National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dabigatran etexilate 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	Consultees	Comments	Action
Appropriateness	Boehringer Ingelheim	It does not appear appropriate to refer this topic to NICE before the manufacturer has submitted the application for marketing authorisation. We wish to postpone this topic until the application for marketing authorisation has been made.	Comment noted. Given that the proposed indication falls within the Department of Health's high priority area of VTE prevention, NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	We consider this guideline appropriate—clinicians will appreciate advice on the use of dabigatran etexilate once it has been authorised for the treatment and secondary prevention of venous thromboembolism.	Comment noted. No action required.
	Pfizer	No comments.	Noted.

Section	Consultees	Comments	Action
	Royal College of Pathologists/British Society of Haematology	Yes but peer reviewed publications of some of the trials appear to be outstanding Evidence from the published trial (RE-COVER) comparing Dabigatran with warfarin in patients treated for a first episode of venous thromboembolism (rather than after recurrent VTE in this current remit) showed non inferiority to warfarin for VTE recurrence with a similar risk of major bleeding. As yet, there are no peer reviewed publications in scientific journals comparing long term treatment with dabigatran vs warfarin in patients with recurrent VTE. Dabigatran has been compared to warfarin with extended maintainance treatment after a primary episode of VTE for up to 36 months (RE-MEDY, presented as an abstract at Kyoto ISTH 2011). This showed non inferiority with warfarin in terms of recurrent VTE, a slightly reduced bleeding risk and slightly increased risk of acute coronary syndrome. Dabigatran has been compared with placebo for 6 months in patients who had already completed 6 to 18 months of anticoagulation for a primary episode of VTE (RE-SONATE presented as an abstract at Kyoto ISTH 2011). This showed a reduced risk of VTE recurrence and an increased risk of bleeding compared to placebo. In summary, there is currently no evidence that dabigatran offers a benefit over warfarin in terms of efficacy, based on randomised trials in patients after a first episode of VTE. In patients at high risk of recurrent VTE, warfarin appears to be highly effective in preventing recurrence (N Engl J Med 1999;340:901–7). Dabigatran may have a slightly different risk profile to warfarin with less intracranial bleeding but peer reviewed publications of randomised trials are required to address this issue in more detail. There appears to be a benefit for Dabigatran in comparison to placebo when used for extended treatment after a first episode of VTE following a period of conventional anticoagulation. Despite the similar efficacy between well controlled warfarin and dabigatran in clinicial trials, Dabigatran and the other new oral anticoagulants offer a significantly different patient experience. Some patients on long term anticoagulation are asking their clinicians (GP's and secondary care	Comments noted. Given that the proposed indication falls within the Department of Health's high priority area of VTE prevention, NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. This includes scheduling of topics on occasion prior to the peer-reviewed publishing of trial evidence. No action required.

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		specialists) if they will have the opportunity to access new oral anticoagulants. The drivers for this interest include no requirements for INR monitoring (with its attendant inconvenience and costs) reduced food and drug interactions and a slightly different risk profile such as reduced intracranial bleeding in comparison to warfarin. A much smaller number of patients on parenteral anticoagulants eg. LMWH (or no treatment at all) because they are not suitable for vitamin K antagonists could also benefit from access to an oral alternative. Availability of new oral anticoagulants like Dabigatran at a local level will be strongly influenced by the outcome of an appropriate NICE appraisal for this patient group and will assist with appropriate patient counselling.	
	UK Clinical Pharmacy Association (UKCPA)	Yes.	Comment noted. No action required.
Wording	Boehringer Ingelheim	The wording of the remit discusses 'symptomatic' venous thromboembolism. Symptomatic venous thromboembolism was not used in the recent rivaroxaban NICE HTA (TA261). Furthermore, when comparing the primary endpoints and patient populations from the pivotal dabigatran and rivaroxaban trials, a differentiation appears not justified and the specificity of 'symptomatic' venous thrombosis should be removed. It may be clearer if this wording is changed to "dabigatran etexilate for the treatment and secondary prevention of DVT and/or PE"	Comments noted. The scope has been amended accordingly.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.

Section	Consultees	Comments	Action
	Royal College of Pathologists/British Society of Haematology	Licensed indication is not yet known. A decision will need to be made as to whether to include 'no treatment' as an additional comparator.	Comment noted. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Yes.	Comment noted. No action required.
Timing Issues	Boehringer Ingelheim	This topic is of low urgency due to the fact that the manufacturer has not submitted an application for marketing authorisation.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.
	Lifeblood Thrombosis Charity	No comments.	Noted.

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	MHRA	It would be helpful to publish recommendations to coincide with relevant authorisation.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.
	Pfizer	It is urgent.	Comment noted. No action required.
	Royal College of Pathologists/British Society of Haematology	Dabigatran does not currently hold a UK marketing authorisation for the indication within this draft remit. As such, there is no clear indication to process urgently.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.

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	UK Clinical Pharmacy Association (UKCPA)	Appraisal process should track marketing authorisation, so that the NHS is guided to appropriate use of the technology for the licensed indication in a timely manner.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.
Additional comments on the draft remit	Boehringer Ingelheim	We strongly advise that NICE postpone the referral of this technology until the manufacturer submits an application for licence.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.
	Lifeblood Thrombosis Charity	None.	Noted.
	MHRA	None.	Noted.
	Pfizer	No comments.	Noted.

Section	Consultees	Comments	Action
	Royal College of Pathologists/British Society of Haematology	None.	Noted.
	UK Clinical Pharmacy Association (UKCPA)	None.	Noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Boehringer Ingelheim	No comments.	Noted.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.
	Royal College of Pathologists/British Society of Haematology	Acceptable.	Comment noted. No action required.
	UK Clinical Pharmacy Association (UKCPA)	In terms of completeness, some text about provoked and unprovoked venous thromboembolism (VTE), relative risk of recurrence and management implications would be useful (e.g. treatment length). In addition, reference to the current ongoing appraisal of rivaroxaban for the treatment of pulmonary embolism (PE) and the prevention of recurrent VTE and anticipated timelines along with the reference to TA261 would also be useful.	Comment noted. The background section of the scope is meant to be a brief description of the topic. Information regarding the recently completed appraisal of rivaroxaban for the treatment of pulmonary embolism (PE) and the prevention of recurrent VTE has been added to the scope.

Section	Consultees	Comments	Action
The technology/ intervention	Boehringer Ingelheim	It is not clear from the description of the technology that there are three pivotal trials comparing dabigatran with warfarin (RECOVER, RECOVER II and REMEDY); and one pivotal trial comparing dabigatran with placebo (RESONATE). Furthermore, it is not stated that dabigatran also has a licence for stroke prevention in non-valvular AF patients.	Comments noted. The scope has been amended to include descriptions of each trial.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	The technology: in addition to the authorisation for preventing thromboembolism after hip or knee replacement, dabigatran is also authorised for prevention of stroke and systemic embolism in non-valvular atrial fibrillation when accompanied by another specified risk factor. Intervention: here or elsewhere, consider stating either the duration of anticogulation treatment or the clinical critera that determine treatment duration (eg recommendations of British Society for Haematology: Br J Haematol 2011; 154:311–24). The duration of treatment is likely to have a bearing on the outcome.	Comments noted. The draft scope only includes a brief description of the topic.
	Pfizer	No comments.	Noted.
	Royal College of Pathologists/British Society of Haematology	Yes. However peer reviewed publication of some of the trials appears to be outstanding.	Comment noted. NICE aims to provide guidance as close to launch as possible. In order to achieve this, NICE must coordinate its potential appraisal topics well in advance to ensure timely guidance can be published. No action required.

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	UK Clinical Pharmacy Association (UKCPA)	Dabigatran has also been compared with warfarin in a clinical trial of adults with symptomatic deep vein thrombosis or pulmonary embolism who have completed 3 to 12 months of anticoagulation treatment (REMEDY).	Comment noted. The scope has been amended to include details of all the trials for dabigatran.
Population	Boehringer Ingelheim	No comments	Noted.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	No comments.	Noted.
	Pfizer	There are differences in the trial populations of the comparator technologies within this appraisal, which need to be taken into account.	Comment noted. No action required.

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	Royal College of Pathologists/British Society of Haematology	There are 2 main groups of patients with VTE - those who require a limited period of anticoagulation (of at least 3 months, usually no more than 6 months) and those that require long term anticoagulation, usually lifelong - beyond the timing of the current trials (with treatment for up to 36 months) Although patients presenting with DVT and PE have a similar risk of recurrent VTE, patients presenting with PE are 3 fold more likely to have PE at recurrence compared with patients who initially present with DVT (Thromb Haemost 2010; 8: 2436-2442). A patient with an unprovoked PE may therefore be considered to be at more risk of fatal PE at recurrence and more likely to benefit from long term anticoagulation. Otherwise PE and DVT should be considered as the same disease. Patients who develop recurrent VTE whilst still on anticoagulant treatment should be considered separately. This is important as the usual treatment is to increase the intensity of treatment with a vit K antagonist or to swap to an alternative anticoagulant (eg. LMWH or fondaparinux). There are no published trials comparing dabigatran with high intensity vit K antagonists (INR target >2.5) or extended LMWH or fondaparinux. Patients with cancer who may also be on chemotherapy will need to be considered as a separate group. Treatment with LMWH for 6 months is recommended in preference to VKA's because of published evidence of improved efficacy and less bleeding. LMWH is costly and may not be well tolerated to there will be interest in using new oral non VKA anticoagulants such as Dabigatran, however cancer patients were excluded from previous trials. Pregnant women and children will probably need to be excluded from the population until further data is available.	Comments noted. These subgroups were discussed at the workshop and consultees agreed that the subgroups for which there may be evidence in the trials are patients with DVT or PE. The analysis should consider both limited-duration and long-term anticoagulation. The other considerations section in the scope has been updated accordingly. The comparators section of the scope has been revised to separate out the comparators relevant to people with cancer in line with Clinical Guideline 144.

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	UK Clinical Pharmacy Association (UKCPA)	Yes. Separate consideration should be given to patients with active cancer.	Comment noted. Scoping workshop attendees stated it was unlikely there would be evidence to consider this group separately. However, in line with CG144, as treatment options differ for people with cancer, the comparators section of the scope has been revised accordingly.
Comparators	Boehringer Ingelheim	'No preventative therapy' should be included as a comparator, as it may be used in clinical practice for low risk patients. Also, this was a comparator in TA261. We note fondaparinux was not listed as a comparator in TA261 but has been included in this referral. LMWH could also be a comparator as some patients who are unable to take VKA stay on this for treatment, and not just the initial 5 days.	Comment noted. The comparator section in the scope has been amended following discussions at the scoping workshop, and is also in line with Clinical Guideline 144. NICE Guidance recommends that patients receive treatment for secondary prevention of VTE, so no preventative therapy is not a relevant comparator,
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.

Section	Consultees	Comments	Action
	MHRA	For initial treatment, (unfractionated) heparin can be given as an alternative to low molecular weight heparin. Also, if warfarin cannot be used for continuing treatment, low molecular weight heparin, or possibly unfractionated heparin, may be selected.	Comment noted. The comparator section of the scope has been updated following discussions at the scoping workshop, and is also in line with Clinical Guideline 144. Unfractionated heparin is not considered an appropriate comparator, as dabigatran is unsuitable or contraindicated in people in whom unfractionated heparin is recommended in Clinical Guideline 144.
	Pfizer	No comments.	Noted.

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	Royal College of Pathologists/British Society of Haematology	The comparators in the draft scope are used in clinical practice. The number of patients on long term LMWH or fondaparinux as opposed to vitamin K antagonists is very small, however this group may show a more clear cut cost effectiveness for dabigatran. It should be noted that dabigatran has not been compared to extended LMWH in randomised trials in patients with recurrent VTE and this patient group may also include cancer patients on chemotherapy who have not been represented in any published dabigatran trials A comparator group including 'no preventative treatment' should be considered for economic analysis and with recent publications (WARFASA and ASPIRE) perhaps low dose aspirin although further research is required in this regard. This represents a very small but real group of patients in clinical practice who do not comply with the requirements for monitoring vit K antagonists or have contraindications to vit K antagonists and do not accept parenteral treatment with LMWH but may be suitable for a new non VKA oral anticoagulant. There is data in abstract form (RE-SONATE) on risk of recurrent VTE in patients treated with dabigatran vs placebo for 6 months after conventional anticoagulation for a primary VTE event It should be noted that a comparator group including 'no preventative treatment' will contain patients who do not adhere with conventional therapy and therefore adherence with dabigatran might also be an issue A decision will need to made regarding the inclusion or exclusion of patients who have developed recurrent VTE whilst on conventional intensity treatment with vitamin K antagonists (INR target 2.5) and require a higher INR target or use of parenteral treatment with LMWH or fondaparinux.	Comments noted. The comparator section in the scope has been updated following discussion at the scoping workshop, and is also in line with Clinical Guideline 144. NICE Guidance recommends that patients receive treatment for secondary prevention of VTE, so no preventative therapy is not a relevant comparator,

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	UK Clinical Pharmacy Association (UKCPA)	As stated, within the scope: patients not able to receive vitamin K antagonists, would be considered for low molecular weight heparin for the duration of the planned treatment course, therefore this should be considered as a separate comparator.	Comment noted. The comparator section of the scope has been updated following discussion at the scoping workshop, and is also in line with Clinical Guideline 144.
Outcomes	Boehringer Ingelheim	Heart failure is listed as a complication. We note this was not included in TA261 and as such it should be removed from this referral. In chronic thromboembolic pulmonary hypertension (CTPH) obstruction of the pulmonary artery and increased vascular resistance in the lung increase the workload of the right ventricle and may lead to serious heart insufficiency. Heart failure is a late sequelae of CTPH. CTPH is included as a relevant complication in the draft scope.	Comment noted. During the scoping workshop, it was noted that right heart failure was a complication known to occur during the treatment of VTE. It was also noted that CTPH only occurs in a very small number of patients, but that the prevalence of right heart failure is higher.
	Lifeblood Thrombosis Charity	Yes.	Comment noted. No action required.
	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.

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	Royal College of Pathologists/British Society of Haematology	The listed outcome measurements capure important health related benefits however currently available published data on dabigatran may not be of sufficient duration to capture long term effects such as post thrombotic syndrome. Adverse events will need to include cardiac complications such as MI and acute coronary syndrome as it is possible that warfarin and dabigatran offer different levels of cardioprotection. No specific time horizon is given in the scope. Data from other treatment indications for dabigatran (eg Atrial Fibrillation) may be considered for this analysis as there is a longer follow up period then in VTE studies to date (eg RELY-ABLE study) although the AF popuation are very different to the VTE population The site of major bleeding should be considered separately in any analysis whenever possible. For example, intracranial bleeding rates (probably lower in patients on dabigatran vs warfarin) should be distinguished from gastrointestinal bleeding (probably higher in patients on dabigatran vs warfarin) as the cost and impact on the patients quality of life will be different As much as is practical (eg using quality of life analysis) the impact of dabigatran vs vit K antagonists on patient lifelstyle should be considered as this will be an important factor driving patient preference, independent of efficacy, adverse events and cost. For example, attending INR testing clinics may have a financial impact on the patient or carer as will the dietary and lifestyle restrictions associated with treatment with vit K antagonists when compared with dabigatran.	Comments noted. The outcome measure 'adverse effects of treatment' was amended following discussion at the scoping workshop.
	UK Clinical Pharmacy Association (UKCPA)	Yes.	Comment noted. No action required.
Economic analysis	Boehringer Ingelheim	No comments.	Noted.

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	Lifeblood Thrombosis Charity	No comments.	Noted.
	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.
	Royal College of Pathologists/British Society of Haematology	No specific time horizon is given in the scope. Based on more recent national and international guidelines (ACCP;BCSH;NICE), an increasing number of patients are recommended indefinite treatment and should be analysed seperately from patients requiring only 3-6 months of treatment. For primary treatment of VTE in the RE-COVER study, Dabigatran was used after a median of 9 days of treatment with therapeutic LMWH and this should be considered in the economic analysis as one might expect a similar treatment strategy for initial treatment of recurrent VTE. For patients swapping from warfarin to dabigatran, LMWH bridging should not be required As there is evidence that patients presenting with pulmonary embolism are 3 fold more likely to represent with PE when compared with patients who initially present with DVT (Thromb Haemost 2010; 8: 2436-2442). This should ideally be considered in the economic analysis as the mortality and morbidity rates are different in patients presenting with PE compared with DVT.	Comment noted. The NICE reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The typical time horizon for most appraisals is a lifetime horizon. The analysis should consider both limited-duration and long-term anticoagulation. If evidence allows DVT and PE patients will be considered as separate subgroups.
	UK Clinical Pharmacy Association (UKCPA)	Yes.	Comment noted. No action required.
Equality and Diversity	Boehringer Ingelheim	No comments.	Noted.
	Lifeblood Thrombosis Charity	The remit does not need changing with regards to equality.	Comment noted. No action required.

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	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.
	Royal College of Pathologists/British Society of Haematology	The lack of need for monitoring may benefit patients with limited mobility who no longer have to attend hospital/GP Heparin and low molecular weight heparin are of porcine origin and therefore a synthetic oral drug like dabigatran may be considered preferable by patients with specific religious or cultural beliefs who are either intolerant or unable to comply with the monitoring requirements of vit K antagonists	Comment noted. This is no longer an issue given the availability of treatment alternatives which either require no monitoring or which are not derived from porcine products.
	UK Clinical Pharmacy Association (UKCPA)	No concerns at this time.	Noted.
Innovation	Boehringer Ingelheim	No comments.	Noted.
	Lifeblood Thrombosis Charity	Yes.	Noted.
	MHRA	No comments.	Noted.
	Pfizer	No comments	Noted.

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	Royal College of Pathologists/British Society of Haematology	Represents similar innovation to Rivaroxaban (NICE TA 261). Clinical outcomes of relevance are efficacy (recurrent thrombosis) and safety (bleeding and cardiovascular events). The main innovation of dabigatran in the patient group included in this draft scope is not efficacy but rather the lack of requirement for monitoring, reduced food and drug interactions and the subsequent impacts on patient lifestyle. This makes the new oral anticoagulants, including dabigatran, highly desirable for some patients currently on vit K antagonists. It is difficult to give sufficient weight to this issue in the QALY calculation. Lack of monitoring may reduce costs associated with the use of vit K antagonists but this could easily be overestimated because the savings may be marginal as long as warfarin monitoring clinics are still required for other patient groups. Further data is expected from peer reviewed scientific publications: NCT00329238 (RE-MEDY) NCT00558259 (RE-SONATE)	Comment noted. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Yes, however it is noted that unlike rivaroxaban which is now licensed for use as a single agent for DVT and PE treatment and prevention, patients receiving dabigatran will still require initial treatment with LMWH, this therefore represents less of a 'step-change' in the management of the condition.	Comment noted. No action required.
Other considerations	Boehringer Ingelheim	No comments.	Noted.
	Lifeblood Thrombosis Charity	No comments.	Noted.
	MHRA	No comments.	Noted.
	Pfizer	No suggestions.	Noted.

Section	Consultees	Comments	Action
	Royal College of Pathologists/British Society of Haematology	No comments.	Noted.
	UK Clinical Pharmacy Association (UKCPA)	None.	Noted.
Questions for consultation	Boehringer Ingelheim	No comments.	Noted.
	Lifeblood Thrombosis Charity	No comments.	Noted.
	MHRA	No comments.	Noted.
	Pfizer	No comments.	Noted.
	Royal College of Pathologists/British Society of Haematology	No comments.	Noted.
	UK Clinical Pharmacy Association (UKCPA)	No comments.	Noted.
Additional comments on the draft scope.	Boehringer Ingelheim	None.	Noted.
	Lifeblood Thrombosis Charity	None.	Noted.

Section	Consultees	Comments	Action
	MHRA	None.	Noted.
	Pfizer	None.	Noted.
	Royal College of Pathologists/British Society of Haematology	None.	Noted.
	UK Clinical Pharmacy Association (UKCPA)	In related guidance section, it would be useful if all completed technology appraisals for apixaban, rivaroxaban and dabigatran werw listed for completeness.	Comment noted. The related guidance section has been updated accordingly.

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

Department of Health
Royal College of Nursing