Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 12/78

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This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
8	Text relating to anticipated marketing authorisation amended to reflect granted marketing authorisation.
39	Text relating to anticipated marketing authorisation amended to reflect granted marketing authorisation.
41	Text relating to anticipated marketing authorisation amended to reflect granted marketing authorisation.
43	Text relating to anticipated marketing authorisation amended to reflect granted marketing authorisation.
61	Text relating to anticipated marketing authorisation amended to reflect granted marketing authorisation.
141	Incorrect text relating to marketing authorisation has been deleted.

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer of dabigatran etexilate (Pradaxa®, Boehringer Ingelheim Ltd.) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). On the 25th April 2014 the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion of the use of Pradaxa® (dabigatran etexilate) for this indication. In July 2014, dabigatran etexilate (hereafter referred to as dabigatran) was granted UK marketing authorisation for the indication that is the focus of this single technology appraisal (STA). The marketing authorisation is for the "treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults."

The final scope issued by NICE for this STA requested a population of "both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong)". The evidence review group (ERG) notes that the manufacturer presented disaggregated evidence for these populations specified in the NICE scope. The data for those who require long-term anticoagulation was presented for those who had received at least 3 months treatment for an acute DVT and/or PE. The ERG acknowledge that this is a reflection of the clinical trial data available and clinical experts advised the ERG that this is similar to the approach that would usually be taken in UK clinical practice, i.e. patients would receive 3–6 months acute treatment and then have an assessment to decided whether to continue treatment long term for secondary prevention of venous thromboembolism (VTE).

The clinical effectiveness trial data for dabigatran presented in the manufacturer's submission (MS) for long term secondary prevention of VTE are from two trials; RE-MEDY (dabigatran versus [vs] warfarin) and RE-SONATE (dabigatran vs placebo). RE-SONATE, the placebo-controlled dabigatran trial was conducted in patients who are at equipoise for the need for continued anticoagulation for secondary prevention of VTE. However, clinical experts advised the ERG that this population is difficult to define and would not be routinely anticoagulated for secondary prevention of VTE.

All of the clinical trial data for the use of dabigatran in VTE in the MS are based on trials of 150 mg BD of dabigatran. The ERG notes that the license for dabigatran recommends this dose with the exception of certain populations (i.e. patients aged 80 years or above and patients who receive concomitant verapamil are recommended 110 mg BD). The ERG also notes that the manufacturer

does not present any trial data for the use of the 110 mg BD dose of dabigatran in VTE treatment and secondary prevention. The ERG is thus concerned about the lack of safety and

In addition, the trial protocols indicate that if any patients aged over 80 years were included in the trials then they would have received the same dose of dabigatran as those patients aged under 80 years. It can thus be concluded that no clinical trial data demonstrating the safety or efficacy of this dose reduction in people aged over 80 years were presented in the MS for this new VTE indication. This issue will be discussed further in section 3.2.

In terms of baseline index event, the ERG considers the distribution within the dabigatran trials to reflect what would be expected in typical UK clinical practice, i.e. higher rates of DVT than PE.

RE-MEDY and RE-SONATE both allowed entry of patients from either of the RE-COVER trials. It should also be noted that less than 50% of patients in RE-MEDY and less than 10% in RE-SONATE were enrolled from the RE-COVER trials. There are thus limited data on people who are treated continuously with dabigatran starting from the acute phase of a VTE through to long term secondary prevention with dabigatran.

The manufacturer reports in the MS that the population in RE-SONATE were at lower risk for recurrence of VTE compared with the population of RE-MEDY. The manufacturer explains this as follows:

"RE-MEDY included patients considered to be at high-risk of recurrent VTE and thus indicated for further anticoagulation following acute VTE, while the remaining clinical trial, RE-SONATE, was a superiority study of dabigatran vs placebo in patients for whom there was considered to be clinical equipoise regarding the need for further anticoagulation."

The clinical advisers to the ERG consider the 'clinical equipoise' population in RE-SONATE to be difficult to define in clinical practice. However, it is thought that they would most likely be people whom currently would not receive ongoing treatment for secondary prevention of VTE. It could thus be considered that the population in RE-SONATE are a different population to that currently treated for secondary prevention of VTE in the UK.

In addition, it is reported by the manufacturer that active cancer was an exclusion criterion for RE-SONATE trial entry and so there are no data available for the subgroup of people with active cancer from this trial.

The ERG and their clinical advisors also have concerns about the definition of active cancer used in the RE-COVER, RE-COVER II and RE-MEDY trials potentially not being consistent with what would be considered active cancer in UK clinical practice. In the MS it is reported that the same definition for active cancer was used in RE-COVER, RE-COVER II and RE-MEDY. The definition

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

The manufacturer reports that dabigatran was submitted to the European Medicines Agency (EMA) for regulatory approval use in treatment and prevention of recurrent VTE on 3 June 2013. CHMP positive opinion was adopted on 25 April 2014[19]. The manufacturer received marketing authorisation in the European Union for this new indication in July 2014.

The EMA positive opinion released on 25 April 2014[20] recommended the approval of dabigatran for following the indication, which is in line with that of this STA and the marketing authorisation granted in July 2014:

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The manufacturer also reported that dabigatran has already gained regulatory approval for use in this indication in Argentina, Chile, Russia, Philippines, Ecuador, Colombia, Mexico, Turkey (acute treatment only), and the USA. In addition, the manufacturer reported that they intend to make a full submission to the Scottish Medicines Consortium (SMC) for dabigatran use in this indication.

The UK marketing authorisation for dabigatran in the acute treatment of VTE restricts its use to after treatment of at least 5 days with a parenteral anticoagulant. This treatment pathway was not explicitly stated in the NICE final scope, but it was reflected in the acute VTE treatment clinical trials data supplied within the MS (RE-COVER and RE-COVER II). The ERG thus considers the data provided by the manufacturer for acute treatment of VTE with dabigatran to reflect 'initial treatment with parenteral anticoagulant and continued dabigatran'. In terms of secondary prevention, this requirement for initial treatment is not applicable as it would usually be expected that the patient would already be on some form of anticoagulation following their primary VTE event.

The standard daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. A dose reduction to 220 mg daily taken as one 110 mg capsule twice daily is recommended for the following groups:

- patients aged 80 years or above;
- patients who receive concomitant verapamil.

To summarise, the ERG considers the intervention in the MS to be consistent with the licence and the NICE final scope for this STA. However, the ERG has concerns regarding the absence of clinical trial data for the 110 mg BD dose of dabigatran in patients requiring acute treatment or ongoing secondary prevention of VTE.

3.3 Comparators

The comparators for this STA listed in the final scope issued by NICE are:

- initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist; or
- rivaroxaban.

For people with cancer, the comparators are:

- low molecular weight heparin; or
- rivaroxaban.

The manufacturer presented data for acute parenteral treatment with heparin (either LMWH or unfractionated heparin [UFH]) or fondaparinux, followed by overlapping dose-adjusted warfarin that is continued without heparin therapy once a therapeutic INR level is reached. The therapeutic INR level was defined by the manufacturer as 2.0 to 3.0; based on clinical expert advice, the ERG consider this to be comparable with the target therapeutic INR level used in equivalent patients in the UK.

The manufacturer has assumed equal efficacy for the different parenteral drugs used within the initial treatment period. In addition, there was no stratification at baseline according to the parenteral therapy used. The ERG notes that the initial parenteral therapy used was similar at baseline between the dabigatran and warfarin groups in the RE-COVER trials.[16;17] However, clinical advisers to the ERG have suggested that the use of UFH and fondaparinux in the RE-COVER trials may be slightly higher than that in the UK, although the ERG has no audit data on their use in the UK. The ERG also acknowledges that the RE-COVER trials were multi-centre international trials and that the baseline parenteral therapies used are likely to reflect variations in clinical practice across the different trial centres.

The ERG is unsure of what effect, if any, the initial parenteral therapy would have on the overall safety and efficacy of dabigatran as no data for this is provided within the MS. In addition, the ERG acknowledges that the numbers for such an analysis would be small. It would also be a non-randomised subgroup thus making it difficult to draw any conclusions. It is thus assumed within this report that the drugs used for initial parenteral therapy (i.e. prior to dabigatran or warfarin therapy) have equal efficacy.

Table 1. Duration and type of initial parenteral therapy in the RE-COVER studies (adapted from MS table 27)

	RE-COVER		RE-COVER II	
	Dabigatran (n = 1,273)	**Warfarin (n = 1,266)**	**Dabigatran (n = 1,280)**	**Warfarin (n = 1,288)**
Treatment after randomisation* (days)	median 6.0 IQR 5.0 - 8.0	median 6.0 IQR 5.0 - 8.0	6.8 ± 3.4 (mean +/- SD)	7.1 ± 3.7 (mean +/- SD)
Unfractionated heparin – n (%)	144 (11.3)	164 (13.0)	198 (15.5)	207 (16.1)
LMW heparin – n (%)	1,138 (89.4)	1,148 (90.7)	1133 (88.5)	1147 (89.1)
Fondaparinux – n (%)	50 (3.9)	36 (2.8)	32 (2.5)	21 (1.6)
*Treatment after randomisation in the single-dummy phase				

The ERG considers the treatment algorithm in the RE-COVER trials to be broadly consistent with the current UK treatment pathway for VTE and how dabigatran would be expected to be utilised in UK clinical practice. However, based on clinical expert opinion, the ERG considers that the planned duration of parenteral therapy in clinical practice may be lower than the median used in the RE-COVER trials as the dabigatran UK marketing authorisation requires a minimum of only 5 days of parenteral anticoagulation. The ERG is unsure whether this would affect the overall safety or efficacy of dabigatran.

RE-COVER and RE-COVER II outcomes

The primary efficacy endpoint in the RE-COVER trials was the composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined in the trials as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT).

The secondary efficacy endpoints and safety outcomes reported in the RE-COVER trials are presented in **Error! Reference source not found.**.

- The results of the AIC [redacted]
- The safety and efficacy data in cancer patients suggests no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-COVER or RE-COVER II.

Long-term secondary prevention of VTE

- Dabigatran was proven non-inferior to warfarin in a population intended for long-term treatment and secondary prevention of symptomatic VTE following anticoagulant treatment for 3 to 12 months after the index acute VTE event.
- There were no statistically significant between-treatment differences for the primary or secondary efficacy endpoints in RE-MEDY.
- The overall incidence of treatment-emergent reported AEs were generally similar between dabigatran and warfarin in RE-MEDY, although the ERG note that there were numerically more episodes of dyspepsia and acute coronary syndrome events with dabigatran compared with warfarin.
- There was no significant difference in major bleeding events between dabigatran and warfarin in RE-MEDY.
- Dabigatran demonstrated superiority compared with placebo for the prevention of recurrent objectively confirmed symptomatic DVT or fatal or non-fatal PE, including unexplained death in RE-SONATE (HR 0.08; 95% CI: 0.02 to 0.25).
- The results for all secondary efficacy outcomes were consistent with the primary endpoint in RE-SONATE, with fewer events with dabigatran compared with placebo.
- The overall numbers of adverse events were similar for dabigatran and placebo (RE-SONATE). However, dabigatran was associated with statistically significantly more bleeding events (any bleeding event: HR 1.82; 95% CI: 1.23 to 2.68; p=0.0027).
- [redacted] The safety and efficacy data in cancer patients suggest no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-MEDY.

1.1.1 Clinical issues

- Absence of clinical trial data to assess the safety and efficacy of the 110mg BD dose of dabigatran in acute treatment and long-term secondary prevention of VTE.