MEDICINES ASSESSMENT ADVISORY COMMITTEE

MINUTES OF THE 83rd MEETING

HELD ON 11TH SEPTEMBER 2007
MINISTRY OF HEALTH
WELLINGTON

Extract from the 83rd meeting of the Medicines Assessment Advisory Committee relating to Dabigtran

5.1.3 Rendix (dabigtran etexilate) capsules. TT50-7557/1.

The Committee considered an application submitted by Boehringer Ingelheim (NZ) Ltd for Rendix (dabigtran etexilate) capsules. The proposed indication is Rendix is indicated for the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Dabigatran etexilate is an oral direct thrombin inhibitor that specifically and reversibly inhibits thrombin, the final agent in the coagulation cascade. Dabigatran etexilate is the orally active prodrug of BIBR 953 ZW, a novel synthetic specific nonpeptide thrombin inhibitor. This agent is devoid of any antithrombin activity in vitro, however after oral administration and absorption from the gastrointestinal tract it is converted by esterases into the active moiety.

The Committee noted that the evaluation of the data relating to the composition, manufacture, quality control, stability and bioavailability of this product had not been completed.

The Committee was shown the following SCRIP article:
New drug candidates vie to fulfil ximelagatran's promise. No.3278, July 20th 2007.

Anticoagulant activity ex vivo is prolonged in a dose dependent manner in rats, monkeys and rabbits and the aPTT is a particularly sensitive assay to monitor drug levels. Antithrombotic activity was tested *in vivo* in two venous status models, one in rats and one in rabbits. There was complete inhibition of thrombus formation with the highest doses of 0.1 and 0.5mg/kg IV in rats and rabbits respectively. There was an approximately linear inverse correlation between reduction of clot size and increased aPTT in both species. Significant bleeding effects were also demonstrated with the highest dose of 1mg/kg IV.

In regards to secondary pharmacodynamic effects there was no effect on the cardiac action potential. Very little effect was demonstrated in regard to cardiovascular parameters in rats dosed up to 300mg/kg orally.

Animal pharmacokinetic studies showed there was low oral absorption. Dabigatran has a short half life of one hour in rats, 2-3 hours in rabbits and about 6-8 hours in the primate species. Distribution is low, with the highest concentration found in the liver and urinary tract. Excretion is generally via faeces.

Single dose toxicology studies showed the approximate lethal dose after single oral administration was above 200mg/kg in mice and rats and above

600mg/kg in dogs and monkeys. As expected, increased bleeding was demonstrated.

In a repeat dose study using 10040 and 200mg for 26 weeks, decreases in ALT and AST were demonstrated.

Few adverse effects have been observed in non-clinical safety studies in animals. In general these were directly or indirectly associated with increased propensity for bleeding events therefore it appears to have low risk in regard to drug safety and with considerable benefit for the treatment and prevention of thrombotic diseases.

The effect of dabigatran was assessed in clinical pharmacodynamic studies using aPTT, INR, thrombin time (TT) and ecarin clotting time (ECT).

Dabigatran etexilate is converted by non specific plasma and hepatic esterases to dabigatran following oral administration. The time to peak plasma levels is delayed to about six hours in the immediate post operative orthopaedic patient. The C_{max} and AUC are decreased to about 25% and 75% respectively of that achieved at steady state. This is considered to be an advantage permitting early dosing after surgery but with a low risk of bleeding due to the lower and delayed C_{max}. There is low plasma protein binding. The volume of distribution is 60 -70 litres indicating moderate extravascular distribution.

Dabigatran is excreted from plasma via the kidney.

The AUC when administered at a dose of 150mg twice daily in phase II studies in patients undergoing major orthopaedic surgery was on average 43% higher in female than in male patients.

The effect of food demonstrated a 27% higher AUC when dabigatran was administered with a high fat, high calorific breakfast. There was a delay of about two hours in time to reach maximum plasma concentration.

The dabigatran etexilate doses tested were selected based upon data from approximately 2000 phase II patients for the indication of primary prevention of VTE following major orthopaedic surgery; 220mg once daily or 150mg once daily each initiated with a half dose on the day of surgery.

The longer duration of prophylaxis undergoing hip replacement was specifically included in the programme design since a longer duration of treatment was anticipated to be introduced in the next versions of the standard guideline documents.

Enoxaparin is considered the gold standard therapy for VTE prevention and was therefore selected as the comparator. The regimen selected was 40mg once daily beginning the night before surgery in the two pivotal EU based studies, but 30mg twice daily beginning 12 – 24 hours post operatively in the mainly North American studies. The primary efficacy end point was total VTE

and all cause mortality. The composite of major VTE and VTE related death was a pre-specified secondary end point.

The two EU pivotal phase III studies REMODEL and RENOVATE demonstrated the non-inferiority of both doses of dabigatran etexilate compared to enoxaparin 40mg daily. In regard to the primary end point the 220mg dose of dabigatran etexilate was slightly better than the enoxaparin while enoxaparin was slightly better than the 150mg dose of dabigatran etexilate. This result was maintained through all study protocols.

The primary end point was not met in the North American based REMOBOLISE study. However the difference in total VTE rates in this study was largely driven by a difference in distal DVTs.

The pooled meta-analysis data revealed no significant difference in major VTE and VTE related mortality across the groups. The North American study differed from the EU studies in three ways. Firstly the time to first oral study medication was later in North American, the treatment duration was longer in North America and the comparator dose regimens were different. The later time of first oral study medication and the higher enoxaparin doses are believed to account for the differences in study results.

In the phase II dose selection studies a clear dose response was seen for both efficacy and safety, and no significant efficacy or safety difference was detected between the 150mg twice a day and 300mg once a day. These dose regimens were considered to have good efficacy but unacceptable rates of clinically important bleeding. At the lower end of 50mg twice a day the total VTE rate was 28.5% in this dose group compared to 24% in the enoxaparin group. This reduction in efficacy was accompanied by an absolute risk reduction from 2% in the enoxaparin group to 0.26% in absolute risk of major bleeding events in the dabigatran group.

Approximately 1200 patients undergoing major orthopaedic surgery were treated with doses >220mg daily with the highest dose being 600mg daily. No safety concerns were raised during the conduct of the non clinical safety programme other than the risk of bleeding. Major bleeding did occur significantly in doses >220mg daily.

Because of the possibility of a rebound effect after stopping any anticoagulant, special efforts were made to evaluate the potential risk of developing acute coronary syndrome. There were 19, 9 and 17 acute coronary syndrome events during treatment in patients treated with dabigatran etexilate 150mg, dabigatran etexilate 220mg and enoxaparin respectively.

Following the public disclosure of the rate of ALT elevations with ximelagatran, additional LVT surveillance was carried out. Liver function tests were carried out for up to three months following treatment. In all studies the total number of patients with ALT greater than three times ULN was 2.5% in

the 150mg group, 2.2% in the 220mg group and 3.5% in the enoxaparin group.

Committee recommendations:
That the application for Rendix (dabigatran etexilate) be deferred under Section 21 of the Medicines Act 1981 *for the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.*

This deferral is pending a satisfactory response to the following:

- **The Part II data relating to the composition, manufacture, quality control, stability and bioavailability of this product are found to be adequate and acceptable, when the evaluation is completed.**
- **The Company is asked to explain why there is a difference in the duration of dosing for knee surgery and hip surgery and to provide a justification for the different doses.**
- **Is there any evidence of rebound on stopping dabigatran?**
- **An explanation is sought on the excessive death rate on treatment.**
- **Should there be a different dosage regimen in women?**
- **What advice would be given in the treatment of VTE when patients are likely to be also taking aspirin.**
- **Should the dose be altered if the patient is also taking aspirin?**
- **The datasheet is to include advice on patient management if dabigatran is prescribed concurrently with heparin or similar.**
- **Is there any data on concurrent use of dabigatran with heparin or similar products available?**

MEDICINES ASSESSMENT ADVISORY COMMITTEE

MINUTES OF THE 85th MEETING

HELD ON 18TH MARCH 2008
MINISTRY OF HEALTH
WELLINGTON

5.2. APPLICATIONS PREVIOUSLY CONSIDERED AND DEFERRED OR DECLINED.

5.2.1 Pradaxa (dabigatran etexilate) capsules. TT50-7557/1

The Committee reconsidered an application submitted by Boehringer Ingelheim (NZ) Ltd for Pradaxa (dabigatran etexilate) capsules for the indication of the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery. The original trade name of this product was Rendix.

Pradaxa was first considered at the MAAC meeting of 11 September 2007 for the indication of the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery. The Committee recommended deferral under Section 21 pending a satisfactory response to the following:

- The Part II data relating to the composition, manufacture, quality control, stability and bioavailability of this product are found to be adequate and acceptable, when the evaluation is completed.
- The Company is asked to explain why there is a difference in the duration of dosing for knee surgery and hip surgery and to provide a justification for the different doses.
- Is there any evidence of rebound on stopping dabigatran?
- An explanation is sought on the excessive death rate on treatment.
- Should there be a different dosage regimen in women?
- What advice would be given in the treatment of VTE when patients are likely to be also taking aspirin.
- Should the dose be altered if the patient is also taking aspirin?
- The datasheet is to include advice on patient management if dabigatran is prescribed concurrently with heparin or similar.
- Is there any data on concurrent use of dabigatran with heparin or similar products available?

The Committee was shown the following SCRIP articles:
RE-NOVATE study highlights VTE study difficulties. No. 3295, September 19th 2007.
Boehringer Ingelheim's dabigatran gets EU nod. No. 3331, January 30th 2008.

The Part II data relating to the composition, manufacture, quality control, stability and bioavailability of this product are found to be adequate and acceptable, when the evaluation is completed.

The Committee noted that the initial evaluation of the data relating to the composition, manufacture, quality control, stability and bioavailability of this product had been completed. The company had been requested to provide further information to the following:

1. The proposed 10-capsule 75 mg and 110 mg carton labels are unacceptable. These presentations are intended as physician starter packs and as such should feature explicit dosage instructions.

2. Draft labelling states a recommended storage temperature of below 30°C. Analysis of the provided stability data, which were undertaken at 25°C,

3. indicates that the storage statement should be altered to "store below 25°C". Revised labelling artworks should be provided.

4. Please provide evidence whether the container closure systems present a risk, however small, regarding the accidental ingestion of desiccant. If so, the container closure systems containing a desiccant should be labelled with a warning not to ingest it.

5. Please confirm whether the provided CMI leaflet or another document is intended as the package insert.

6. Please follow the guidelines in Volume 4 of the New Zealand Regulatory Guidelines for Medicines and submit the CMI to the CMI coordinator, Medsafe, Wellington as both electronic and hard copy with a signed declaration that the CMI complies with the requirements. Please note that the CMI cannot be used (or included as a package insert) until the above regulatory requirements have been fulfilled.

7. Please provide evidence that the proposed site of drug product manufacture is capable of conducting drug product testing to GMP or GLP standards.

8. Please provide evidence that the analytical test methods have been validated, either through re-validation or the use of a technology transfer protocol, at the alternate site for testing of drug product, located at Binger Strasse 173, 55216 Ingelheim/Rhein.

9. Please tighten the drug product shelf life acceptance criterion for the active ingredient BIBR 1048 from 90 - 105% to 92.5 - 105%.

10. Please provide information regarding sampling frequency and sample size for the proposed packaging materials. Certificates of Analysis should be provided for the respective materials.

The Company is asked to explain why there is a difference in the duration of dosing for knee surgery and hip surgery and to provide a justification for the different doses.

Previous data were provided to support four to five week prophylaxis in hip replacement but that data were not available for knee replacement. The seventh ACCP consensus guideline does, however, recommend at least 10 days of prophylaxis for knee joint replacement. The doses remain the same but the duration is different. Justification was given for the half dose starting on the day of surgery, balancing efficacy and safety.

Is there any evidence of rebound on stopping dabigatran?

The company provided data that showed there was no increase in the risk of developing VTE or death during the follow-up period compared with enoxaparin. In regard to acute coronary syndrome, there is no evidence of this being more prominent following the treatment period.

An explanation is sought on the excessive death rate on treatment.

The company stated there was no clear difference in the death rate during the overall study period and any difference in the number of deaths appeared to be due to the small numbers and play of chance. The mortality rate during the treatment periods up to 11 days was similar between low molecular heparin and dabigatran and also extended through to Day 38 for extended treatment.

Should there be a different dosage regimen in women?
Plasma concentrations are approximately 35% higher in females compared to males undergoing both hip and knee joint replacements. This is thought to be largely due to differences in renal function. The company did not recommend any change in dose based on gender, because efficacy and safety were similar in males and females.

What advice would be given in the treatment of VTE when patients are likely to be also taking aspirin.
Concomitant treatment with low-dose aspirin did not appear to increase the risk of major bleeding events, but there was a slight increase in major bleeding events amongst patients receiving any dose of aspirin. The company does not recommend the use of aspirin in doses greater than 160mg per day in patients receiving dabigatran.

Should the dose be altered if the patient is also taking aspirin?
There were insufficient numbers of events to determine if the addition of aspirin significantly increased efficacy and allowed a lower dose of dabigatran. No dose adjustment was recommended.

The datasheet is to include advice on patient management if dabigatran is prescribed concurrently with heparin or similar.
The concurrent use of dabigatran and heparin or similar agents has not been evaluated and is not recommended.

Is there any data on concurrent use of dabigatran with heparin or similar products available?
Concurrent use of dabigatran with heparin or similar agents was not permitted during the clinical trial programme.

Committee recommendations:
That the application for Praxada (dabigatran etexilate) be approved under Section 21 of the Medicines Act 1981 for *the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.*

This approval is subject to a satisfactory response to the following:
- **The outstanding Part II issues are resolved satisfactorily**

That dabigatran etexilate (Pradaxa) be considered for IMMP.

MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC) REPORT ON THE EVALUATION OF THE PRECLINICAL AND CLINICAL DATA OF A NEW MEDICINE APPLICATION

ASSESSOR:

COMPOUND: Dabigatran etexilate

PRODUCT: Rendix

MEDSAFE FILE No: **TT50-7557/1**

DOSE FORM: 75 mg and 110 mg capsules

INDICATION: Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery

PROPOSED DOSAGE: 220 mg daily (standard dose)
150 mg daily (in patients with moderate renal impairment)

BACKGROUND

The prevalence of peri-operative deep vein thrombosis (DVT) after major orthopaedic surgery is 40-60%. Up to one-third of these events involve the proximal deep veins. Currently available anticoagulants are unfractionated heparin, low molecular weight heparins (LMWHs), direct thrombin inhibitors and coumarin derivatives (warfarin). Unfractionated heparin, LMWHs and the available direct thrombin inhibitors must be given parenterally. Warfarin is difficult to use, because it has a narrow therapeutic index, a slow onset of action, numerous drug interactions and needs continual monitoring. An oral direct thrombin inhibitor has several potential advantages: fast onset of action, it can be administered in a fixed dose and no requirement for monitoring. One area of concern is that another direct thrombin inhibitor (ximelagatran) was associated with acute hepatocellular toxicity in clinical trials 1-6 months after starting treatment.

Dabigatran does not have marketing authorization anywhere in the world, but applications have been submitted to the EMEA, TGA, South Africa and Switzerland.

NON-CLINICAL PHARAMCOLOGY

PHARMACODYNAMICS

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran (D). After absorption DE is converted by esterases into D. D is a synthetic, non-peptide, competitive, rapidly acting, reversible inhibitor of thrombin. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, inhibition of thrombin prevents the development of thrombus. D also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. DE does not have anticoagulant activity.

Two intermediate are formed by esterase-catalysed hydrolysis. One of these intermediates inhibits thrombin to a similar extent to D, but it does not make a significant contribution to anti-thrombotic activity due to the small amounts present in plasma and its short half-life. The other intermediate has little anti-thrombotic effect.

In vitro, DE is active in coagulation assays that simulate intrinsic, extrinsic and common pathways activation. The concentration required to achieve a 2-fold increase in APTT was 0.23 μM, ecarin clotting time (ECT) 0.18 μM and PT 0.83 μM. DE also prolongs the APTT, ECT and PT in rat, rabbit and rhesus monkey plasma. *Ex vivo* anticoagulant activity is prolonged in a dose-dependent manner in rats, rhesus monkeys and rabbits.

Rats were treated orally with doses between 5-30 mg/kg. With 5 mg/kg, 80% inhibition of thrombus formation was achieved after 30 mins. Doses ≥ 20 mg/kg resulted in complete inhibition of thrombus formation after 30 mins. Significant anti-thrombotic activity was present for up to 2 hours post-dosing. In rabbits given doses of 1-20 mg/kg, the lowest dose (1 mg/kg) was ineffective; ≥10 mg/kg resulted in maximum thrombus inhibition. Anti-thrombotic activity with 10 mg/kg was maintained for up to 7 hours.

When D was administered intravenously to rats, doses 5 times higher than the dose resulting in complete inhibition of thrombus formation induced significant bleeding.

SECONDARY PHARMACODYNAMIC STUDIES. In pigs administered the highest dose (30 mg/kg) iv, blood pressure was initially elevated and then decreased. There were no other significant proarrhythmic, cardiovascular, respiratory, gastrointestinal, renal or liver effects.

SAFETY PHARMACOLOGY STUDIES. No significant problems were identified.

PHARMACOKINETICS

Absorption and plasma pharmacokinetics. *In vivo* absorption after one oral dose was low: mice 12%, rats 21%, rabbits 5% and rhesus monkeys 5%. Pharmacokinetics was dose-linear. There was no consistent effect of gender or repeated dosing. Volume of distribution after iv administration was in the order of magnitude of the total body mass: 0.6 L/kg in rats, 1.2 L/kg in rabbits, 1.3 L/kg in rhesus monkeys and 0.8 L/kg in humans. $T_{½}$ was ~1 hour in rodents, 2-3 hours in rabbits and 6-8 hours in primates.

Tissue distribution and protein binding. Drug-related radioactivity in blood was found almost exclusively in plasma with negligible amounts in erythrocytes. After oral, iv or subcutaneous administration in rats, there was distribution into most tissues except for the central nervous system. Tissue levels were low, indicating incomplete absorption. The highest concentrations were found in the liver and urinary tract. There was no evidence of accumulation after a single dose. There was minor distribution across the placenta. There were low levels of plasma protein binding: 22% in mouse, 39% in rhesus monkey.

Metabolism. Cleavage of DE to the active moiety by esterase-catalysed hydrolysis was the most prevalent metabolic reaction. There was only a minor contribution of CYP isoenzymes to the metabolism. D was the dominant compound in plasma, urine and faeces following oral administration of DE and iv administration of D.

Excretion. >80% of radioactive-labelled drug was excreted following oral or intraduodenal administration in rats, rhesus monkeys, mice or rabbits. Only 2-11% of the dose was eliminated in the urine and 0.3-8% via bile in different species. >95% of the total dose was recovered after oral dosing. Only 0.08-0.13% of the dose was secreted into breast milk. An additional metabolite identified in breast milk of rats accounted for 21-31% of the sample radioactivity, but this metabolite was not detected in other species.

Toxicology.
Single dose toxicity studies. The lethal dose of DE after oral administration was >2000 mg/kg in mice and rats, and > 600 mg/kg in dogs and rhesus monkeys.

Repeat dose toxicity studies. In repeat dose toxicity studies (up to 26 weeks in rats and up to 52 weeks in rhesus monkeys), DE was generally well tolerated, but anticoagulant effects were observed in all species. Deaths were due to haemorrhage. There was no evidence of adverse effects on the liver.

Genotoxicity studies. There was no evidence of genotoxic or mutagenic potential.

Reproductive and developmental toxicity studies. DE produced parental toxicity related to the pharmacodynamic activity of the compound. Impairment of intrauterine viability due to bleeding into the maternal genital tract started at a dose of 70 mg/kg in rats. Pharmacodynamic effects of DE on the mothers were responsible for post-natal deaths at doses of 70 mg/kg. The embryo-fetal development toxicity study in rabbits also indicated maternal effects at 200 mg/kg. No teratogenic effects were observed.

Local tolerance studies. There was no evidence of local intolerance except for haemorrhages induced by DE.

Immunotoxicity. In rats there was a slight reduction in splenic lymphocytes in females at doses of 100 and 300 mg/kg. This was not dose-related and males did not show similar changes. There was no histopathological abnormality in the spleen, other lymphatic or haemopoietic organs of affected animals. The change in splenic lymphocytes was not thought to be drug-related.

SUMMARY.
D is a specific inhibitor of thrombin. *In vivo* there is a relatively wide safety window between anti-thrombotic activity and bleeding side effects. Adverse effects were associated with bleeding events.

CLINICAL STUDIES

PHARMACODYNAMICS

The maximum effect on APTT, PT, thrombin time and ECT occurred at the same time as C_{max}. In patients who are bleeding, an APTT >2.5x control suggests excessive anticoagulation.

PHARMACOKINETICS

Absorption and distribution. DE is rapidly absorbed after oral administration. It is rapidly converted to D. DE is only transiently detectable in plasma. Two intermediates, one of which is a thrombin inhibitor, are detectable at low concentrations for <6 hours following oral dosing. Peak plasma concentrations of D occur 1-2 hours after administration in healthy volunteers, but the time to the peak plasma level is delayed to about 6 hours in the post-operative patient. In post-operative patients, C_{max} is decreased to 25% and AUC is decreased to about 75% of that achieved at steady state. There is a low level of concentration-independent plasma protein binding. The volume of distribution of D is 60-70 L. There is dose linearity for doses of 10 to 600 mg of DE. Absolute bioavailability of D after oral administration of DE is 6.5%.

Many of the Phase I clinical trials were performed before the development of the capsule formulation used in the Phase II and III studies. Limited data are available from Phase I studies with the final formulation, but pharmacokinetic data is available from a Phase II study in patients with atrial fibrillation, which also used the capsule formulation.

Metabolism and excretion. D is primarily excreted via the kidneys. The rate of renal clearance is similar to the GFR, which suggests D is eliminated via filtration without net tubular secretion or absorption. 85% of ^{14}C-labelled iv D is excreted in the urine within 168 hours in healthy male volunteers and 6% was excreted in faeces. Following oral administration of labeled DE, 86% was recovered in the faeces (because of low oral bioavailability of DE) and 7% in urine.

Renal impairment. In otherwise healthy volunteers with mild renal impairment (CrCl 50-80 mL/min), the AUC for D increased 1.8-fold, compared with healthy volunteers with normal renal function. The corresponding increase in the AUC for moderate impairment was 2.7-fold and 6.8-fold for severe impairment.

Hepatic impairment. Following a single oral dose of DE, the mean AUC in normals and patients with hepatic impairment were comparable. The conversion of DE to D was slightly slower. Protein binding and the extent of glucuronidation of D in subjects with moderate hepatic impairment were unchanged.

Elderly subjects. The steady state AUC in subjects > 65 was 2x higher than in healthy subjects 18-40 years old. The difference between elderly and younger subjects was largely due to a decline in CrCl.

Post-operative patients. The pharmacokinetic profile of D administered 1-3 hours after orthopaedic surgery was characterised by slow, prolonged absorption and a flat plasma

concentration-time profile. The mean availability of D after the first dose was taken <4 hours after surgery was 75% of the steady state AUC measured on Day 4 after surgery.

Gender. Steady state AUC in patients undergoing surgery was 43% higher in females than in males.

Drug interactions. There was no evidence of metabolism, inhibition or induction of cytochrome P450 isoenzyme-mediated metabolism. Erythromycin had no effect on *in vitro* metabolism of DE. Co-administration of amiodarone resulted in an increase of D AUC and C_{max}. In healthy volunteers, co-administration of pantoprazole resulted in a 30% decrease in steady state exposure.

Food. In healthy volunteers, average bioavailability of D was 27% higher when DE was given with a high fat, high calorie breakfast compared to the fasted state. There was a delay of 2 hours in the time to reach maximum plasma concentrations with a 8.5% increase in C_{max}.

CLINICAL EFFICACY

Study 1160.19 (BISTRO II). This was a Phase II randomised, double-blind, active-controlled in 1973 patients undergoing THJR or TKJR surgery. The aim was to establish the dose-response relationship for efficacy and safety. This study used a capsule, which was similar but not identical to the marketed formulation. The same formulation was used in the Phase III trials. Patients were randomised to DE 50mg bid, DE 150 mg bid, DE 225 mg bid, or DE 300 mg qd started 1-4 hours after surgery or enoxaparin 40 mg qd started 12 hours before surgery for 5-10 days. 1464 patients were evaluable for the primary outcome. VTE occurred as follows: 50 mg bid 28.5%, 150 mg bid 17.4%, 300 mg qd 16.6%, 225 mg bid 13.1% and enoxaparin 24.0%. There was a significant dose-dependent decrease in VTE with increasing doses of DE. The 150 mg bid ($p = 0.0015$) and 225 mg bid ($p<0.001$) groups each significantly reduced VTE compared with 50 mg bid. When compared with enoxaparin, significantly lower VTE rates were seen in patients receiving DE 150 mg bid (OR 0.65, $p = 0.04$), 300 mg qd (OR 0.61, $p = 0.02$) and 225 mg bid (OR 0.47, $p = 0.0007$). There was no significant difference in VTE rate between DE 300 mg qd and DE 150 mg bid. In a post hoc analysis, patients who received the first dose <2 hours post-operatively had a lower incidence of DVT compared with those who had the first dose >2 hours after surgery. It was concluded that the dose best balancing efficacy and safety was 100-300 mg per day.

There has been one pivotal (RE-MODEL) and one "supportive" study (RE-MOBILIZE) in total knee joint replacement surgery and a pivotal study in total hip replacement surgery (RE-NOVATE). These trials used a randomized, double-blind, parallel group design. The main endpoints were (1) total VTE and all-cause mortality; (2) major VTE and VTE-related mortality. Total VTE included proximal and distal DVT detected by routine venography; symptomatic DVT confirmed by compression ultrasound, venography, or autopsy; and pulmonary embolism (PE). Major VTE included proximal DVT or PE.

RE-MODEL and RE-NOVATE compared 2 doses of DE (150 mg and 220 mg once daily) with enoxaparin 40 mg once daily. The first dose of DE was administered 1-4 hours pre-operatively, while the initial dose of enoxaparin was given prior to surgery. In RE-MOBILIZE a higher dose of enoxaparin (30 mg twice daily) was used.

The primary goal of each trial was to demonstrate non-inferiority of DE compared with enoxaparin for total VTE and all-cause mortality. The non-inferiority margins were defined as an absolute difference of 9.2% for the primary endpoint for RE-MOBILIZE and RE-MODEL and 7.7% for RE-NOVATE. Patients were followed for 13 weeks after surgery.

Study 1160.25 (RE-MODEL). Patients requiring TKJR were recruited. There were 3 treatment groups: DE 220 mg qd (n = 693), DE 150 mg qd (n = 708) and enoxaparin 40 mg qd (n = 699). Treatment duration was 6-10 days.

Table: Total VTE and all-cause mortality:

Treatment	n	Incidence	Risk diff. vs. enox.	OR vs. enox	Effectiveness of enox. (%)
DE 220 mg	503	36.4%	-1.3% (-7.3, +4.6%)	0.9 (07,1.2)	83%
DE 150 mg	526	40.5%	+2.8% (-3.1, +8.7%)	1.1 (0.9,1.4)	69%
Enox 40 mg	512	37.7%			

enox = enoxaparin, DE = dabigatran etexilate, OR = odds ratio, risk diff = risk difference

The upper bound of the 95% CIs of the risk difference between each DE group and the enoxaparin group was below the pre-specified non-inferiority margin of 9.2%. Therefore, both doses of DE were non-inferior to DE. The biggest contribution to the primary endpoint was asymptomatic DVTs detected by venography: 36.0% for DE 220 mg, 39.5% for DE 150 mg and 35.9% for enoxaparin. One patient in each group died. Non-fatal PE occurred during the treatment period in 1 patient randomized to DE 150 mg; there were no non-fatal PEs in the other 2 groups. The incidence of major VTE and VTE-related mortality was 2.6% (DE 220 mg), 3.8% (DE 150 mg) and 3.5% (enoxaparin).

Study 1160.48 (RE-NOVATE). Patients for THJR were randomised to DE 220 mg qd (n= 1157), DE 150 mg qd (n = 1174) or enoxaparin 40 mg qd (n = 1162). Treatment duration was 28-42 days.

Table: Total VTE and all-cause mortality

Treatment	n	Incidence	Risk diff. vs. enox.	OR vs. enox	Effectiveness cf. enox (%)
DE 220 mg	880	6.0%	-0.7% (-2.9,+1.6 %)	0.9 (0.6,1.3)	93%
DE 150 mg	874	8.6%	1.9% (-0.6, +4.4%)	1.3 (0.9,1.9)	81%
Enox 40 mg	897	6.7%			

The upper bound of the 95% CI of the differences in total VTE and all-cause mortality between the DE groups and the enoxaparin group were within the pre-specified non-inferiority margin of 7.7%.

Asymptomatic DVTs occurred in 4.5% of the DE 220 mg group, 7.2% of DE 150 mg group and 6.2% of the enoxaparin group. Symptomatic DVTs occurred in 5 patients in the DE 220 mg group, 9 patients in the DE 150 mg group and 1 patient in the enoxaparin group. Non-fatal PEs: DE 220 mg (n = 5), DE 150 mg (n = 0), enoxaparin (n = 3). The incidences of major VTE and VTE-related mortality were 3.1% (DE 220 mg), 4.3% (DE 150 mg) and 3.9% (enoxaparin).

Study 1160.24 (RE-MOBILIZE): Patients undergoing TKJR were randomised to DE 220 mg qd (n = 862), DE 150 mg qd (n =877) or enoxaparin 30 mg bid (n = 876). Duration of treatment was 12-15 days. There were several differences in the trial design compared with the other two trials. In the first 2 studies, patients were randomized before surgery, enoxaparin was started the evening before surgery and the first dose of DE was given 1-4 hours after surgery. In RE-MOBILIZE, patients were randomised at the completion of surgery, enoxaparin was started 12-24 hours after surgery and the first dose of DE was given 6-12 hours after surgery.

Table: Total VTE and all-cause mortality

Treatment	n	Incidence	Risk diff. vs. enox.	OR vs. enox	Effectiveness cf. enox (%)
DE 220 mg	604	31.1%	5.8% (0.8, 10.8%)	1.3 (1.0,1.7)	60.9%
DE 150 mg	649	33.7%	8.4% (3.4, 13.3%)	1.5 (1.2, 1.9)	49.8%
Enox 60 mg	643	25.3%			

The upper bound of the 95% CI of the differences in total VTE and all-cause mortality between both DE dose groups and the enoxaparin group exceeded the pre-specified non-inferiority margin of 9.2%; i.e. enoxaparin was superior to both doses of DE.

Table:

	DE 220 mg	DE 150 mg	Enoxaparin
Asymptomatic DVTs	28.8%	32.7%	23.8%
Symptomatic DVTs	n = 7	n = 6	n = 5
Non-fatal PE	n = 6	n = 0	n = 5
Major VTE/VTE-related mortality	3.4%	3.0%	2.2%

The risk difference of major VTE or VTE-related mortality vs. enoxaparin was 1.2% (-0.7%, 3.0%) in DE 220 mg group and 0.8% (-0.9%, 2.5%) in DE 150 mg group.

Analysis of the combined results of the three Phase III trials.

***Table: Major VTE and VTE-related mortality during treatment period*:**

Treatment	n	Incidence (%)	Diff. vs. Enox. (%)	(95% CI)
DE 220 mg	2033	62 (3.0)	- 0.2 %	(-1.3, 0.9)
DE 150 mg	2071	78 (3.8)	+ 0.5 %	(-0.6, 1.6)
Enoxaparin	2096	69 (3.3)		

DE 220 mg resulted in an absolute risk reduction of 0.2% compared with enoxaparin and DE 150 mg produced a 0.5% increase in risk compared with enoxaparin. In other words, there was no significant difference among the three treatment arms.

SAFETY

7942 subjects have received at least one dose of DE in 30 Phase I, 2 Phase II and 3 Phase III trials. The only safety concern raised in the non-clinical programme was the risk of bleeding. The frequencies of any adverse event (AE), severe AEs, investigator-judged drug-related AEs, AEs leading to discontinuation of the study drug and serious AEs in the 1 Phase II and 3 Phase III VTE prevention studies was similar between each of the dose regimens of DE proposed for marketing and enoxaparin. The only AE that demonstrated a dose-response effect related to DE is bleeding. The other AEs occurred at rates comparable to the rates observed in patients treated with enoxaparin.

Table: Treatment-emergent adverse events in actively controlled VTE prevention trials

	<150 mg	150mg	220mg	>220mg	Enox
Number	389	2737	2682	1168	3108
Any AE	312 (80.2)	2235 (81.7)	2190 (81.7)	970 (83.0)	2558 (82.3)
Severe AE	9 (2.3)	98 (3.6)	99 (3.7)	65 (5.6)	102 (3.3)
Drug-related	55 (14.1)	238 (8.7)	238 (8.9)	206 (17.6)	317 (10.2)
AE→discont.	16 (4.1)	151 (5.5)	145 (5.4)	88 (7.5)	166 (5.3)
Serious AEs	16 (4.1)	192 (7.0)	179 (6.7)	61 (5.2)	191 (6.1)

Major Bleeding events. In the trials that used pre-operative randomisation, the rate of major bleeding events showed a clear dose-response relationship. The rates of major bleeding events at the doses proposed for marketing were comparable: DE 150 mg 1.3%, DE 220 mg 1.8% and enoxaparin 1.6%. The rate of major bleeding events at doses >220 mg was higher (4.2%). In RE-MOBILIZE (post-operative randomization) the rates of major bleeding events were: DE < 150 mg 0, DE 150 mg 0.6%, DE 220 mg 0.6%, DE > 220 mg 0, enoxaparin 1.4%. Higher rates of major bleeding events were reported in patients with renal impairment and patients >75.

The rate of clinically relevant bleeding events tended to be higher in the pre-operative randomisation trials: DE < 150 mg 2.3%, DE 150 mg 5.5%, DE 220 mg 4.8%, DE > 220 mg 4.1%, enoxaparin 3.9%.

Deaths. The death rates were: DE <150 mg 0.3%, DE 150 mg 0.3%, DE 220 mg 0.3%, DE >220 mg 0.1%, enoxaparin 0.2%.

Acute coronary syndrome. Because of the possibility of a rebound effect after stopping an anticoagulant, the risk of developing an acute coronary syndrome was monitored. There were 19, 9 and 17 acute coronary syndrome events during treatment in patients treated with DE 150 mg, DE 220 mg and enoxaparin respectively. During follow-up, there were 2, 1 and 7 events in the same groups.

Liver function tests. In the 3 active-controlled Phase III VTE prevention studies, the total number of patients with ALT >3x the upper limit of normal was 2.5% in 150 mg DE group, 2.2% in DE 220 mg group and 3.5% in the enoxaparin group. It is possible that DE could cause hepatotoxicity with longer terms of treatment

POST-MARKETING EXPERIENCE.
Nil

DATA SHEET

SUMMARY
In 2 of the Phase II trials (RE-MODEL and RE-NOVATE), DE 150 mg and 220 mg were non-inferior to enoxaparin for the primary and secondary efficacy endpoints. In the third

Phase III trial (RE-MOBILIZE), non-inferiority was not demonstrated: enoxaparin was superior to both doses of DE. The application attributes this difference to the other two trials to differences in methodology. When the results of the three trials are combined, non-inferiority is demonstrated. It should be noted that the vast majority of the endpoint events were asymptomatic DVTs; symptomatic DVTs, PE and VTE-related death were uncommon in all treatment groups.

Bleeding is the main safety, but the risk of bleeding complications associated with DE 150 mg and DE 220 mg was similar to the rate on enoxaparin. Another oral direct thrombin inhibitor is associated with hepatotoxicity 1-6 months after starting treatment. Although there is no indication that hepatotoxicity occurs with DE from the data presented, the possibility of hepatotoxicity with longer duration of treatment has not been excluded.

Extract from the minutes of the 37th meeting of the Medicines Classification Committee relating to the classification of Dabigatran.

Full minutes are available on the Medsafe Website

CLASSIFICATION OF MEDICINES

Minutes of the May 2007 Medicines Classification Committee Meeting

**MINUTES OF THE 37TH MEETING
OF THE MEDICINES CLASSIFICATION COMMITTEE
HELD IN THE MEDSAFE BOARDROOM
LEVEL 6, DELOITTE HOUSE, 10 BRANDON STREET WELLINGTON
ON 17 MAY 2007 COMMENCING AT 9:30 AM**

7. NEW MEDICINES FOR CLASSIFICATION

Only one new chemical entity had been referred by the Medicines Assessment Advisory Committee for classification.

Dabigatran etexilate

The proposed indication for dabigatran etexilate was the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

The Committee agreed that dabigatran etexilate should be classified as a prescription medicine.

Recommendation

That dabigatran etexilate should be classified as a prescription medicine.