National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Betrixaban for preventing venous thromboembolism in people hospitalised for acute medical conditions

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AntiCoagulation Europe	We note that there is no marketing authorisation in UK, what is the current status with regard to any pending application?	Comment noted. Betrixaban does not currently have a marketing authorisation in the UK for preventing venous thromboembolism. Information on the anticipated indication is commercial in confidence.
	Portola Pharmaceuticals	Yes, it is appropriate that NICE reviews betrixaban. The risk of pulmonary embolism and deep-vein thrombosis following admission for acute medical illness remains markedly increased for at least the first month after hospital discharge (Amin 2012). The VTE Epidemiology	Comment noted. No action required.

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		Group (VEG) registry shows that the risk of VTE between hospital discharge through to Day 35 is approximately the same as the risk during hospitalisation (Cohen, 2011). No therapies are currently approved to reduce morbidity and mortality due to VTE through to Day 35 following admission; some such as enoxaparin and fondaparinux are approved for 6 to 14 days of treatment and this period of treatment usually corresponds to when the patients are hospitalised (depending on the severity of their precipitating event). Therefore, about half of VTE events are not addressed in these patients. A report from the House of Commons Health Committee published in 2005 estimated that 25,000 people in the UK die from preventable hospital-acquired VTE each year, including patients admitted to hospital for medical care and surgery (House of Commons Health Committee, 2005). The majority (over 80%) of hospitalised patients that die from VTE are medical patients (Cohen 1996). Clearly there is an immediate unmet need for effective therapy in this patient population.	
Wording	AntiCoagulation Europe	Yes	Comment noted. No action required.
	Portola Pharmaceuticals	We would suggest the following wording to reflect that acutely ill patients with a medical condition who are at risk of thromboembolism and the duration of that risk. *"To appraise the clinical and cost effectiveness of betrixaban within its marketing authorisation for extended venous thromboembolism prophylaxis in the acutely ill medical patient population during and following hospitalisation for 35 to 42 days"*	Comment noted. The remit is always a broad outline of the appraisal. However, the population section of the scope has been amended to take your comments into account.

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Timing Issues	AntiCoagulation Europe	NICE CG 92 guidelines in place for this population with pharmacological and mechanical prophylaxis recommended(including GEKO technology which has just been reviewed by NICEMTG 19) An oral treatment, Betrixaban appears to extend the duration of a prophylaxis treatment to reduce risk of VTE to patients post discharge over a longer period which could benefit patients.	Comment noted. No action required.
	Portola Pharmaceuticals	This proposed appraisal is relatively urgent in that oral betrixaban has been studied for between 35-42 days in the APEX trial demonstrating a net clinical benefit compared to 6-14 days of treatment with subcutaneous enoxaparin in the acutely ill medical population, thus offering an important advance in addressing this unmet need as described above.	Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required.
Additional comments on the draft remit	AntiCoagulation Europe	None.	No action required.
	Portola Pharmaceuticals	**References:** Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. J Hosp Med 2012; 7: 231-8. Cohen, A., S. Rietbrock, and C. Martinez, Incidence of venous thromboembolism (VTE) in the medically-ill population – vte epidemiology group (VEG) study. ISTH Abstract O-MO-096. J Thomb Haemost, 2011. 9(Supplement s2): p. 41. Cohen AT, Edmondson RA, Phillips MJ, Ward VP, Kakkar VV. The changing pattern of venous thromboembolic disease. Haemostasis. 1996 Mar-Apr;26(2):65-71. House of Commons Health Committee (2005) The prevention of venous thromboembolism in hospitalised patients. London: The Stationery Office.	References noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AntiCoagulation Europe	Adequate	Comment noted. No action required.
	Portola Pharmaceuticals	This appears accurate.	Comment noted. No action required.
The technology/ intervention	AntiCoagulation Europe	Adequate, it would be helpful to provide a link to the published trial data for ease of reference for non-clinical audience	Comment noted. The company has the opportunity to provide published trial data in its submission. No action required.
	Portola Pharmaceuticals	Yes.	Comment noted. No action required.
Population	AntiCoagulation Europe	Too generalised, implies 'any acute medical condition' does this include cancer patients, palliative care patients… All excluded groups need to be addressed	Comment noted. An appraisal can only cover the population covered by the marketing authorisation. At the workshop, it was agreed that the population be amended

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			to include adults hospitalised with acute medical illness who require extended venous thromboembolism prophylaxis
	Portola Pharmaceuticals	The population definition (adults who are hospitalised for an acute medical condition and are at risk of venous thromboembolism) is incomplete. The target population includes adult patients who are at risk for VTE, who experience a period of acute illness. Many of these patients remain at risk for VTE and require extended prophylaxis. As suggested above we would re-phrase the population definition to be within the licensed indication of betrixaban which is expected to be: *Adults with acute medical conditions at risk of venous thromboembolism, who require extended VTE prophylaxis.*	Comment noted. Following discussion at the scoping workshop, the population has been amended to include adults hospitalised with acute medical illness who require extended venous thromboembolism prophylaxis
Comparators	AntiCoagulation Europe	If Doacs and warfarin are currently being used in clinical practice, they potentially should be included as comparators here. As a patient group, this information is very important when considering the range of options currently available and how they are utilised in acute medicine.	Comment noted. Workshop attendees disagreed that new oral anticoagulants (such as apixaban, dabigatran, edoxaban, rivaroxaban) were used in clinical practice and they do not have marketing authorisations for the

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			population specified in this scope. Consultees and workshop attendees agreed with the comparators listed in the scope.
	Portola Pharmaceuticals	The comparators are appropriate in the hospital setting. However, none of the products typically used in UK clinical practice have demonstrated net clinical benefit nor have they been approved for extended use. There are no other relevant comparators	Comment noted. Consultees and workshop attendees agreed with the comparators listed in the scope.
Outcomes	AntiCoagulation Europe	Compliance and adherence by patient to undertake treatment(oral medication opposed to injection) Health and Safety implications(needle stabs)	Comment noted. Workshop attendees agreed that the outcomes listed in the scope were appropriate.
	Portola Pharmaceuticals	The outcomes listed will capture the most relevant health related benefits. Other outcomes from the APEX pivotal study will also be presented regarding the patient related benefit of betrixaban.	Comment noted. Workshop attendees agreed that the outcomes listed in the scope were appropriate.
Economic analysis	AntiCoagulation Europe	No comments	Comment noted. No action required

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	Portola Pharmaceuticals	Aspects of the economic analysis, such as the time horizon, will be detailed in the submission	Comment noted. No action.
Equality and Diversity	AntiCoagulation Europe	Patients who are needle phobic and may not wish to be treated with an animal derived (porcine) product for religious/cultural reasons may benefit from an alternative treatment. Those unable to be considered for mechanical prophylaxis treatments (skin problems, hygiene)	Comments noted. The issue of animal-derived products will be brought to the Committee's attention. At the workshop, clinicians commented that this does occur but is very uncommon. See Equality Impact Assessment for more information.
		Scope needs to specify any disease areas which would not be eligible for this treatment i.e cancer patients?	Comment noted. Trials excluded people with cancer, however, the eligible population will depend on the marketing authorisation granted by the European Medicines Agency.

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	Portola Pharmaceuticals	No issues identified	Comment noted.
Innovation	AntiCoagulation Europe	On reviewing article: *Extended Thromboprophylaxis with Betrixaban in acutely ill medical patients* http://www.nejm.org/doi/full/10.1056/NEJMoa1601747 we note that continuance of parenteral anticoagulant treatment adherence/compliance may be compromised after discharge from hospital? If this oral treatment is as effective and non- inferior in both safety and efficacy as LMWH, ACE acknowledges that patients may welcome an alternative oral treatment which will offer protection against VTE risk from immediate risk assessment and one that can continue to be taken after discharge. Any injectable has a risk of infection and can cause pain and discomfort to an individual. It also may reduce resources needed when administering and supporting patients requiring LMWH. People who are poorly may prefer an oral medication over the current treatment comparator here.	Comments noted. The company is invited to provide evidence on the innovative nature of the technology in its submission.
	Portola Pharmaceuticals	Portola does consider the technology to be innovative and betrixaban has the potential to make a significant and substantial impact on health-related benefits. Betrixaban when approved will be the first innovative medicine for extended VTE prophylaxis in both inpatient and outpatient settings for patients at risk of events due to acute medical conditions. Unlike fondaparinux sodium, low molecular weight heparin and unfractionated heparin which are administered by subcutaneous injection, betrixaban is administered orally which will enable more convenient dosing for patients particularly after discharge when they will continue to be at risk of an event.	Comments noted. The company is invited to provide evidence on the innovative nature of the technology in its submission

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Other considerations	AntiCoagulation Europe	No comments	No action required.
	Portola Pharmaceuticals	*Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.* Portola is not seeking specific treatment combinations with other products. For the APEX study, the patient population included a large proportion of patients over 75 years of age at high risk of VTE. Also APEX was the first trial in this area that included patients with renal impairment <30 mL/min.	Comment noted. No action required.
Questions for consultation	AntiCoagulation Europe	No comments	No action required
	Portola Pharmaceuticals	*Have all relevant comparators for betrixaban been included in the scope?* Yes, for the period of up to 14 days while hospitalised. *Which treatments are considered to be established clinical practice in the NHS for preventing venous thromboembolism in people who are hospitalised for an acute medical condition? Are warfarin and the newer oral anticoagulants such as rivaroxaban, dabigatran etexilate, apixaban and edoxaban used in clinical practice for this indication?* Warfarin and the non-VKA anticoagulants (NOACs) e.g. rivaroxaban, apixaban, dabigatran and edoxaban are not used for the clinical indication that is being sought for betrixaban. None of the NOACs are licensed for VTE prophylaxis in medically ill patients in either the inpatient or outpatient settings for patients are at elevated risk of events due to acute medical conditions. All previous studies with NOACs in this patient population have failed to show a net clinical benefit compared to enoxaparin (ADOPT study – apixaban; MAGELLAN – rivaroxaban) leading to the manufacturers of these agents not to pursue a license for this indication.	Comment noted. Consultees and workshop attendees agreed with the comparators listed in the scope.

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		Are there any subgroups of people in whom betrixaban is expected to be more clinically effective and cost effective or other groups that should be examined separately? No *Where do you consider betrixaban will fit into the existing NICE pathway, venous thromboembolism?* Betrixaban will be prescribed in line with the existing NICE pathway i.e. at the point where pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE. It will be started as soon as possible after risk assessment has been completed and for an extended duration after discharge while patients continue to be at risk of VTE, again in line with the NICE pathway. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process.* Portola Pharma UK Ltd agrees that betrixaban should be appraised through the STA process.	Comment noted. No subgroups were identified by consultees. Comments noted

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

Department of Health
Pfizer