism while therapeutically anticoagulated and need a higher target INR	Comments noted. Cancer is already included as a sub group and therefore no action required. Rivaroxaban is contraindicated in pregnancy and therefore use in this setting would be outside of the marking authorisation for this drug. NICE issues guidance in line with the marketing authorisation and therefore pregnancy related pulmonary embolism is outside of this scope remit.
	British thoracic society	In the table the target population is listed as 'People with acute symptomatic pulmonary embolism, with or without symptomatic deep vein thrombosis.', whereas the title of the paper suggests the group will also be looking at rivaroxaban secondary prevention of recurrent VTE.	Comment noted - No change required to the scope as it includes both treatment and prevention of next VTE
	Clinical leaders of thrombosis	Yes	No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes & No	No action required
Comparators	Vascular society	Agreed	No action required

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	LEO Pharma	The comparators are appropriate. The reference to low molecular weight heparin (LMWH) only gives reference to enoxaparin and we would suggest adding the names of the other injectable LMWH as well and including tinzaparin and dalteparin.	Comment noted, the other injectable LMWH have been added
	Bayer	Management and treatment of VTE is covered in NICE CG 144. Unfractionated heparin (UH) is generally used in the management of PE where thrombolysis or surgical intervention is required in unstable patients. Rivaroxaban is not indicated in this situation: the draft SmPC states that rivaroxaban is not recommended as an alternative to UH in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Therefore UH is not an appropriate comparator. NICE Clinical Guideline 144 (CG144): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. http://guidance.nice.org.uk/CG144	Comment noted – UH has been removed as comparator within the main population. However, if evidence allows UH should be considered as a comparator for specific patients for whom it is recommended in the clinical guideline 144, as detailed in the other considerations section of the scope.
	The Royal College of Pathologists and The British Society for Haematology.	The comparators are standard NHS treatments for acute pulmonary embolism in current practice. Both LMWH / VKA and sustained LMWH can be described as 'best alternative care' , i.e. essentially equivalent as far as existing evidence can determine.	Comment noted - No action required to scope
	NHS Somerset	There is a considerable cost difference between warfarin, acenocoumarol and Phenindione. The appraisal may need to carry out further analysis of cost effectiveness of Rivaroxaban compared to Phenindione alone.	Comment noted - No action required to scope

Section	Consultees	Comments	Action
	British Society of Haemostasis and Thrombosis	The current standard treatment for the majority of patients with pulmonary embolism in the United Kingdom is quite rightly described as initially low molecular weight heparin or unfractionated heparin then conversion to a vitamin K antagonist or continuing on a low molecular weight heparin if a vitamin K antagonist is not felt to be appropriate. Fondaparinux is also licensed for the treatment of pulmonary embolism although it is only used in a small number of cases. It must also be noted that the 'gold standard' treatment of patients who have had either a cancer or pregnancy associated thrombosis is heparin.	Comment noted – the background section of the scope has been updated. Fondaparinux has been added as a comparator.
	Clinical leaders of thrombosis	Yes	No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
Outcomes	Vascular society	I think we would all agree that the the post phlebitic limb as an outcome comparator would be difficult to quantify and would need a long follow up. Recurrent DVT would be fine on it's own.	Comment noted - No action required to scope
	LEO Pharma	Yes	No action required
	Bayer	No comment	No action required
	The Royal College of Pathologists and The British Society for Haematology.	Yes, but the key outcomes of (1) mortality, (2) recurrence (3) direct complications of pulmonary embolism [pulmonary hypertension and heart failure] and (4) bleeding are more important in the context of the treatment of acute symptomatic pulmonary embolism.	Comment noted – no action required

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	NHS Somerset	None at present	No action required
	British Society of Haemostasis and Thrombosis	These outcomes are reasonable.	No action required
	Clinical leaders of thrombosis	Yes	No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
Economic analysis	Vascular society	Presumably the lack of the need for repeated INR checks, surgery attendances and nursing time are to be included in the economic analysis.	Comment noted - No action required
	LEO Pharma	This seems appropriate	No action required
	Bayer	No comment	No action required
	The Royal College of Pathologists and The British Society for Haematology.	No comment	No action required
	NHS Somerset	None at present	No action required

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	British Society of Haemostasis and Thrombosis	The economic analysis must take into account that the length of treatment for pulmonary embolism can vary between patients dependent on certain factors, usual lengths are three months, six months, twelve months and long-term. When performing the economic analysis is should be considered that although the number of INR tests will reduce if patients start rivaroxaban the 'cost per test' for the remaining patients on vitamin K antagonists may increase, given that fewer patients will be using a service that has considerable overheads of staff and equipment	Comment noted - No action required
	British thoracic society	Please clarify whether the economic analysis will include the costs involved in INR monitoring for patients on warfarin.	Comment noted - No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
Equality and Diversity	Vascular society	Agreed	No action required
	LEO Pharma	None	No action required
	Bayer	No comment	No action required
	The Royal College of Pathologists and The British Society for Haematology.	There are no elements of this appraisal that can be seen to constitute discrimination against any group in any sense. Accordingly, no additional elements can be proposed that would further promote equality in these terms.	No action required
	NHS Somerset	Separate consideration of those patients unable to take warfarin	Comment noted – no action required

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	British Society of Haemostasis and Thrombosis	There are no obvious equality issues with this drug.	No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	None	No action required
Innovation *Do you consider*	Vascular society	Yes	No action required
	LEO Pharma	Yes	No action required

Section	Consultees	Comments	Action
the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?	Bayer	Yes, rivaroxaban is highly innovative in this regard. There are many challenges with current therapy provided to patients, and several health-related benefits provided with rivaroxaban that offers the NHS a step-change in the management of patients with PE. The advantages that rivaroxaban could bring to the NHS include: ▪ Treatment of VTE could be made with a single oral agent, administered at a fixed dose. ▪ No requirement for routine monitoring of coagulation parameters during treatment. ▪ No need for "bridging" therapy with LMWH injections. ▪ Continued therapy with a secondary prevention dose after an initial intensified regimen. ▪ Ease of treatment administration for patients and healthcare practitioners, due to the simplicity of dosing and lack of coagulation monitoring requirements. Reduced NHS resource consumption and costs for those patients who would otherwise have required assistance with injections, and the potential for earlier hospital discharge. Being a fixed dose oral anticoagulant without any requirement for routine monitoring or coagulation parameters and with no need for bridging therapy, rivaroxaban potentially offers a novel oral single drug approach with significant opportunities for service redesign. The supportive data for these statements are ▪ The draft SmPC ▪ The findings of the EINSTEIN-PE study ▪ Cano et al 2012, which describes the validity of patient satisfaction instrument ▪ Prins et al 2012, which measures the improved treatment satisfaction with rivaroxaban using the validated scale ▪ Van Bellen et al 2012, which measures and compares lengths of stay associated with rivaroxaban and enoxaparin/VKA in the EINSTEIN trials Cano et al. Health Qual Life Outcomes. 2012; 10(1):120. Prins M et al. Patient-Reported Treatment Satisfaction with Oral Rivaroxaban Versus Standard Therapy in the Treatment of Acute Symptomatic Pulmonary Embolism. Accepted for poster presentation at the Annual meeting of the American Society of Haemotology; 12 Dec; 2012. Van Bellen B, Prins M, Bamber L, Wang M, Lensing A. Reduction in Initial Length of Stay with Rivaroxaban Single-Drug Regimen versus LMWH-VKA Standard of Care: Findings from the EINSTEIN Trial Program. Accepted for poster presentation at the annual meeting of American Society of Haematology; 12 Dec; 2012.	Comment noted – no action required

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	The Royal College of Pathologists and The British Society for Haematology.	The technology can be considered to be innovative (a 'step-change') due to the seamless use of a single agent (R) rather than two agents that are switched after a variable period (the time taken to achieve a 'therapeutic' INR on VKA).	Comment noted – no action required
	NHS Somerset	Yes	No action required
	British Society of Haemostasis and Thrombosis	The major benefit of this new drug is the change from a drug that requires monitoring and at times complex dosing to a 'one-dose' drug for all. This drug would significantly reduce the requirement for interactions between the health service and patients, from the initial management, where this drug would facilitate easier outpatient management or speedier discharge from hospital to significantly reducing the number of outpatient appointments the patient requires to attend.	No action required
	Clinical leaders of thrombosis	Rivaroxaban will offer a more straightforward method of treatment than warfarin by removing the need for testing. It also offers the benefit of not requiring injections compared with LMWH. Side-effects associated with long-term LMWH use will be reduced. However, the lack of follow-up testing increases the probability of patient non-compliance.	Comment noted – no action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	Yes	No action required
Other	Vascular society	None	No action required

Section	Consultees	Comments	Action
considerations	LEO Pharma	It should be noted that rivaroxaban is contraindicated in pregnancy and breast feeding whereas injectable LMWHs are not.	Comment noted. However, as NICE only issues guidance in line with the marketing authorisation pregnancy and breast feeding are outside the remit of this scope and therefore no action required
	Bayer	No comment	No action required
	The Royal College of Pathologists and The British Society for Haematology.	The use of Rivaroxaban has already been approved by NICE as an option in the treatment of acute Deep Vein Thrombosis. Since a significant proportion of individuals with acute DVT will in the short term be discovered to have symptomatic pulmonary embolism, non-approval of Rivaroxaben as an option for treatment of symptomatic Pulmonary Embolism would introduce untoward complexities in treatment.	Comment noted – no action required
	British Society of Haemostasis and Thrombosis	It is also important to consider if how well the patient is controlled on their vitamin K antagonist affects their outcomes.	Comment noted – no action required
	NHS Somerset	There is a considerable cost difference between warfarin, acenocoumarol and Phenindione. The appraisal may need to carry out further analysis of cost effectiveness of Rivaroxaban compared to Phenindione alone.	Comment noted – no action required
Questions for consultation:	Vascular society	Yes	No action required
	LEO Pharma	No	No action required

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Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?	The Royal College of Pathologists and The British Society for Haematology.	However, evidence that this change will make a 'significant and substantial impact on health-related benefits' is not currently available. Furthermore, the technology provides the means to implement simpler, 'leaner' acute treatment protocols with fewer logistic pitfalls than current LMWH / VKA regimens. This may well improve cost-effectiveness within treating institutions that might not be fully captured by QALY analyses. However, there is no current data to support this possibility.	Comment noted – no action required
	NHS Somerset	Yes	No action required
	UKCPA Haemostasis, Anticoagulation & Thrombosis (HAT) Group	No	No action required
Questions for consultation: *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*			
Additional comments on the draft scope.			

Section	Consultees	Comments	Action

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

Pfizer
Department of health
Royal college of nursing