Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dabigatran etexilate mesilate

Proprietary Product Name: Pradaxa

Sponsor: Boehringer Ingelheim Pty Ltd

May 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications, New Strength, Changes to Currently Approved Strengths
Decision:	Approved
Date of Decision:	29 April 2011
Active ingredient(s):	Dabigatran etexilate mesilate
Product Name(s):	Pradaxa
Sponsor's Name and Address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde NSW 2113
Dose form(s):	Capsules
Strength(s):	75, 110 and 150 mg
Container(s):	Bottles and blister packs
Pack size(s):	10 capsules in blister packs 60 capsules in both bottles and blister packs
Approved Therapeutic use:	Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement) (see Dosage and Administration section for details of treatment duration). Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.
Route(s) of administration:	Oral
Dosage:	Venous thromboembolic events prevention: 220 mg daily or 150 mg daily in moderate renal impairment for 10 days (knee replacement) or 28-35 days (hip replacement). Atrial fibrillation: 150 mg twice daily or 110 mg twice daily in moderate renal impairment may be considered. Patients 75 years and above should take 110 mg twice daily and patients at higher risk of major bleeding should consider 110 mg twice daily.
ARTG Number (s):	137832, 138402, 138415, 138421, 168211, 168215

Product Background

This AusPAR describes the evaluation of a submission by the sponsor (Boehringer Ingelheim Pty Ltd) to extend the indications of dabigatran etexilate mesilate (Pradaxa) to include the prevention of stroke, systemic embolism and reduction of vascular mortality in

patients with atrial fibrillation. The submission also includes an application to register Pradaxa capsules in a new strength of 150 mg and to register manufacturing changes for the 75 mg and 110 mg strengths in order to align them with those proposed for the new 150 mg strength.

Pradaxa is currently approved in Australia for the prevention of thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). Pradaxa is currently registered in oral capsules of 75 mg and 110 mg strengths.

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran, a potent, competitive and reversible thrombin inhibitor. After oral administration, DE is rapidly absorbed and converted to dabigatran by serum esterase-catalysed hydrolysis in the plasma and the liver. The absolute oral bioavailability of dabigatran is approximately 6.5%.

Regulatory Status

The product received initial ARTG registration on November 2008.

At the time of submission, Pradaxa was not approved in any country for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF). The sponsor stated that similar applications to extend the indications to include AF, register a new 150 mg strength capsule, and make manufacturing changes to the 75 mg and 110 mg capsules have been, or will be, submitted to a number of countries in which Pradaxa has been approved for the prevention of venous thromboembolism (VTE) in orthopaedic surgery (OS) patients. The countries and regions in which Pradaxa is approved for the prevention of VTE in OS patients include the European Union (EU) and New Zealand.

Pradaxa was not submitted in the USA for the prevention of VTE in OS patients. However, Pradaxa 75 mg and 150 mg capsules were approved in the US on 19 October 2010 for the following Indication:

Pradaxa is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Pradaxa 110 mg and 150 mg capsules were approved in Canada on 26 October 2010 for the following Indication:

Prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Introduction

Dabigatran etexilate (Pradaxa) 75 mg and 110 mg capsules are currently registered in Australia in both polyamide-Al/PVC-Al blister packs and polypropylene bottles by Boehringer Ingelheim. The capsules contain dabigatran etexilate mesilate equivalent to the stated quantity of dabigatran etexilate.

The present submission seeks to extend the currently approved indication. In view of the increased dose recommended for the new indication (150 mg twice daily), the sponsor

also proposed to register a 150 mg capsule. In addition, a number of changes were proposed to the drug substance and to the currently registered capsules.

Drug Substance (active ingredient)

Dabigatran etexilate is a weakly basic substance that is soluble in acidic media (> 5% in 0.1 M HCl) but practically insoluble in neutral and basic media (0.0003% at pH 7.4).

The sponsor proposed several amendments to the method of synthesis of the drug substance, including an alternative method for synthesising the key 'amidine' intermediate. An alternative manufacturer was also proposed, milling of the drug substance to a specified particle size distribution was now mandatory, and the limit for polymorph II has been increased from 1% to 30%. The latter change has been justified on the basis of a study that showed bioequivalence of capsules manufactured from polymorph I or polymorph II (Study 1160.66) (see below).

The changes proposed to the drug substance were acceptable.

Drug Product

The currently registered 75 mg and 110 mg capsules are manufactured using the so-called first generation process, which involves coating of the tablet cores in a rotating pan. The sponsor proposed to replace this process with the second generation process, which involves fluid bed coating. Several other changes were proposed to the process, including amended drying conditions for the bulk capsules.

The proposed 150 mg capsules will also be manufactured using the second generation process and will be a direct scale of the new 75 mg and 110 mg capsules (that is, the three strengths differ only in the fill weight of the capsule contents).

The changes to the 75 mg and 110 mg capsules have been justified on the basis of comparative dissolution data and on the basis of a study that showed bioequivalence of first generation and second generation 150 mg capsules (Study 1160.70) (see below). The routine quality control dissolution limit for the capsules has been tightened.

The large size 150 mg capsules are too big to allow free movement in the standard pharmacopoeial basket apparatus. This resulted in sporadic low dissolution results. This has been overcome by developing a slightly larger basket apparatus, which allows free movement of the capsules. The sponsor satisfactorily demonstrated that an appropriate dissolution method could not be developed using standard apparatus and agreed to provide the TGA with the large size baskets for product testing purposes. The modified dissolution method has, therefore, been accepted.

Adequate stability data have been submitted to support a shelf life of 3 years below 30°C in both packaging types (polypropylene bottles and polyamide-Al/PVC-Al blister packs).

Biopharmaceutics

Dabigatran etexilate is a prodrug that is rapidly absorbed following oral administration and converted by non-specific plasma and hepatic esterases into the active moiety, dabigatran. Conversion to dabigatran involves the hydrolysis of two functional groups: an ethyl ester and the etexilate group. There are two intermediate metabolites, depending upon which of these groups is hydrolysed first. Dabigatran etexilate and the two intermediate metabolites are only transiently detectable in plasma. Dabigatran is further metabolised to four pharmacologically active acyl glucuronides. The total area under the plasma concentration time curve (AUC) of the four glucuronides is approximately 25% of the AUC of free dabigatran. In the submitted bioavailability studies, the sponsor analysed

both free dabigatran and 'total dabigatran' (dabigatran concentration after alkaline hydrolysis of the glucuronides).

The absolute bioavailability of dabigatran after oral administration of dabigatran etexilate capsules is approximately 6.5%.

Three bioavailability studies were evaluated in the context of the present submission:

Study 1160.66 was a single dose, replicate study (each treatment was given to each subject twice) in 66 healthy elderly subjects, comparing 150 mg capsules manufactured from polymorph 1 or polymorph 2. The two capsules were found to be bioequivalent, as shown in Tables 1 and 2 (results based on an unscaled average bioequivalence analysis).

Table 1: Pharmacokinetic parameters for free dabigatran in Study 1160.66

Free dabigatran	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_t (ng.h/mL)**	**$AUC_¥$ (ng.h/mL)**	**$t_{½}$ (h)**
A: polymorph I	2.0	97.1 ± 45.5	907 ± 420	940 ± 420	9.9 ± 2.2
Range:	1.2 – 3.5				
B: polymorph II	2.0	98.0 ± 49.1	918 ± 472	953 ± 470	10.2 ± 2.5
Range:	1.5 – 4.0				
Statistical analysis:		***ratio (%)***	***ratio (%)***	***ratio (%)***	
B vs A Estimate		96.0%	97.3%	98.3%	
90% CI		87.1 – 105.9%	89.0 – 106.3%	90.5 – 106.7%	

T_{max}: time to maximal plasma concentration
C_{max}: maximal plasma concentration
AUC_t: area under the plasma concentration time curve for a dosing interval
AUC_∞: area under the plasma concentration time curve from time zero to infinity
$t_{1/2}$: half-life

Table 2: Pharmacokinetic parameters for total dabigatran in Study 1160.66

Total dabigatran	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_t (ng.h/mL)**	**$AUC_¥$ (ng.h/mL)**	**$t_{½}$ (h)**
A: polymorph I	2.0	118 ± 53	1170 ± 495	1200 ± 495	11.6 ± 3.2
Range:	1.2 – 3.5				
B: polymorph II	2.1	120 ± 57	1190 ± 555	1230 ± 555	11.4 ± 2.7
Range:	1.2 – 4.0				
Statistical analysis:		***ratio (%)***	***ratio (%)***	***ratio (%)***	
B vs A Estimate		95.5%	96.9%	97.8%	
90% CI		86.6 – 105.4%	88.7 – 105.9%	89.9 – 106.3%	

Study 1160.70 was a single dose, replicate study in 66 healthy elderly subjects, comparing 150 mg capsules manufactured using the first generation or second generation processes. On the basis of a scaled average bioequivalence analysis, the sponsor claimed that the two products are bioequivalent. However, strict bioequivalence was not

demonstrated when an unscaled average bioequivalence approach was used, with the second generation capsules having a 13% higher C_{max} and AUC than the first generation capsules (see Tables 3 and 4).

Table 3: Pharmacokinetic parameters for free dabigatran in Study 1160.70

Free dabigatran	T_{max} (h)	C_{max}	AUC_t	$AUC_¥$	$t_{½}$
A: 1st generation	2.0	97.1 ± 57.0	939 ± 578	970 ± 579	9.8 ± 1.6
Range:	1.4 – 3.5				
B: 2nd generation	2.1	108 ± 57.8	1030 ± 565	1060 ± 564	9.9 ± 1.8
Range:	1.2 – 4.2				
Statistical analysis:		***ratio (%)***	***ratio (%)***	***ratio (%)***	
B vs A Estimate		113.3%	112.5%	112.1%	
90% CI		101.6 – 126.3%	101.6 – 124.6%	101.8 – 123.5%	

Table 4: Pharmacokinetic parameters for total dabigatran in Study 1160.70

Total dabigatran	T_{max} (h)	C_{max}	AUC_t	$AUC_¥$	$t_{½}$
A: 1st generation	2.1	119 ± 65	1210 ± 687	1240 ± 687	10.8 ± 1.8
Range:	1.5 – 4.0				
B: 2nd generation	2.1	132 ± 67	1330 ± 681	1360 ± 682	10.8 ± 1.8
Range:	1.2 – 4.2				
Statistical analysis:		***ratio (%)***	***ratio (%)***	***ratio (%)***	
B vs A Estimate		113.2%	113.1%	112.3%	
90% CI		101.4 – 126.2%	102.0 – 125.4%	101.9 – 123.9%	

The scaled average bioequivalence approach is the most appropriate for this replicate study but the TGA currently does not have access to the appropriate statistical software to repeat that analysis. Therefore, the free dabigatran data were re-analysed, treating periods 3 and 4 as though they were a different set of subjects from those in periods 1 and 2, that is, the data were analysed as a 130 subject, two period, two sequence analysis of variance (ANOVA). The results of this analysis (point estimate and 90% confidence intervals) are shown below.

Gen 2 vs Gen 1

C_{max}	AUC_t	$AUC_¥$
113.3% (102.5 – 125.1%)	112.5% (102.2 – 123.8%)	112.1% (102.4 – 122.7%)

On the basis of this re-analysis and the scaled average bioequivalence analysis applied by the sponsor, the two generations of capsule were considered bioequivalent.

Study 1160.87 compared the 150 mg capsule swallowed whole with the contents sprinkled on food and with a pH 1.8 oral solution of the drug. The results are shown in the Table 5.

Table 5: Pharmacokinetic parameters for total dabigatran in Study 1160.87

Total dabigatran	C_{max} *ratio (%)*	AUC_{∞} *ratio (%)*
Sprinkle/whole capsule	187%	175%
90% CI	148 – 237%	142 – 216%
Solution/whole capsule	167%	155%
90% CI	133 – 208%	127 – 188%

Previous studies showed that food has little or no effect on the bioavailability of capsules swallowed whole, so this study indicates that removal of the contents from the capsule shell (either sprinkled on food or given as an oral solution) causes a considerable increase in the bioavailability of the drug. This is of some concern because it indicates that the capsules are not optimally formulated, with the consequence that bioavailability could be variable from one batch to another. Nevertheless, the currently registered, first generation capsules have been in clinical use for some time, and the second generation capsules have been shown to be bioequivalent to the registered capsules.

All of the above bioavailability studies were conducted on the new 150 mg capsule. The company provided a justification for not conducting similar studies on the 75 mg and 110 mg capsules. The three strengths of capsule differ only in the fill weight of the dabigatran etexilate pellets, and their dissolution profiles are comparable. Dabigatran etexilate mesilate is highly soluble under acidic conditions, and pharmacokinetics linear over the dose range. The arguments provided were accepted.

Quality Summary and Conclusions

There were no objections in respect of chemistry, manufacturing and controls to registration of Pradaxa 150 mg capsules. There were also no objections to the proposed changes to the active ingredient and the currently registered Pradaxa 75 mg and 110 mg capsules. The three strengths of capsule are considered bioequivalent at equal dose, and the new 75 mg and 110 mg capsules are bioequivalent to the currently registered capsules.

III. Nonclinical Findings

Pharmacology

Primary and secondary pharmacodynamics

Dabigatran is a thrombin inhibitor. Four pharmacodynamic studies were provided in this submission. Both the mesilate salt and the base of dabigatran etexilate prolonged thrombin time (TT) and activated partial thromboplastin time (APTT) in rats 24 hours (the only sampling time) after an oral dose of 70 mg/kg (base equivalent). The increase in APTT was small (< 20%), compared with a 13-fold increase in an earlier study in the same species within 3 hours of an oral dose of 100 mg/kg mesilate salt. Blood concentrations of

dabigatran were not determined in the new study but the finding suggests that dabigatran was most likely still present in plasma but at very low levels 24 hours after dosing.

Another rat study with intravenous (IV) infusion of dabigatran (0.1 μmol/kg/h) showed that recombinant factor VIIa [Novoseven, 0.1 mg/kg] as well as activated prothrombin complex concentrate [Feiba, 50 U/kg] reversed the prolonged bleeding time (BT) induced by dabigatran. The prolongation of APTT induced by dabigatran was partially reversed by Novoseven, whereas no reversal was observed with Feiba. The study findings suggest that Novoseven and Feiba may be effective in the treatment of dabigatran-induced bleeding.

The anticoagulant activity of the intermediate metabolites (also named mono-prodrug), BIBR 951 and BIBR 1087, were also studied. BIBR 951 prolonged TT and APTT and doubled TT and APTT at 0.04 and 0.37 μM, respectively, with a median inhibitory concentration (IC_{50}) value of 20.7 nM for TT, while BIBR 1087 displayed minimal anticoagulant activities with an IC_{50} value of 1.96 μM for TT. The anticoagulant activity of BIBR 951 was comparable with that of dabigatran, which doubled APTT at 0.23 μM. Since only trace amounts of BIBR 951 were detected in humans after administration of dabigatran etexilate mesilate, it is unlikely that this intermediate metabolite has any significant contribution to the anticoagulant effect of dabigatran etexilate mesilate.

Screening of dabigatran and the prodrug for binding to receptors and ion channels showed no significant binding of dabigatran to any receptor and moderate binding of the BIBR 1048 MS to 16 receptors (for example, benzodiazepine and calcium channel) with IC_{50} values in the micromolar range. Since the prodrug is rapidly hydrolysed to dabigatran *in vivo* and it is present in plasma at very low concentrations (around 5-10 nM) in patients for a short period after dosing, the moderate binding to receptors and ion channels observed in the screening assay is not of safety concern.

Pharmacokinetics

Analysis

The stability of dabigatran etexilate mesilate (BIBR 1048 BS), the intermediate metabolites (mono-pro-drugs, BIBR 1087 SE and BIBR 951 BS) and dabigatran in mouse plasma was studied. Citric acid and paraoxone were tested for their suitability as a stabiliser for the above substances. BIBR 1048 and 951 are unstable in mouse plasma and the two compounds are rapidly hydrolysed to BIBR 1087 (an intermediate pro-drug) and BIBR 953 (active moiety), respectively. Addition of citric acid stabilises BIBR 1048 but has little effects on the stability of BIBR 951 at room temperature. BIBR 1087 is stable in mouse plasma, but rapidly breaks down in the presence of citric acid. Paraoxone stabilises BIBR 951 and partially BIBR 1048, and does not affect the stability of BIBR 1087 in mouse plasma. The findings indicate neither paraoxone nor citric acid is a satisfactory stabiliser for all dabigatran pro-drugs; etexilate mesilate and the intermediates. More than one plasma sample with different stabilisers would be required for the accurate measurement of plasma dabigatran etexilate mesilate, BIBR 1087, BIBR 951 and dabigatran (BIBR 953) concentrations. If mouse plasma is untreated, any BIBR 1048 and BIBR 951 present in the blood at the time of sampling would be converted to BIBR 1087 and BIBR 953 *ex vivo*, respectively.

Dabigatran measured in mouse plasma samples in the toxicity studies might include BIBR 951, which is rapidly hydrolysed to BIBR 953 *ex vivo* after sampling. However, since BIBR 951 has similar anticoagulant activity to dabigatran, the safety assessment is not compromised by the measurement of both BIBR 953 and BIBR 951 as the active moiety, BIBR 953, in mouse plasma.

Metabolism

The metabolism of dabigatran by glucuronidation was studied *in vivo* in mice and *in vitro* with human liver and intestinal microsomes and expressed UGT isoenzymes.

In vitro assays showed glucuronidation of dabigatran in human liver and intestinal microsomes, with maximum enzyme velocity (V_{max})/Michaelis Menton constant (Km) ratios over 200 fold higher in liver microsomes (0.46-4.1 µL/mg/min) than in intestinal microsomes (0.002-0.02 µL/mg/min). UGT2B15 was identified as the major enzyme for the formation of 1-O-acylglucuronide metabolite (V_{max}/Km ratio 0.062 µL/mg/min), with UGT1A9 and UGT2B7 (V_{max}/Km ratio 0.002-0.004 µL/mg/min) likely playing a minor role in the glucuronidation of dabigatran.

Analysis of dabigatran and potential conjugate metabolites in two strains (NRMI and CD1) of mice after an oral dose of dabigatran etexilate mesilate showed strain differences in pharmacokinetic profile. No glucuronide conjugates were formed in either strain; consistent with previously evaluated studies showed that glucuronidation was not a feature of dabigatran metabolism in this species.

Pharmacokinetic interactions

Glucuronide conjugation of dabigatran was inhibited by ritonavir (IC_{50} 10.4 µM = 6.5 µg/mL, compared with clinical plasma concentration 6-10 µg/mL), ketoconazole (IC_{50} 57.8 µM = 30.7 µg/mL, compared with clinical concentration 1.5-4.5 µg/mL after a 200 mg tablet), niflumic acid (IC_{50} 55.7 µM), amiodarone (IC_{50} 106.6 µM=68.79 µg/mL, compared with clinical plasma steady state concentration 1-2 µg/mL) and diclofenac (IC_{50} 155.2 µM compared with clinical plasma C_{max} 5 µM for a 50 mg tablet) *in vitro*. Since dabigatran is primarily eliminated in the unchanged form in the urine in humans (*Product Information*), UGT inhibitors are not expected to significantly alter plasma dabigatran concentrations in patients.

In vitro assays using Caco-2 cells and MDR1-expressing LLC-PK1 cells showed that dabigatran etexilate mesilate is a low to medium affinity substrate of P-glycoprotein (P-gp). The transport of dabigatran etexilate mesilate was moderately inhibited by P-gp modulators (amiodarone, clarithromycin, digoxin, itraconazole, quinidine and ritonavir), but 50% inhibition was achieved only at high concentrations of the P-gp inhibitors (mostly > 10 µM except for itraconazole with an IC50 of 0.47 µM). These findings suggest that the oral absorption of dabigatran etexilate mesilate may be increased by co-administration of strong P-gp inhibitors. Clinical studies with several P-gp inhibitors showed increases in plasma AUC and C_{max} of dabigatran from co-administration of dabigatran etexilate and a P-gp inhibitor (sponsor's *Clinical Overview*).

The active drug, dabigatran, is not a substrate of P-gp. Neither the pro-drug (dabigatran etexilate mesilate) nor dabigatran is a P-gp inhibitor. Thus, dabigatran and its prodrug is unlikely to alter P-gp mediated absorption, distribution or excretion of other therapeutic agents.

Relative exposure

The safety assessment of the previous application for the prevention of venous thromboembolic events in major orthopaedic surgery of the lower limb was based on the clinical exposure from oral doses, including 150 mg twice daily (bd), which is the proposed dose for the new indication. Therefore, animal/human exposure ratios calculated in the previous evaluation are applicable to the new indication and dosage.

Toxicology

Genotoxicity

Mutagenicity of dabigatran was assessed only in a bacteria assay in the previous submission. A mutagenicity assay in mammalian cells (mouse lymphoma cells) was provided in this submission. Negative results were obtained in the mouse lymphoma cell assay, which was adequately performed with appropriate controls. Previously evaluated *in vivo* micronucleus assays in rats dosed with the etexilate mesilate prodrug, which is readily hydrolysed to dabigatran, showed no evidence of genetic toxicity. Dabigatran etexilate and the active moiety, dabigatran, are not genotoxic.

General toxicity and carcinogenicity

A comprehensive package of toxicology studies performed with dabigatran etexilate was reviewed in the previous evaluation. The studies included repeat dose and carcinogenicity studies and are adequate to support the long term use of the drug. Risks associated with long term use were haemorrhage related to the pharmacological action of the drug and ovarian changes observed in rodents after long term exposure. The assessment of the ovarian findings from the previous nonclinical evaluation is transcribed below.

"Ovarian weight was increased at ≥ 30 mg/kg/day in the 13-week and 2 year mouse study; and the 2 year rat study; systemic exposures at these doses were similar to therapeutic exposure levels based on AUC. An increase in the incidence of ovarian cysts was seen at all dose levels in the 13-week study in mice (relative exposure ≈ 1-8). At the high-dose (HD) in the mouse carcinogenicity study there was an increased incidence of cystic ovarian bursa (relative exposure ≈ 5). These findings were not associated with a significant increase in mortality rate or clinical signs in mice, but deaths due to haemorrhage of large haemorrhagic ovarian cysts was seen at 100 and 200 mg/kg/day in the carcinogenicity study. In the rat study, increased ovarian weight at 30 and 100 mg/kg/day (relative exposure ≈ 1-3) was correlated with peri-ovarian sac distension (macroscopic examination) which was often (but not always) associated with cystic ovarian bursa seen microscopically. A marked increase in ovarian cysts was also observed at 200 mg/kg/day (relative exposure ≈ 8). The presence of increased mortality and clinical signs attributable to the pharmacological action of the drug at all doses suggested that the maximum tolerated dose (MTD) may have been exceeded in rats. No findings were detected in the ovaries of monkeys in studies of up to 1 year; relative animal:human exposure ratios were generally slightly lower in this species (up to about 3 x anticipated clinical exposure). In addition, small group sizes and a shorter proportion of lifetime that the animals were dosed may have contributed to this result. Overall, the findings in the ovaries of mice and rats were clearly attributable to exposure to dabigatran etexilate but were seen only in repeat dose studies of extended duration representing significant proportions of the rodent's lifetime. In addition, ovarian cysts and cystic ovarian bursa were generally seen at doses that induced systemic toxicity including severe haemorrhagic events. Given the maximum proposed duration of treatment with dabigatran etexilate is about 35 days in patients with hip replacement these findings appear unlikely to be of particular clinical importance."

With the proposed long term use of dabigatran etexilate mesilate for the new indication, ovarian findings observed in mice and rats at exposures similar to the clinical exposure are a potential risk in patients. These potential adverse effects on the ovaries should be monitored in patients and form part of the Risk Management Plan (RMP) (see Section V).

Carcinogenicity studies showed a slight increase in ovarian granulosa cell tumours in rats at the mid- (100 mg/kg/day) and high (200 mg/kg/day) doses (3 and 8 times the clinical exposure, respectively). The nonclinical evaluator of the previous evaluation considered

the increase likely to be related to treatment. Since the MTD was exceeded because of significant mortalities at these doses, a clear No Observed Effect Level (NOEL) for tumour formation was demonstrated in rats, no increase in the incidence of these tumours was observed in the mouse carcinogenicity study and the compound was not genotoxic, it was considered that dabigatran etexilate was unlikely to pose a carcinogenic risk to humans.

Phototoxicity

Dabigatran etexilate mesilate absorbs UV/visible light (270 - 800 nm). The phototoxic potential of dabigatran etexilate was investigated in the 3T3 NRU assay. The study showed that dabigatran etexilate was weakly phototoxic. Cytotoxicity was observed at ≥1.95 µg/mL in the first assay and at ≥7.81 µg/mL in the repeat assay in the presence of irradiation. The median effective concentration (ED_{50}) was determined to be 11 µg/mL. No cytotoxicity was observed in the absence of irradiation in both assays.

There were no data on light absorption or phototoxicity of the active moiety, dabigatran in the submission. The above study did not measure the concentration of dabigatran in the cell culture. Thus, it is unknown whether the cells were exposed to the active metabolite. The sponsor claimed that dabigatran has similar UV absorption spectra and UV erasing structural elements to the prodrug, and inferred that the active moiety has similar phototoxicity potential to the prodrug. The sponsor also explained that since the prodrug is weakly phototoxic in the 3T3 NRU *in vitro* assay and dabigatran has low permeability, no phototoxicity studies with dabigatran were performed in the *in vitro* assay. The sponsor's explanation is acceptable. The active drug is not expected to have similar phototoxicity to the prodrug.

Tissue distribution studies in rats with radiolabelled dabigatran etexilate and the active moiety showed higher concentrations of drug-related radioactivity in the epidermis than in plasma (<3 fold at T_{max}). However, the prodrug was only weakly phototoxic in the 3T3 NRU assay and the ED_{50} (11 µg/mL prodrug, equivalent to 7.2 µg/mL dabigatran) in the presence of irradiation was 29 fold higher than the plasma C_{max} of dabigatran (0.245 µg/mL) at the clinical dose of 150 mg. Dabigatran etexilate mesilate is not expected to pose a significant risk to patients from exposure to sunlight. The sponsor claimed that clinical experience did not provide any evidence of phototoxicity in humans.

Impurities

Genotoxicity studies for several impurities were provided in the submission. All but one test returned negative results. A weakly positive finding was observed in the bacterial gene mutation assay for ethyl bromoacetate, a potential impurity in the starting material of BIBR 1048 MS synthesis. It was reported that ethyl bromoacetate induced gene mutations in the mouse lymphoma assay, though negative in the bacterial assay.[1] The limited data suggest this impurity could cause genetic damage and the level in the drug substance should be controlled to not more than (NMT) 5 parts per million (ppm), which, at the daily dose of 300 mg, would give an intake of 1.5 µg/day, the threshold of toxicological concern for genotoxic impurities.

The impurities that are detected in the drug substance, BIBR 1154, BIBR 1150, BIBR 1155 and CDBA 513, were negative in the bacterial mutation assay and/or chromosome aberration assay *in vitro*. These impurities and several other impurities (BIBR 951, BIBR 1087 and alkyl methanesulfonates) have been previously considered to be toxicologically qualified for the daily dose of 220 mg for the prevention of venous thromboembolic events

[1] http://ntp.niehs.nih.gov/index.cfm?objectid=6F5EA164-F1F6-975E-76C018A113AA6AE3; accessed 23 July 2010.

in adult patients with elective total hip or knee replacement.[2] The specified levels for these impurities are also qualified for the new indication with a daily dose of 300 mg.

Nonclinical Summary and Conclusions

The maximum recommended clinical dose for the new indication in atrial fibrillation patients is 36.4% higher than the previously recommended dose of 220 mg once daily for the approved indication in patients with major orthopaedic surgery of the lower limb. The treatment duration for the new indication is life-long, compared to the short term use (up to 35 days) for the approved indication.

New pharmacodynamic, pharmacokinetic, genotoxicity (dabigatran and impurities) and phototoxicity data were provided in submission.

The results of new pharmacodynamic studies were consistent with previously evaluated studies on the anticoagulant activity of dabigatran etexilate mesilate in rats. Recombinant factor VIIa [Novoseven] and the activated prothrombin complex concentrate [Feiba] reversed the prolonged bleeding time induced by dabigatran in rats, although the prolonged APTT was only partially reversed by Novoseven and not affected by Feiba. Reversal of prolonged bleeding time by Novoseven or Feiba in rats suggests that these products might be useful for treating dabigatran-induced bleeding, as acknowledged in the Overdosage section of the Product Information.

The intermediate metabolite BIBR 951 had similar anticoagulant activity to dabigatran, but the other intermediate metabolite BIBR 1087 displayed minimal anticoagulant activities. Since only trace amounts of BIBR 951 were detected in humans after administration of dabigatran etexilate mesilate, it is unlikely that this intermediate metabolite has any significant contribution to the anticoagulant effect of dabigatran etexilate mesilate.

Receptor binding screening of dabigatran and the prodrug showed no significant binding of dabigatran to any receptor and moderate binding of the BIBR 1048 MS to 16 receptors (for example, benzodiazepine and calcium channel) with IC_{50} values in the micromolar range. Since the prodrug is rapidly hydrolysed to dabigatran *in vivo* and it is present in plasma at very low concentrations (around 5-10 nM) for a short period after dosing in patients, the moderate binding to receptors observed in the screening assay does not raise safety concerns.

The prodrug and the intermediate pro-drug, BIBR 951 are unstable in mouse plasma: the two compounds are rapidly hydrolysed to BIBR 1087 (an intermediate pro-drug) and BIBR 953 (active moiety), respectively. The other intermediate pro-drug, BIBR 1087, was stable in mouse plasma. However, since BIBR 951 has similar anticoagulant activity to dabigatran, the safety assessment is not compromised by the measurement of both BIBR 953 and BIBR 951 as equivalent to the active moiety, BIBR 953, in mouse plasma.

No stability data for the pro-drug and intermediate mono-pro-drugs in rat and monkey plasma was provided in the previous or current submissions. This is a deficiency of the submission and should be addressed by the sponsor. The stability of all the pro-drugs in human plasma should also be addressed by the sponsor.

Acylglucuronide of dabigatran is formed in human *in vivo*. An *in vitro* study with human liver and intestinal microsomes showed a significantly faster conversion to the glucuronide form in liver microsomes than in intestinal microsomes (by over 200 fold). UGT2B15 was identified as the major enzyme for the formation of the 1-O-acylglucuronide

[2] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

metabolite, with UGT1A9 and UGT2B7 playing a minor role in the glucuronidation of dabigatran. Glucuronide conjugation of dabigatran was inhibited by UGT inhibitors. Since dabigatran is primarily eliminated in the unchanged form in the urine in humans, UGT inhibitors are not expected to significantly alter plasma dabigatran concentrations in patients.

In vitro assays using Caco-2 cells and MDR1-expressing LLC-PK1 cells showed that dabigatran etexilate mesilate is a substrate of P-glycoprotein (P-gp), suggesting plasma concentrations of dabigatran may be altered by P-gp inhibitors or inducers. The active drug, dabigatran, is not a substrate of P-gp. Neither the prodrug (dabigatran etexilate mesilate) nor dabigatran is a P-gp inhibitor. Thus, dabigatran and its prodrug are unlikely to alter P-gp mediated absorption, distribution or excretion of other therapeutic agents.

Dabigatran was not mutagenic in the mouse lymphoma cell assay. The new study and previously evaluated studies indicated that dabigatran etexilate and the active moiety, dabigatran, are not genotoxic.

Previously evaluated repeat dose and carcinogenicity studies indicated that risks associated with long term use of dabigatran etexilate were haemorrhage related to the pharmacological action of the drug and ovarian effects. Increased ovarian weight and an increase in the incidence of ovarian cysts and/or cystic ovarian bursa were seen in mice and rats that were treated with dabigatran etexilate for a significant proportion of their lifetime (≥ 3 months for mice, 2 years for rats). Carcinogenicity studies showed an increase in ovarian granulosa cell tumours in rats at the mid- (100 mg/kg/day) and high (200 mg/kg/day) doses (3 and 8 times the clinical exposure). Although no ovarian findings were noted in studies with rhesus monkeys treated for up to 52 weeks, the ovarian effects observed in rodents are potential risks in patients from long term use of the drug. These potential adverse effects should be monitored in patients and form part of the Risk Management Plan (RMP).

An *in vitro* phototoxicity assay showed that dabigatran etexilate was weakly phototoxic. Given the weak phototoxicity in the *in vitro* assay and high ED_{50} value in the presence of irradiation, dabigatran etexilate mesilate is not expected to pose a significant risk to patients from exposure to sunlight. The sponsor also stated that clinical experience with dabigatran did not provide any evidence of phototoxicity in humans.

New data on impurities did not raise concerns over the safety of impurities that had been previously evaluated. Ethyl bromoacetate, a potential impurity in the starting material of the BIBR 1048 MS synthesis, was weakly positive in the bacterial reverse mutation assay. It was also reported that ethyl bromoacetate induced gene mutations in the mouse lymphoma assay but was negative in the bacterial assay. The limited data suggest this impurity could cause genetic damage and the level of ethyl bromoacetate in the drug substance should be controlled to NMT 5 ppm.

No critical safety issues were raised by new nonclinical data provided in this submission. However, previously evaluated studies indicated that the ovaries are potential targets with the long term use of dabigatran etexilate. There were no nonclinical objections to the approval for the new indication provided the potential adverse effects on the ovaries are monitored in patients and form part of the RMP.

IV. Clinical Findings

Introduction

The submitted pharmacokinetic (PK) data included bioequivalence (BE) studies with the proposed 150 mg capsule, a justification for not providing BE data for the 75 mg and 110

mg capsules, relative bioavailability studies (powder, pellet, capsules), drug-drug interaction studies with P-gp inhibitors (quinidine, verapamil, ketoconazole, and clarithromycin) and inducers (rifampicin), PK/pharmacodynamic (PD) drug-drug interaction studies (enoxaparin and clopidogrel), and population PK studies in patients and healthy subjects. The pivotal Phase III efficacy and safety study [RE-LY] included a PK and PD sub-study, as did the supportive Phase II exploratory clinical safety study [1160.20, PETRO]. All relevant PK and PD studies have been fully evaluated.

The submission included one pivotal Phase III clinical efficacy and safety study [RE-LY; 1160.26]. RE-LY was a multi-national, multi-centred, **p**rospective, **r**andomized, **o**pen trial with **b**linded outcome **e**valuation study (PROBE design) comparing two doses of dabigatran etexilate (DE) (110 mg bd and 150 mg bd) with warfarin [WF] (dose to maintain international normalised ratio [INR] 2-3) in 18,113 randomized patients with non-valvular AF and at least one additional risk factor for stroke. The study has been published [Connolly, 2009 and Connolly, 2010] as was a rationale of RE-LY [Ezekowitz, 2009].[3,4,5]

The submission included three, Phase II, exploratory, dose-ranging, clinical safety studies [1160.20 [PETRO], 1160.42 [PETRO-ex], and 1160.49]. None of these three studies were powered to assess efficacy and all were open-label in design. The safety data from these three studies have been reviewed but are not considered to be pivotal.

The submission also included a Japanese Phase II, randomized, placebo-controlled study comparing the efficacy and safety of DE (110 once daily [qd], 150 qd, 220 mg qd) for the prevention of venous thromboembolism (VTE) in patients undergoing primary elective total knee replacement (TKR) surgery [study 1160.50]. The treatment duration with DE and placebo was 11 to 14 days. This study was submitted to support proposed amendments to the Pradaxa Product Information (PI) relating to VTE. The results from this study have been examined to confirm that they support the proposed PI changes. The study was not formally evaluated as the patient population differed from that being proposed and the duration of the study was too short to provide meaningful comparative safety data on DE and placebo.

The submission also included a Phase II, dose-response venous thromboembolism (VTE) study. The objective of this study was to establish a dose-response relationship for efficacy and safety of DE (50 mg bd, 150 mg bd, 225 mg bd and 300 mg qd) after 6-10 days treatment in patients who had undergone primary elective total hip or knee replacement surgery [Study 1160.19]. The study included an enoxaparin control. The PK results from this study were included in the population pharmacokinetic study [U09-1399-02] and have been mentioned in the evaluation of this study. The study was not formally evaluated as the patient population differed from that being proposed and the duration of the study was too short to provide meaningful comparative safety data for DE for the purposes of the current submission.

The submission also included a recently completed Phase III study in patients with acute symptomatic venous thromboembolism (VTE) which compared dabigatran 150 mg bd with warfarin given for 6 months to prevent recurrent VTE events and deaths related to VTE (composite endpoint) following initial (5-10 days) treatment with standard parenteral anticoagulant therapy [RE-COVER, 1160.53, U09-1400-01]. This study has been

[3] Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009; 361: 1139-51.
[4] Connolly SJ et al. Newly Identified Events in the RE-LY Trial. NEJM 2010; 363: 1875-6.
[5] Ezekowitz MD, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009; 157: 805-810.

evaluated as it included 6 months safety data comparing dabigatran 150 mg bd with warfarin, although in a different patient population from that being proposed.

During the course of the evaluation the sponsor informed the TGA that the primary US FDA review of the RE-LY data had detected inconsistencies in the original recorded INR results used to monitor WF dose and the original recorded transfusion data (that is, data used to identify major bleeds). The errors in the INR dataset included transcription, transposition, and auditing errors. The US FDA considered that the identified inconsistencies raised questions about the reliability of the results and the validity of RE-LY. The sponsor acknowledged the need for a systematic re-assessment of the data, and implemented measures to evaluate data quality and detect possible unreported outcome events. The sponsor reviewed all adverse events (AEs) and serious adverse events (SAEs) for unreported bleeding events. In addition, the sponsor reviewed all SAE narratives (n=4501) for possible unreported outcome events. The outcome events of interest were stroke, death, systemic embolic event (SEE), clinical and silent myocardial infarction (MI), pulmonary embolism (PE), transient ischemic attacks (TIA), and major bleeds.

The data cross-checks identified 3,054 patients from RE-LY with evidence of data inconsistencies relating to potential under-reporting of outcome events. The sponsor further reviewed these patients and identified 425 with possible outcome events. Investigators at the relevant individual study sites were requested to re-evaluate the data held on these patients. The investigators provided information on 409 of the 425 patients and verified events in 95 patients. The investigator verified events in 95 patients plus the events in the 16 patients for whom no response was received were sent for adjudication (that is, 115 events in 111 patients). Of the 111 patients with possible events, 81 additional events in 80 patients were confirmed as true events. In addition, there were 326 patients with potential new pathologic Q-waves of whom 28 were adjudicated as having experienced silent myocardial infarctions. Potential additional outcome events were adjudicated using the same blinded process used to assess the original outcome events.

The provided data included a comprehensive summary of the procedures and methods undertaken to review and check the original outcome data. The original confirmed events (n=3504), the new adjudicated clinical events (n=81) and silent MIs (n=28), together with additional events identified from a previous post-database lock sensitivity analysis (n=22) and not included in the original analysis (database lock 17 June 2009) were merged and integrated into a combined outcomes re-analysis of the pivotal study. The re-analysis of the new data used the same statistical methodology pre-specified in the original study. The re-analysis resulted in all efficacy and safety summary tables in the sponsor's original study report being replaced by amended tables. The additional outcome events did not significantly alter the primary and secondary efficacy analyses, but the additional MI data reduced the risks for this event in DE treated patients relative to WF resulting in both the respective hazard ratios becoming non-statistically significant. The relevant efficacy and safety tables in this AusPAR include the data from the integrated re-analysis, and the relevant comments and discussion relate to the results of this integrated re-analysis.

Pharmacokinetics

Introduction

The submission included two, new, pivotal BE studies in healthy elderly subjects [1160.66, 1160.70]. These studies are also discussed in Section II.

The submission did not include BE studies for the DE 75 mg and DE 110 mg capsules comparing formulations containing polymorphs I and II or formulations manufactured by first and second generation methods. However, the sponsor provided a justification for not

submitting *in vivo* bioavailability data for the DE 75 mg and DE 110 mg capsules. This justification was discussed in Section II and the clinical aspects of this justification have also been reviewed and were considered to be acceptable.

The submission included one new study comparing the relative bioavailability of pellets, powder and capsule formulations of DE in healthy subjects [study 1160.87]. This study was also discussed in Section II. The submission included one new DE repeat dose study in healthy Japanese and Caucasian males [study 1160.61].

The submission included four new PK drug-drug interaction studies in healthy subjects with DE co-administered with protein P-glycoprotein (P-gp) inhibitors. The studied P-gp inhibitors were verapamil [study 1160.74], clarithromycin [study 1160.82], quinidine [study 1160.90], and ketoconazole [study 1160.101]. The submission also included a previous PK drug-drug interaction study with quinidine which had been prematurely discontinued due to the high occurrence of gastrointestinal (GIT), CNS and cardiovascular (CVS) adverse events (including one serious adverse event of hypotension) after administration of quinidine to subjects who had been pre-treated with repeat doses of DE 150 mg [study 1160.75]. The submission also included one new PK drug-drug interaction study in healthy subjects in which DE was co-administered with the P-gp inducer rifampicin [study 1160.100]. The submission included two new PK-PD drug-drug interaction studies in healthy subjects with DE co-administered with enoxaparin [study 1160.78] or clopidogrel [study 1160.83].

The submission included PK data in subjects with AF being treated with DE in the pivotal efficacy and safety study [RE-LY; study 1160.26]. The submission also included PK data in subjects with AF being treated with DE with or without concomitant acetylsalicylic acid (ASA) in a sub-group analysis in an exploratory clinical safety study [study 1160.20]. The submission also included a population PK study [study U09-1399-02]. The submission also included a meta-analysis comparing the PKs of different oral formulations of DE and investigation of the effects of the MDR-1 genotype on the PKs of DE [study U09-1363-02]. The submission also included a population PK study comparing the effects of DE in Japanese and Caucasian subjects. This study has not been evaluated as it was not directly relevant to the current Australian application.

The submission included a PK study [1160.68] aiming to establish BE of Ivax brand warfarin 10 mg and Coumadin (Coum) brand warfarin was used in the pivotal efficacy and safety study and demonstration of BE with Bristol-Myer Squibb's US reference product (Coumadin) was required to support filing of the NDA in the USA. The study showed that the formulations were bioequivalent as assessed by the geometric mean (gMean) $AUC_{0-\infty}$ ratio [Ivax/Coum] (99.4% [90% Confidence Intervals [CI]: 97.6-101.1%]), and gMean C_{max} ratio [Ivax/Coum] (92.1% [90%CI: 86.9-97.6%]). This study was not evaluated as it was not relevant to the Australian submission. In Australia there are two registered warfarin formulations, Coumadin (sponsored by Sigma) and Marevan (sponsored by Fawn's and McCallum). These two products are not considered to be interchangeable as bioequivalence has not been tested. Consequently, it was considered that establishing the bioequivalence of Ivax warfarin to US Coumadin and/or one or both of the Australian warfarin formulations is not relevant to the evaluation of RE-LY.

Methods

General Matters [All PK Studies]

The Phase I PK studies used standard and appropriate non-compartmental methods to derive the various PK parameters. These methods have been reviewed but have not been described in any detail as they are standard, accepted methods and are consistent with relevant guidelines. The PK/PD studies used standard methods to assess coagulation. All

studies used validated analytical methods to assay relevant analytes in human plasma and urine.

The safety data for each of the studies have been reviewed. No major safety issues were identified in the PK studies in healthy subjects. Consequently, the safety data from the PK studies have not been described unless notable effects were observed.

All studies complied with national and international ethical standards and guidelines relating to approval and supervision of clinical studies in humans. The protocols were approved by relevant independent ethic committees/boards and, where relevant, national bodies. The studies complied with the principles of the Declaration of Helsinki (1996 Version), and were carried out in accordance with the ICH Guideline for Good Clinical Practice (GCP). All subjects provided written informed consent.

Statistical Methods to Assess BE in the Pivotal BE Studies 1160.66

Both of the pivotal BE studies were undertaken using a randomized, double-blind, single-dose, two-treatment, four-period, crossover with replicate design. The replicate design was used in order to be able to perform the BE statistical analysis using the scaled average bioequivalence approach (primary analysis) and also to reduce the variability for the BE statistical analysis using the unscaled average bioequivalence approach (secondary analysis).

Both pivotal BE studies used the scaled average bioequivalence approach (primary analysis) to determine the BE of the two primary parameters of total dabigatran $AUC_{0-\infty}$ and C_{max}. This method has been described in the literature as being applicable to BE analysis of highly variable drugs characterised by large within-subject variation in the bioequivalence parameters [Tothfalusi et al, 2001; Haidar et al, 2007].[6,7] The method is not described in the TGA-adopted EU guidance on the subject.[8] This guideline recommends an unscaled average bioequivalence method to determine the bioequivalence of two products. The unscaled average bioequivalence method was used in the two pivotal BE studies as the secondary BE analysis. The approach adopted in the two pivotal studies was considered acceptable given that the PKs of dabigatran are known to be highly variable.

To claim scaled average bioequivalence, the 95% upper CI of the difference must be ≤ 1 (that is, rejects the null hypothesis of bioinequivalence of the T and R formulations). In both studies, the secondary analysis of unscaled average bioequivalence followed standard methods.

The ANOVA model used in both the unscaled and scaled bioequivalence analyses included effects accounting for the sources of variation of “sequence”, “subjects”, “period” and “treatment”. The “subject” effect was considered to be random, and the “sequence”, “period” and “treatment” effects were considered fixed. In addition, in the ANOVA used to assess unscaled average bioequivalence the subject-by-treatment interaction was considered a random effect and was used to determine intra-individual variability. The gMean was chosen as the descriptive statistic for central tendency due to the log-normal distribution of most of the PK endpoints. Both studies included a per-protocol set (PPS) and a treated set (TS) of subjects. The primary PK analysis was conducted in the PPS. The safety analysis and the evaluation of demographic and baseline characteristics were

[6] Tothfalusi et al. Evaluation of the bioequivalence of highly-variable drugs and drug products. Pharmaceutical Research 2001; 18:728-733.

[7] Haidar SH. Bioequivalence approaches for highly variable drugs and drug products. Pharmaceutical Research 2008; 25; 237-241.

[8] EMEA. Committee for Proprietary Medicinal Products (CPMP), 26 July 2001. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. CPMP/EWP/QWP/1401/98.

conducted on the TS. The PPS included all subjects who performed all study procedures as planned in the protocol.

Bioequivalence (BE) and Bioavailability (BA) Studies

BE of Two Different Polymorphs of DE 150 mg Capsules [1160.66]

This study was briefly described in Section II. The study was carried in a single centre in Germany from 14 May 2008 to 27 August 2008. The study included 66 healthy female and male elderly subjects aged ≥ 60 years and ≤ 85 years.

The results for the primary analysis of scaled average bioequivalence of the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran are summarised in Table 6, Tables 1 and 2 (results based on an unscaled average bioequivalence analysis).

As the upper 95% confidence limit for both the $AUC_{0-\infty}$ and the C_{max} was negative (≤ 0), polymorphs I and II can be considered to be bioequivalent as regards total dabigatran. The (intra-individual) within-reference standard deviations of C_{max} and $AUC_{0-\infty}$ were 0.43 and 0.38, respectively, which are larger than the pre-specified limit variability (σ_{Wo}) of 0.25. The high observed variability can considered to justify the use of the scaled average bioequivalence as the primary criterion for assessment of bioequivalence in this trial.

Table 6: Trial 1160.66 - Scaled average bioequivalence for total dabigatran based on the Hyslop approximation (log scale, per protocol set [n=64]).

Parameter	Δ means	SE	Within R SD	σ_{Wo}	Scaled limit	Degrees of Freedom	Upper 95% CL
C_{max} ng/mL	-0.0461	0.059	0.427	0.25	0.893	62.0	-0.104
$AUC_{0-\infty}$ ng.h/mL	-0.0226	0.051	0.383	0.25	0.893	62.0	-0.086

Δ means = Difference between means. SE = Standard Error. Within R SD = Intra-individual within-reference standard deviation. σ_{Wo} = The limit variability for the reference treatment was defined as 0.25. Upper 95% CL = Upper 95% confidence limit of linearized criterion.

The results for the secondary analysis of unscaled average bioequivalence of the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran are summarised in Table 2. The adjusted gMean ratio (T/R) are close to 100% for both C_{max} and $AUC_{0-\infty}$, and the two-sided 90% CIs for the adjusted gMean ratios of both parameters are completely within the pre-defined bioequivalence acceptance range of 80% to 125%. The results show that polymorphs I and II are bioequivalent as regards total dabigatran as assessed by both primary endpoints of C_{max} and $AUC_{0-\infty}$.

Comments

This was a good quality PK study in an elderly population. The study used scaled average bioequivalence as the primary analytical method to assess BE. This method is not described in the TGA-adopted EU BE guidelines but is supported in the published literature for BE estimation of drugs having high within-subject variability. The conventional method of BE assessment using unscaled average bioequivalence analysis was the secondary analytical method. BE of the two polymorphs as assessed by the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran was satisfactorily established by both scaled and unscaled bioequivalence analyses. Similarly, BE as assessed by these two endpoints for free dabigatran was also demonstrated by both analytical methods.

BE of First and Second Generation DE 150 mg Capsules [1160.70]

This study was briefly described in Section II. The study was carried out in a single centre in Germany from 6 May 2008 to 30 August 2008. The methods, endpoints, statistical analyses, and bio-analytical methods used in this study were similar to those used in *Study 1160.66.*

The results for the primary analysis of scaled average bioequivalence of the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran are summarised in Table 7. As the upper 95% confidence limit for both the $AUC_{0-\infty}$ and the C_{max} was negative (≤ 0), the formulations manufactured by first and second generation processes can be considered to be bioequivalent as regards total dabigatran.

Table 7: Trial 1160.70 -Assessment of scaled average bioequivalence for total dabigatran, based on the Hyslop approximation (log scale, per protocol set [n=65]).

Parameter	Δ means	SE	Within R SD	σ_{Wo}	Scaled limit	Degrees of Freedom	Upper 95% CL
C_{max} ng/mL	0.1235	0.066	0.508	0.25	0.893	63.0	-0.128
$AUC_{0-\infty}$ ng.h/mL	0.1163	0.059	0.485	0.25	0.893	63.0	-0.119

Δ means = Difference between means. SE = Standard Error. Within R SD = Intra-individual within reference standard deviation. σ_{Wo} = The limit variability for the reference treatment was defined as 0.25. Upper 95% CL = Upper 95% confidence limit of linearized criterion.

The results for the secondary analysis of unscaled average bioequivalence of the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran are summarised in Table 4. The adjusted gMeans for C_{max} and $AUC_{0-\infty}$ were about 13% and 12% higher, respectively, with the R formulation compared with the T formulation. The 90% CI of the AUC_{0-inf} gMean ratio (T/R) is contained within the pre-specified BE acceptance limit of 80-125%. However, the 90% CI of the C_{max} gMean ratio (T/R) is not within the BE acceptance limit with the upper 90% CI (126.2%) of the ratio being slightly above the upper acceptance limit of 125%.

Comments

This was a good quality PK study. BE of the first and second generation formulations in healthy elderly male and female subjects as assessed by the primary endpoints of $AUC_{0-\infty}$ and C_{max} for total dabigatran was satisfactorily demonstrated by the primary analysis (scaled average bioequivalence) and secondary analysis (unscaled average bioequivalence). The C_{max} ratio for the two formulations as assessed by the unscaled average bioequivalence was marginally outside the accepted bioequivalence limits but this is considered not to be clinically significant. The analyses of the secondary endpoint analyses support the results of the primary endpoint analyses. It was considered that the study has satisfactorily demonstrated bioequivalence of the first and second generation 150 mg DE capsule formulations.

Justification of Not Submitting BE Studies for DE 75 mg and 110 mg Capsules

The sponsor submitted a justification for not providing BE studies for the 75 mg and 110 mg DE capsules comparing formulations containing polymorphs I and II or formulations containing products manufactured by first and second generation methods. The justification was considered acceptable with the main supportive factors being demonstrated BE of the highest dose capsule formulations, dose proportional AUC and C_{max} dabigatran over the DE dose range 10-400 mg, minor changes in the BE of the 75 mg and 110 mg capsules are unlikely to affect clinical efficacy and safety, *in vitro* dissolution profiles essentially the same for the three dose strengths, and the 75 mg, 110 mg, and 150 mg capsules are directs scales with the only difference being pellet weight.

Relative Oral BA of Pellets, Powder, and Capsules [1160.87]

This study was briefly described in Section II. The study was conducted in a single centre in Germany from 19 March 2009 to 4 May 2009. The primary endpoint was relative bioavailability primarily investigated on the basis of the $AUC_{0-\infty}$ and C_{max} of total and free dabigatran. The relative bioavailability of the pellets (T1) and of the powder (T2), both compared to capsules (R), was investigated by the average bioequivalence method using

the ratio between PK parameters ($AUC_{0-\infty}$ and C_{max}) of the two respective treatments (standard conventional methodology).

The relative bioavailability of the 150 mg pellet compared with the 150 mg capsule for total dabigatran is summarised in Table 5. The results showed that the C_{max} following the pellets was 86% higher compared with the capsules and the AUCs were about 75% to 82% higher. Similar results were seen for the relative bioavailability of the 150 mg reconstituted powder compared with the 150 mg capsule. The C_{max} for the powder was about 67% higher than for the capsules and the AUCs were about 55% to 61% higher. The 90% CIs were outside the 80%-125% acceptance interval for each of the relevant powder/capsule ratios. Similar results were observed for the relative bioavailability assessments as regards free dabigatran.

Comment

This was a good quality study. The two test formulations of pellets and solution reconstituted from powder had a significantly higher relative bioavailability compared to the reference capsule formulation. Neither the pellets nor the powder were bioequivalent to the capsules. The results indicate that the capsule should always be swallowed intact and not chewed or broken open and sprinkled on food or put into drinks. This is an important observation as capsules are often broken open and sprinkled on or mixed with food in elderly patients who have difficulty swallowing capsules.

Dose Proportionality and Time Dependency [1160.61]

The objectives of this Phase I study were to investigate and compare the pharmacokinetics, safety and pharmacodynamics of DE following oral administration of multiple doses (110 mg or 150 mg bd for 7 days) in healthy young Japanese and Caucasian males. The study provided information on the PKs of total and free dabigatran following multiple dosing, including accumulation factors, at the doses used in the pivotal clinical efficacy and safety study. There were no other studies in the submission investigating the multiple dose PKs of DE. Subject numbers in this multiple dose study were small and limited to young healthy adult males. The study was undertaken in a single centre in Japan from 5 May 2006 to July 2006.

The study was an open-label, two-dose level, multiple-dose study. The study was not crossover in design and separate cohorts of Japanese and Caucasian subjects received the two doses. A total of 48 healthy male subjects (24 Japanese and 24 Caucasians) aged ≥ 20 years and ≤ 45 years participated in the trial. Overall, all 24 Caucasian subjects and 23 of the 24 Japanese subjects completed the study (1 discontinued due to periodontitis).

The primary endpoints were the PK parameters of $C_{max,ss}$ (maximal plasma concentration at steady state over a uniform dosing interval τ), and $AUC_{\tau,ss}$ (area under the plasma concentration time curve at steady state over a uniform dosing interval τ). Bioavailability using standard methods was assessed primarily on the basis of the $C_{max,ss}$ and $AUC_{\tau,ss}$ after the last dose on Day 7 for total dabigatran.

The results showed that at steady state, 150 mg capsules administered bd can be considered to be "bioequivalent" in Japanese and Caucasian subjects, although the lower 90% CI limit was marginally outside the acceptance limits of 80-125%.

Comment

This was a good quality PK/PD study. It showed that exposure to total dabigatran following the higher dose of DE (150 mg bd) was similar in Caucasian and Japanese subjects, while exposure to total dabigatran following the lower dose of DE (110 mg bd) was about 30% higher in Japanese subjects as assessed by steady state C_{max} and AUC. In

Caucasian subjects, exposure to both total and free dabigatran increased about 1.73-fold as assessed by the AUC following multiple bd doses of DE 150 mg and about 1.45-fold as assessed by the C_{max}. In Caucasians, exposure to both total and free dabigatran also increased following DE 110 mg bd, but to a marginally smaller extent than following DE 150 mg bd (about 1.30-1.35 fold as assessed by C_{max} and about 1.65-fold as assessed by AUC). Overall, this study in small number of healthy young Caucasian and Japanese males showed that total and free dabigatran following dabigatran capsules 110 mg bd and 150 mg bd did not significantly accumulate following multiple dosing over 13 days.

PK Drug-Drug Interaction Studies – Efflux Transporter P-gp

Overview

DE is a substrate for the efflux transporter protein P-glycoprotein (P-gp). There were a series of studies in healthy subjects of both sexes which investigated the effects of co-administration of DE and P-gp inhibitors on the bioavailability of total dabigatran compared with DE alone. One study investigated the effect of the P-gp inducer rifampicin on the bioavailability of DE, and the time taken for P-gp activity to return to normal following cessation of rifampicin.

There were various secondary objectives in each of the studies and these generally included safety and tolerability, PK parameters, and assessment of coagulations factors. In addition, some studies included an investigation of the effects of DE on the PKs of the p-GP inhibitor. In this AusPAR, the focus is on the primary objectives of the studies relating to the effects of co-administration on total dabigatran bioavailability. Data in the studies generally showed that time to coagulation (aPTT, ECT, TT) was prolonged after co-administration of DE and P-gp inhibitors reflecting the increase in total dabigatran plasma concentrations. Overall, the safety data in the studies did not raise significant concerns or identify new or unexpected safety signals.

Quinidine [1160.90]

Quinidine is a known inhibitor of both P-gp and cytochrome P450 (CYP)3A4. Of the available P-gp inhibitors, quinidine is the most selective for P-gp inhibition relative to CYP3A. A previous interaction study between quinidine sulphate (QS) and DE was prematurely discontinued due to the high rate of reported AEs after DE+QS co-administration in 17 healthy subjects [study 1160.75]. These included one serious AE of severe hypotension. The most commonly reported AEs in the study included diarrhoea, nausea, vomiting, confusion, dizziness, headache, electrocardiogram (ECG) QT prolongation, hyperhidrosis, blurred vision, palpitations, tremor and sinus tachycardia. Pre-treatment with a single dose of QS increased both the $AUC_{\tau,ss}$ and $C_{max,ss}$ of total and free dabigatran by a factor of about two.

The primary objective of the new study 1160.90 was to evaluate the safety of co-administration of DE with QS. The primary endpoint was a comparison of the blood pressure lowering effects of DE+QS and DE alone. In addition, a number of standard PK parameters were assessed. The PDs were assessed using aPPT, TT and ECT. The study was carried out in a single centre in the USA from 5 March 2009 to 27 April 2009. The main study was conducted as two-way crossover, where QS+DE (test) and DE alone (reference) were administered in a random order. Of the 42 enrolled subjects, 32 completed the 7-day QS run-in period and were randomized to the crossover part of the study.

Bioavailability Total Dabigatran

The effect of co-administration was to increase the total dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by about 53% and 56%, respectively. The 90% CI for both ratios was outside the 80-125%

interval showing that the two treatments were not bioequivalent as regards total dabigatran.

Bioavailability Quinidine

The results showed that the last dose of DE 150 mg bd given 1 hour after the last of 5 consecutive doses of QS 200 mg did not significantly change the bioavailability of QS given without DE as assessed by the plasma AUC from time point 0 after the fifth dose of QS to the last quantifiable plasma concentration within the uniform dosing interval τ ($AUC_{0\text{-}tz,5}$) and the maximum plasma concentration after the fifth dose of QS ($C_{max,5}$).

Symptomatic Hypotension

The primary objective of this study was the effect of the co-administration of DE and QS on systolic blood pressure and symptomatic hypotension compared with DE alone. This analysis was undertaken in the 32 subjects who completed the 7-day QS (5x 200 mg) run-in period and entered the crossover phase of the study. The results showed no significant difference between treatments for the primary blood pressure (BP) endpoint.

Comment

This was good quality study. It showed that the bioavailability of total dabigatran (steady state) increased following co-administration of DE+QS compared with DE alone. The $AUC_{\tau,ss}$ increased by about 53% and the $C_{max,ss}$ by about 56%, and the 90% CI for both ratios was outside the 80-125% limits indicating that the treatments were not "bioequivalent" as regards total dabigatran. In this study the last dose of QS (fifth dose of 200 mg administered every 2 hours) was given 1 hour before DE 150 mg (steady state 150 mg bd). The elimination half-life of DE when given alone was not significantly affected when DE was given in combination with QS. The bioavailability of quinidine was not significantly affected following QS co-administered with DE compared with QS administered alone. The effects on systolic blood pressure and symptomatic hypotension of DE co-administered with QS were not significantly different from DE administered alone. The current PI contraindicates the concomitant use of DE and quinidine based on the initial interaction study [1160.75]. Based on the current interaction study the sponsor proposed to downgrade the Contraindication to a Precaution. This was considered reasonable based on the results of this study.

Verapamil – [1160.74]

The primary objective of this Phase I study was to investigate the effect of co-administration of DE and the P-gp inhibitor verapamil (V) on the bioavailability of total dabigatran as assessed by $AUC_{0\text{-}\infty}$ and C_{max} compared with DE alone. DE was administered as a single 150 mg dose, and V administered at different doses (120 mg single dose, 240 mg/day and 480 mg/day), in different formulations (immediate release [IR] and extended release [ER]), and with different intervals between dosing of DE and V. The secondary objectives were to determine the safety and tolerability of co-administered DE and V, to determine the effect of DE on the PKs of V, and to determine the PDs of DE with and without co-administration of V by measurement of the blood coagulation parameters. The study was undertaken in a single-centre in Germany between 13 June 2008 and 28 August 2008.

Comment

This was a good quality study. The greatest increase in dabigatran bioavailability was observed when single dose DE 150 mg was given 1 hour after a single dose of VIR 120 mg (increase in C_{max} of 179% and $AUC_{0\text{-}\infty}$ of 143%). When single dose DE 150 mg was given together with a single dose of VIR 120 mg a marked increase in dabigatran bioavailability

was also observed (increase in C_{max} of 129%, and $AUC_{0-\infty}$ of 108%). The bioavailability of dabigatran was also increased when a single dose of DE 150 mg was administered 1 hour after a single dose of VER 240 mg (increase in C_{max} of 91% in $AUC_{0-\infty}$ of 71%). The single dose studies showed that the bioavailability of dabigatran was markedly increased irrespective of whether a single dose of DE150 mg was given 1 hour after or together with a single dose of VIR 120 mg, and that the bioavailability of dabigatran was increased to a greater extent when DE 150 mg was administered 1 hour after VIR 120 mg compared with 1 hour after VER 240 mg. The single dose interaction data showed that DE had no significant effect on the bioavailability of verapamil suggesting that *in vivo* DE does not inhibit P-gp activity.

The steady state data showed that the bioavailability of dabigatran increased to a lesser extent when a single dose of DE 150 mg was given 2 hours before a dose of VIR 120 mg at steady state 240 mg/day (increase in C_{max} of 12% and $AUC_{0-\infty}$ of 18%), compared with when single a dose of DE 150 mg was given 1 hour after a dose of VIR 120 mg at steady state 240 mg/day (increase in C_{max} of 63% and $AUC_{0-\infty}$ of 54%). The results suggest that at steady state verapamil induces P-gp, and that when DE is given 2 hours before steady state verapamil significant absorption of dabigatran occurs before P-gp is further inhibited by the following dose of verapamil. There were no interaction data between DE at steady state and verapamil. The available data suggest that if DE and verapamil are to be co-administered then DE should be given 2 hours before verapamil and only when verapamil steady state has been achieved. Initiation of treatment with both drugs simultaneously should be avoided, as should initiation of treatment with verapamil in patients stabilised on DE.

Ketoconazole [1160.101]

The primary objective of this Phase I study was to investigate the effects of co-administration of DE and the P-gp inhibitor (and CYP3A4 inhibitor) ketoconazole (KZ) on the bioavailability of total dabigatran compared with DE alone. The secondary objective was to determine the safety and tolerability of DE and KZ when co-administered. This study was carried out in a single centre in Germany from 9 June 2009 to 23 July 2009. The study was an open-label, 3-period, fixed-sequence design. The primary comparison was between single dose DE 150 mg + KZ 400 mg at steady (once daily for 6 days) versus single dose DE 150 mg. There was an additional comparison between single dose DE 150 mg + single dose KZ 400 mg versus single dose DE 150 mg.

Comments

This was a good quality study. It showed that total dabigatran $AUC_{0-\infty}$ and C_{max} markedly increased following single dose DE co-administered with both single dose KZ and steady state KZ compared with DE given alone. The results are consistent with KZ mediated inhibition of P-gp in the intestinal mucosa resulting in increased DE absorption. The results indicate that co-administration of DE and KZ should be contraindicated.

Clarithromycin [1160.82]

This Phase I study was an open-label, fixed-sequence study investigating the relative bioavailability of total dabigatran following the P-gp inhibitor clarithromycin (CM) co-administered with DE compared with DE alone. The secondary objectives of the study were to assess safety and tolerability, to investigate the affect of co-administration on blood coagulation parameters, and to investigate the affect of DE co-administration on the PKs of CM. This study was conducted in a single centre in Germany from 23 June 2008 to 8 August 2008.

Comments

This was a good quality PK study. It showed that co-administration of DE (single dose) and CM (steady state, multiple doses) increased the bioavailability of total dabigatran compared with DE (single dose) alone as assessed by both the $AUC_{0-\infty}$ (increase of 19%) and C_{max} (increase of 15%). Co-administration of DE (single dose) and CM (single dose) reduced the bioavailability of total dabigatran as assessed by both the $AUC_{0-\infty}$ (reduced 9%) and C_{max} (reduced 13%). The results suggest that the observed PK interaction is unlikely to be of major clinical significance. The results for co-administration of DE and CM are unusual as clarithromycin is considered to be a potent inhibitor of P-gp *in vitro* with an IC_{50} of 4.1 µmol/L. Consequently, it would have been expected that co-administration should have significantly increased the bioavailability of total dabigatran. The reasons for the unexpected results are unknown. The sponsor speculated that the relative poor solubility of CM results in lower intestinal concentrations than might be expected from the relatively large administered dose. The sponsor also speculated that CM might target different sides of the P-gp efflux pump (inside rather than outside the intestinal cell wall). DE (single dose) did not significantly affect the steady state bioavailability of CM suggesting that *in vivo* DE is not an inhibitor of P-gp activity. The data suggests that DE and CM can be co-administered, but caution is required given the known P-gp inhibitory activity of CM.

Rifampicin [1160.100]

The primary objective of this Phase I study was to investigate the effects of the potent P-gp inducer rifampicin (RF) on the bioavailability of total dabigatran when co-administered with dabigatran etexilate (DE). The secondary objectives were to determine safety and tolerability of co-administration of rifampicin and dabigatran etexilate and to determine the duration of rifampicin mediated P-gp inhibition. The study was undertaken at a single centre in Germany from 30 June 2009 to 17 July 2009. The study was an open-label, 4-period, fixed-sequence study. The study compared the bioavailability of total dabigatran following a single dose of DE 150 mg with a single dose of DE 150 mg + steady state rifampicin 600 mg (600 mg once daily for 7 days). The study also compared the bioavailability of total dabigatran following a single dose of DE 150 mg before rifampicin washout with a single dose of DE 150 mg following 7 and 14 day rifampicin washouts.

Comment

This was a good quality PK study. Total dabigatran $AUC_{0-\infty}$ and C_{max} were both significantly reduced when a single DE 150 mg capsule was co-administered with rifampicin 600 mg at steady state. The results indicate that co-administration of DE with rifampicin significantly reduces the bioavailability of DE and is likely to impair the efficacy of DE. The results following single DE 150 mg capsule administration 14 days after rifampicin washout-out showed that total dabigatran $AUC_{0-\infty}$ and C_{max} values were nearly back to values prior to treatment with rifampicin.

Pharmacodynamic and Pharmacokinetic Drug-Drug Interaction Studies

Enoxaparin subcutaneous switched to DE oral [Study 1160.78]

The objective of this Phase I study was to investigate the PK (dabigatran) and PD (coagulation) effects of switching from repeat once daily subcutaneous doses of enoxaparin (EN) to a single oral dose of DE. The bioavailability of dabigatran and anti-FXa/anti-FIIa activity after 3 daily doses of EN 40 mg subcutaneous (SC) followed by a single dose of 220 mg DE (DE+EN) on the following day (24 hours after the last dose of enoxaparin) were compared with those following a single oral dose of 220 mg DE alone. The study was an open-label, 2-way crossover design and the two treatments were

separated by a 5 day washout. The study was undertaken in a single centre in Germany from 19 August 2008 to 22 September 2008.

Comment

This was a good quality study. It showed that the relative bioavailability of DE was reduced by 3 days pre-treatment with EN. Both the $AUC_{0-\infty}$ and C_{max} of total and free dabigatran were about 15% lower when DE was given 24 hours after EN compared with DE given alone. The intra-individual variability was high, and the 90% CIs of the intra-subject relevant ratios were outside the 80-125% "bioequivalence" limits. However, the reduction in DE bioavailability seen following EN pre-treatment is unlikely to be clinically significant.

EN is believed to exert its anticoagulant effect mainly by anti-FXa activity, whereas anti-FIIa activity is considered to be a marker for the anticoagulant effect of DE. The ER_{max} of relative anti-FXa/anti-FIIa activity was 15% higher and the $AUEC_{0-48h}$ was 64% higher after EN pre-treatment followed by DE compared with DE alone. The high relative anti-FXa/anti-FIIa activity observed with DE+EN compared with DE alone is most likely due to a carryover effect of anti-FXa activity from pre-treatment with EN. The changes in the aPTT, ECT, TT and anti-FIIa activity with DE+EN compared with DE alone are unlikely to be clinically significant. Similarly, the increase in relative anti-FXa/ant-FIIa activity following switching from EN to DE is unlikely to be clinically significant.

Clopidogrel [1160.83]

The objectives of the study were to assess the PK and PD effects of co-administration of clopidogrel and DE compared with each drug when administered alone. The study was undertaken at a single centre in Germany from 6 February 2009 to 23 July 2009.

Comment

This was a good quality study. The bioavailability of total dabigatran (steady state) was essentially unchanged as assessed by the $AUC_{\tau,ss}$ (8% decrease) and $C_{max,ss}$ (5% decrease) following [C75+D150] compared with [D150] alone. However, the bioavailability (steady state) of total dabigatran increased as assessed by the $AUC_{\tau,ss}$ (32%) and $C_{max,ss}$ (31%) when a higher single dose of clopidogrel 600 mg [C160] was co-administered with DE150 mg (bd steady state) [C600+D150] compared with [D150] alone. The bioavailability of clopidogrel (steady state) increased as assessed by the $AUC_{\tau,ss}$ (15%) and $C_{max,ss}$ (8%) following [C75+D150] compared with [C75] alone. However, the bioavailability of clopidogrel (single dose) was essentially unchanged as assessed by the $AUC_{\tau,ss}$ (3% increase) and $C_{max,ss}$ (0.2% decrease) following a higher single dose of clopidogrel 600 mg co-administered with DE 150 mg bd (steady state) [C160+D150] compared with [C600] alone. Overall, the bioavailability of clopidogrel does not appear to be markedly affected by DE co-administration. There was evidence that DE might increase platelet aggregation as inhibition of platelet aggregation observed with C alone (steady state) was reduced when DE (steady state) was co-administered with C (steady state). The effect of DE alone on platelet function requires further investigation.

Pharmacokinetic Studies in Patients

RE-LY Study 1160.26 (Pivotal Efficacy and Safety Study)

The descriptive statistics of the trough and post dose plasma concentrations for the DE 110 mg bd and 150 mg bd treatment groups showed that the steady state pre-dose trough concentrations ($C_{pre,ss}$) and 2-hour post-dose concentrations ($C_{2,ss}$) were highly variable in both dose groups. The dose-normalized steady state plasma concentrations showed that the DE 110 mg bd and DE 150 mg bd were dose proportional.

Comment

There appears to be an association with the safety outcome of major bleeding and plasma total dabigatran concentrations at trough and 2-hour post-dose, but not between the efficacy outcome of stroke/SEE. The results suggest that monitoring total dabigatran plasma concentrations might be a useful method of assessing the risk of major bleeding in patients being treated with DE. The concomitant use of various medications did not appear to significantly change dose-normalized steady state trough and 2-hour post-dose total dabigatran plasma concentrations for a range of clinically relevant medications.

PETRO Study 1160.20 (Exploratory Clinical Safety Study)

In *study 116.20* [PETRO], DE alone or in combination with ASA was compared with warfarin over 12 weeks in patients with chronic atrial fibrillation. Trough total dabigatran plasma concentrations were collected from 413 male and female patients treated with DE 50 mg bd, DE 150 mg bd or DE 300 mg bd. The results showed that trough concentrations remained stable over the three visits for each of the three treatment groups, that there was a linear relationship between concentration and dose, and that there was marked inter-individual variation in concentration. Steady state plasma concentrations of total dabigatran were obtained on or before the first assessment (that is, 4-7 days after randomization).

Comment

The increase in gMean urinary 11-dehydrothromboxane B_2 concentrations observed with DE compared with WF is a signal that increased platelet aggregation might be occurring with DE compared with WF. The effects of DE on platelet function should be further investigated given that there was an increased risk of MI observed in patients treated with DE compared with WF in the pivotal efficacy and safety study.

Population Pharmacokinetic Study – U09-1399-02

The objectives of the population PK (popPK) study were: to compare the PKs of dabigatran in orthopaedic surgery (OS) and atrial fibrillation (AF) patients; to characterise the effects of selected intrinsic and extrinsic factors on the PKs of dabigatran in OS patients and AF patients; to compare the effect of renal function (creatinine clearance: CrCl) on the PKs of dabigatran in OS and AF patients and in healthy subjects; to explore possible DE dose modifications for clinically relevant covariates, such as CrCl and P-gp inhibitors; and to explore PK/PD relationships. Data analysis was performed using non-linear mixed-effects modelling techniques (NONMEM), combined with graphical visualisation and statistical software programs. The methodology was comprehensively described. The study complied with the TGA-adopted guideline for reporting the results of popPK analyses.[9] The population PK study included analysis in three subject groups (Group I, II, and III).

Group 1 included OS and AF patients from studies 1160.19 (OS), 1160.20 (AF), and 1160.49 (AF). The PK dataset contained 7931 observation records and 82859 dosing records from 1965 subjects (1005 males, 960 females). DE doses ranged from 50 mg bd to 300 bd, and the two most common doses were 50 mg bd (23.9%) and 150 mg bd (29.4%). The analysed covariates were sex, alcohol use, indication, race, smoking status, and left ventricular dysfunction.

Group II included "healthy" subjects from studies 1160.52, 1160.58 and 1160.23. The PK dataset contained 1031 observation records and 218 dosing records from 80 subjects (38 males, 42 females). DE doses ranged from 50 mg bd to 300 mg bd, and the two most

[9] EMEA. Committee for Medicinal Products for Human Use (CHMP), 21 June 2007. Guideline on Reporting the Results of Population Pharmacokinetics Analyses, CPMP/EWP/185990/06.

common doses were 50 mg bd (23.5%) and 150 mg bd (31.4%). The only analysed covariate was CrCl.

Group III included patients and "healthy" subjects from studies 1160.11 (OS), 1160.20 (AF), 1160.61 (healthy males). The PK/PD dataset contained 7659 observation records from 762 subjects (532 males, 230 females). DE doses ranged from 25 mg bd to 300 mg bd, and the two most common doses were 150 mg bd (28.4%) and 300 mg bd (23.2%). The analysed covariates were indication, age, sex, CRCL and acetyl salicylic acid (ASA).

Other PK Studies

U09-1363-02: The submission included a meta-analysis comparing the PKs of different oral formulations of DE (that is, solution, tablet, and capsule). This meta-analysis was based on PK data from Phase I and II studies involving healthy male and female subjects and patients (OS and AF). The investigators concluded that "all differences in PK related to demographic factors like age, gender or body weight were most likely caused by the intrinsic difference in renal function. The PK seemed to be unaffected by the indication and hence highly comparable between healthy volunteers, orthopaedic surgery patients or patients with atrial fibrillation". The results of the meta-analysis have been examined. The effects on the total dabigatran PK exposure parameters of gender, age, body-weight, healthy subjects and patients are considered to be consistent with the findings in the large popPK Study U09-1399-02 and individual PK studies. This study also included an investigation of the effect of the MDR1 genotype on the PKs of dabigatran; P-gp is encoded by the MDR1 gene and the gene has several different polymorphs. No association was found between exposure to dabigatran and relevant MDR1 single nucleotide polymorphs (SNPs) and related haplotypes.

Evaluator's Overall Conclusions on Pharmacokinetics

The submitted clinical PK data package was extensive. The provided clinical PK studies were of high quality and complied with current standards relating to such studies.

The two pivotal BE studies satisfactorily established the bioequivalence of the proposed DE 150 mg formulation and the currently marketed formulation as regards polymorphs and manufacturing processes [1160.66, 1160.70] The submission did not include relevant BE studies for the proposed DE 75 mg and 110 mg formulations. However, satisfactory justification was provided for not submitting these studies. A relative bioavailability study showed the importance of not chewing the capsules or opening the capsules and sprinkling the pellet contents on food, as the relative $AUC_{0-\infty}$ and C_{max} values increased by 75% and 87%, respectively, for the pellets compared with the capsules [1160.87]. In a repeat dose study, exposure to total and free dabigatran as assessed by the AUC and C_{max} increased by about 1.73 fold and 1.45 fold, respectively, following repeat DE doses (150 mg bd) in healthy Caucasian subjects [1160.61]

The PK drug-drug interaction study between DE (150 mg bd) and the P-gp inhibitor quinidine sulfate (200 mg x 5 doses) showed that co-administration *increased* total dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 53% [90%CI: +45%, +62%] and 56% [90%CI: +46%, +67%], respectively, compared with DE alone [1160.90]. DE did not significantly affect the bioavailability of quinidine sulfate. Co-administration of DE and quinidine sulfate did not result in a fall in systolic hypotension compared with DE alone, and no subjects experienced symptomatic hypotension following co-administration. The data suggest that DE and QS can be co-administered, but with precaution.

The PK drug-drug interaction study between DE and the P-gp inhibitor verapamil showed that the effects of co-administration were complex and depended on whether DE was co-administered with steady state or single dose verapamil and the time relationship

between DE and verapamil administration [1160.74]. When DE (150 mg, single dose) was *given 2 hours before* steady state verapamil IR 120 mg (120 mg bd, 240 mg/day) bioavailability as assessed by total dabigatran $AUC_{0-\infty}$ and C_{max} *increased* by 18% [90%CI: -9%, +52%] and 12% [95%CI: -16%, +49%], respectively. When DE (150 mg, single dose) was given *1 hour after* steady state verapamil IR 120 mg (120 mg bd, 240 mg/day) bioavailability as assessed by total dabigatran $AUC_{0-\infty}$ and C_{max} *increased* by 54% [90%CI: +19%, +99%] and 63% [90%CI: +22%, +117%], respectively. Even greater increases in total dabigatran bioavailability were observed when DE (150 mg, single dose) was given *1 hour after* single dose verapamil IR 120 mg (single dose) with the $AUC_{0-\infty}$ and C_{max} being *increased* 143% and 179% respectively. The data suggest that simultaneous initiation of DE and verapamil should be avoided (contraindicated), as should initiation of verapamil in patients stabilised on DE. The data suggests that the two drugs could be co-administered with caution provided DE is initiated with verapamil at steady state and DE dosing occurs 2 hours before administration of verapamil. There are no PK drug-drug interaction data between DE at steady state and verapamil at steady state. Single dose co-administration of DE (150 mg) and verapamil IR (120 mg) had no significant effect on the bioavailability of verapamil compared with the administration of VIR (120 mg) alone.

The PK drug-drug interaction study between DE and the P-gp inhibitor ketoconazole showed that single dose co-administration of DE 150 mg and ketoconazole 400 mg *increased* total dabigatran $AUC_{0-\infty}$ by 138% [90%CI: +117%, +161%] and C_{max} by 135% [90%: +105%, +170%], respectively, compared with DE alone [1160.1]. An even higher increase in total dabigatran bioavailability was seen when single dose DE (150 mg) was co-administered with steady state ketoconazole (400 mg once daily, repeat doses). The data suggest that co-administration of DE and ketoconazole should be avoided (contraindicated).

The PK drug-drug interaction study between DE and clarithromycin showed that single dose co-administration of DE (150 mg) with steady state clarithromycin (500 mg bd x 6 days) *increased* total dabigatran bioavailability as assessed by both the $AUC_{0-\infty}$ and the C_{max}, 19% [90%CI: -10%, +58%] and 15% [90%: -16%, +57%], respectively, compared with DE alone [1160.82]. However, total dabigatran bioavailability was reduced when single dose DE (150 mg) was co-administered with single dose clarithromycin (500 mg), compared with DE alone. The bioavailability of clarithromycin was not affected when single dose DE (150 mg) was co-administered with steady state clarithromycin (500 mg bd), compared with clarithromycin alone. The data suggest that DE and the P-gp inhibitor clarithromycin can be co-administered, but with precaution.

The PK drug-drug interaction between DE and rifampicin showed that co-administration of single dose DE (150 mg) and steady state rifampicin (600 mg once daily x 7 days) *reduced* total dabigatran bioavailability as assessed by both the $AUC_{0-\infty}$ and the C_{max}, -67% [90%CI: -73%, -59%] and -65% [90%CI: -73%, -56%], respectively, compared with DE (150 mg) alone [1160.100]. P-gp activity appeared to be almost back to baseline levels by 7 days following discontinuation of rifampicin. The data suggest that co-administration of DE and the P-gp inducer rifampicin should be avoided.

The PK/PD drug-drug interaction study between DE and enoxaparin showed that administration of single dose DE (220 mg) 24 hours after the last dose of sc enoxaparin (40 mg daily x 3 days) reduced the bioavailability of total dabigatran as assessed by both the $AUEC_{0-\infty}$ and the C_{max}, -16% [90%CI: -33%, +5%] and -14% [90%CI: -33%, +10%], respectively, compared with DE alone [1160.78]. The small reduction in bioavailability is unlikely to be clinically significant. The PD analysis showed that the AUC_{0-48h} and the ER_{max} for relative anti-FXa/anti-FIIa activity increased by 63% and 15%, respectively, after pre-treatment with EN followed by DE compared with DE alone. The data suggest that the

increased anti-FXa activity observed with DE+EN compared with DE alone is due to pre-treatment with EN. This suggests that there is likely to be a carry-over anti-coagulant effect due to EN still present when switching to DE occurs at 24 hours after the last dose of EN. The other anticoagulation tests (that is, aPTT, ECT, TT and anti-FIIa) were not substantially changed by DE+EN compared with DE alone. The PK and PD data suggest that switching to DE can occur 24 hours after the last dose of EN.

The PD drug-drug interaction study between DE and clopidogrel showed that the bioavailability of total dabigatran did not significantly increase when steady state DE (150 mg bd x 3 days) was co-administered with steady state clopidogrel (300 mg loading/75 mg maintenance x 5 days) compared with DE alone [1660.83]. However, co-administration of steady state DE (150 mg bd x 3 days) and single dose clopidogrel (600 mg) increased the bioavailability of total dabigatran as assessed by both the $AUC_{\tau,ss}$ and the $C_{max,\tau,ss}$, 32% [90%CI: +12%, +56%] and 43% [90%CI: +20%, +70%], respectively, compared with DE alone. Inhibition of ADP platelet aggregation due to clopidogrel was marginally reversed when DE was co-administered with DE. This suggests that DE might promote platelet aggregation and further investigation of the affects of DE on platelet function is warranted. There was no significant difference observed on coagulation factors aPTT, ECT, and TT between steady state clopidogrel co-administered with steady state DE, compared with steady state DE alone, and single dose clopidogrel co-administered with steady state DE, compared with single dose clopidogrel alone. Overall, the PK and PD data suggest that the two drugs can be co-administered, but caution is required when initiating treatment with a clopidogrel loading dose of 600 mg.

In AF [1160.26; sub-study RE-LY], dose normalised steady state plasma dabigatran concentrations in patients taking DE 110 mg bd and DE 150 mg bd were comparable indicating dose proportionality; trough and 2-hour post-dose dabigatran plasma concentrations were 30% higher in female compared with male patients; trough plasma dabigatran concentrations increased with age, with patients aged ≥ 75 years having concentrations 30% higher than patients aged ≥ 65 to < 75 years, and 68% higher than patients aged < 65 years, and similar trends were seen for 2-hour post-dose concentrations; trough and 2-hour post-dose dabigatran plasma concentrations increased with decreasing body weight; mean plasma dabigatran concentrations increased with decreasing CrCl; mean plasma concentration in patients with moderate renal impairment (CrCl 30-50 mL/min) was 2.3 fold higher than in patients with normal renal function (CrCl ≥ 80 mL/min); trough and 2-hour post-dose concentrations were 1.5 and 1.3 fold higher, respectively, in patients with mild renal impairment (CrCl 50-80 mL/min) compared with patients with normal renal function; no differences in trough and 2-hour post-dose plasma concentrations observed in patients with and without the primary efficacy endpoint of time to first occurrence of stroke/SEE; increased trough (57%) and 2-hour post-dose (37%) dabigatran plasma concentrations were observed in patients experiencing a major bleed compared with patients without a major bleed; increased trough concentrations of 1.02 to 1.16 fold and increased 2-hour post-dose concentrations of <0 to 1.20 fold were observed with concomitant DE and P-gp inhibitors; and no significant changes in dabigatran plasma concentration were observed with concomitant DE and ASA or DE and PPIs.

In patients with AF, increased gMean urinary 11-dehydrothromboxane B_2 concentrations were observed with DE compared with WF [1160.20]. This increase is a signal that increased platelet aggregation might be occurring with DE compared with WF. The effects of DE on platelet function should be further investigated given that there was an increased risk of MI observed in patients treated with DE compared with WF in the pivotal efficacy and safety study.

In the population PK study [U09-1399-02], the principal findings were: decreasing CrCl increased exposure to dabigatran; apparent total body clearance (CL/F) linearly declined by about 0.64% for one unit decrease in CrCl below 120 mL/min; apparent total body clearance (CL/F) changed by 0.66% for every year above (decrease) and below (increase) the age of 68 years; females had a 12.5% lower apparent body clearance (CL/F) than males; dabigatran bioavailability increased by 15% in patients receiving concomitant P-gp inhibitors and decreased by 14% in patients receiving concomitant PPIs; and similar relationship between aPPT and plasma dabigatran concentration observed in patients and healthy subjects.

Efficacy

Introduction

The submission included one pivotal Phase III efficacy and safety study supporting the application to register Pradaxa (DE) for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation [RE-LY; 1160.26]. This study was a prospective, multi-national, multi-centred, randomized, open-label for warfarin (WF) and double-blind for DE (110 mg or 150 mg bd), parallel-group, non-inferiority study comparing both doses of DE with WF. The acronym RE-LY stands for Randomized Evaluation of Long-Term Anti-coagulation Therapy.

The submission also included three exploratory Phase II studies in which the major objective was to investigate the safety and tolerability of DE over a range of doses [studies 1160.20, 1160.42, and 1160.49]. None of these three studies were powered to assess efficacy, and *study 1160.42* (extension to *study 1160.20*) did not include a control group. In *study 1160.20 [PETRO]*, the safety and tolerability of DE alone and in combination with ASA were compared with WF in a randomized parallel-group trial of 12-weeks duration, open-label for WF and ASA but double-blinded for DE dose. In *study 1160.42 [PETRO-ex]*, the long-term safety of DE 150 mg (qd and bd) and DE 300 mg (qd and bd) were investigated in a randomized, double-blind, parallel-group extension of *study 1160.2*. In *study 1160.49*, the safety and tolerability in Japanese patients of DE at doses of 110 mg bd and 150 mg bd were compared with WF in a randomized, parallel-group trial of 12-weeks duration, open-label for WF but double-blind for DE.

Each of the four studies were undertaken in accordance with the regulatory requirements relating to ethical approval and supervision, and were conducted according to the ICH principles of GCP and the ethical principles of the Declaration of Helsinki. The three Phase II studies have been briefly outlined above. The pivotal Phase III study has been fully evaluated for efficacy and safety and this evaluation is described in the relevant efficacy and safety sections of this AusPAR. The evaluated and summarised efficacy and safety data from the pivotal study are from the integrated re-analysis of this study.

Dose Response Studies

PETRO [1160.20]

PETRO was an exploratory, Phase II, 12-week safety and tolerability study of dabigatran etexilate (DE) alone or in combination with acetylsalicylic acid (ASA), compared with a standard anticoagulant regimen of warfarin (WF) dose adjusted to target INR 2-3 in patients with chronic atrial fibrillation (AF). It was designed as a 3x3 factorial of three doses of DE (50, 150, and 300 mg bd) and three doses of ASA (0, 81, and 325 mg qd), with WF as an active control group (ten treatments). However, increased bleeding rates were observed with the DE 300 mg bd plus ASA regimen and consequently additional ASA was discontinued for patients randomized to DE 300 mg bd. The study was double-blind with respect to DE, but open-label for patients randomized to WF. It was designed to identify a

DE dose, with and without concomitant ASA, that appeared safe (as measured by bleeding) and potentially effective (inhibition of D-dimer generation) for further study in large-scale Phase III studies. Downward dosing adjustment was permitted based on GFR and aPTT assessment. The primary endpoint of the study was the frequency of bleeding. There were a number of secondary endpoints including biochemical indicators of coagulation and composite clinical endpoints of thromboembolic and cardiac events. The median age of the population in the study was 70-75 years. The study was conducted in 53 centres in 4 countries (Denmark, Netherlands, Sweden and the USA). The study has been published [Ezekowitz et al., 2007].[5]

A **major bleeding event** was defined as any bleed fulfilling one of the following conditions: fatal or life-threatening; retroperitoneal, intracranial, intraocular, or intraspinal bleeding; bleeding requiring surgical treatment; clinical overt bleeding leading to a transfusion of ≥ 2 units of packed cells or whole blood; and clinical overt bleeding leading to a fall in haemoglobin of ≥ 20 g/L. A **minor bleeding event** was any bleed that did not qualify as a major bleed. A minor bleed was further categorised as a **clinically relevant bleeding event** if it fulfilled one of the following criteria: skin hematoma ≥ 25 cm^2; spontaneous nose bleed > 5 minutes duration; macroscopic haematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours; spontaneous rectal bleeding (more than spotting on toilet paper); gingival bleeding > 5 minutes; bleeding leading to hospitalisation; bleeding leading to transfusion of < 2 units of packed cells or whole blood; and any other bleeding event considered clinically relevant by the investigator. All minor bleeding events not fulfilling one of the criteria for clinically relevant bleeding were classified as nuisance bleeds.

Major bleeding events were reported only with DE 300 mg bd in combination with ASA 81 mg qd (2.9%, 1/34) and with ASA 325 mg qd (10.0%, 3/30). No major bleeding was observed with WF (0/70). **Major plus clinically relevant bleeding events** were observed for all DE doses alone and in combination with ASA, apart from DE 50 mg bd alone. The highest rates were observed with DE 300 mg in combination with ASA 81 mg qd (14.7%, 5/34) and ASA 325 mg (20.0%, 5/34). Major plus clinically relevant bleeding was observed with DE 150 mg bd alone (8.9%, 9/101), DE 150 mg bd plus ASA 81 mg qd (5.6%, 2/36) and DE 150 mg bd plus ASA 325 mg qd (6.1%, 5/34). The rates for major plus clinically relevant bleeding for DE 50 mg alone, DE 300 mg alone, and WF were 0% (0/59), 5.7% (6/105), and 5.7% (4/70), respectively. **Any bleeding events** were observed most commonly with DE 300 mg bd in combination with ASA 81 mg qd (32.4%, 11/34) and with ASA 325 mg qd (46.7%, 14/30). The rates observed with DE 150 mg alone and in combination with ASA 81 mg qd and ASA 325 mg qd were 14.9% (15/101), 22.2% (8/36), and 21.2% (7/33), respectively. The rates for DE 50 mg bd alone, 300 mg bd alone and WF were 3.4% (2/59), 13.3% (14/105), and 17.1% (12/70), respectively.

Comment

It was considered that this exploratory Phase II study included only limited clinical data directly relevant to the submission. It was primarily a safety study designed to investigate the effect of various DE doses alone and in combination with ASA on bleeding in patients with chronic AF. No formal statistical hypothesis was tested. The number of patients in each treatment group was small, particularly in the DE plus ASA groups. There was no primary efficacy endpoint, and the study was not powered to evaluate the differences among the treatment groups for the occurrences of stroke and thromboembolic events. The study included data on DE 150 mg bd alone (n=91) and in combination with ASA 81 mg qd (n=34) and ASA 300 mg qd (n=33); DE 150 mg is one of the doses being proposed for approval by the sponsor. No major bleeds were observed with DE 150 mg bd alone and in combination with ASA (both doses). However, major plus clinically relevant bleeds

occurred with DE 150 mg alone and in combination with ASA (both doses), but ASA (both doses) did not increase the rate seen with DE 150 mg bd alone. The incidence of any bleeds with DE 150 mg bd was higher when combined with ASA (both dose) compared with DE 150 mg bd alone. There was no obvious dose response relationship between DE 150 mg bd alone and DE 300 mg bd alone as regards the incidence of minor bleeds. The study included no data on DE 110 mg bd, the other dose being proposed for approval by the sponsor.

PETRO-EX [1160.42]

PETRO-Ex was designed as an exploratory, Phase IIa, multi-national, multicentred, open-label, four-treatment, extension study for patients who had been treated with at least 50 mg bd dabigatran etexilate (DE) in PETRO and who had not prematurely discontinued therapy. The study was uncontrolled and the four DE treatments were 150 mg qd, 150 mg bd, 300 mg qd, and 300 mg bd, with aspirin being added at the discretion of the investigator. The study was initially planned to run for 2 years but this was extended to 5 years. The study enrolled 361 patients from PETRO. The mean±SD age of the 361 patients was 71.0±8.2 years [range: 40-90]. Of the 361 patients who entered the extension study, 208 (57.6%) remained in the study until it ended and consequently were retained for > 4 years. The study was conducted in 50 centres and 4 countries (Denmark, Netherlands, Sweden, and the United States) from 6 January 2004 to 21 January 2009.

The primary objective of the study was to assess the long-term safety and efficacy of DE, with or without concomitant treatment with ASA, in patients with atrial fibrillation, CAD, and at least one additional risk factor for thromboembolic events. The primary efficacy endpoint was a composite clinical endpoint including the incidence of stroke (fatal or non-fatal), TIAs, systemic thromboembolism, myocardial infarction (fatal or non fatal), other major adverse cardiac events and all cause death. This composite endpoint contained all types of stroke including ischaemic and haemorrhagic. The primary safety endpoint was the frequency of any bleeding. There were a number of secondary efficacy and safety endpoints. As the study was an exploratory safety study no formal hypotheses were tested, no formal sample size was calculated, and all analyses were descriptive rather than analytical. In PETRO and PETRO-ex combined, a total of 432 patients were exposed to DE. The exposures were 50 mg qd (n=1), 50 mg bd (n=105), 150 mg qd (n=102), 150 mg bd (n=256), 300 mg qd (n=90), and 300 mg bd (n=161).

Results (Primary Efficacy – composite of stroke/TIA/STE/MI/MACE/all cause death)

The yearly event rates for the primary composite efficacy endpoint in PETRO and PETRO-ex combined for DE 50 mg qd, 50 mg bd, 150 mg qd, 150 mg bd, 300 mg qd and 300 mg bd were, respectively: 0%, 17.0%, 5.0%, 5.7%, 4.5%, 2.4%, and 5.4%.

Results (Primary Safety - Bleeding)

The yearly event rates for *major bleeding* in PETRO and PETRO-ex for DE 50 mg qd, 50 mg bd, 150 mg qd, 150 mg bd, 300 mg qd, and 300 mg bd were, respectively: 0%, 0%, 6.6%, 3.1%, 0.8%, and 7.3%. The respective yearly event rates for *any bleeding* were 0%, 25.5%, 21.5%, 14.7%, 14.9%, and 58.5%.

Comment

No conclusions can be made about the efficacy of DE from this exploratory study, uncontrolled study. The exploratory bleeding data suggests that a dose of 300 mg bd is too high for safe use. The yearly event rate for major bleeding for 150 mg bd was 3.1% which puts it in the range 0% (lowest with 50 mg qd and bd) to 7.3% (highest with 300 mg bd). The yearly event rate for any bleeding for 150 mg bd was 14.1% which puts it in the range

0% (lowest with 50 mg qd) to 58.5% (highest with 300 mg bd). In the absence of a control treatment it was difficult to make meaningful conclusions regarding safety.

Study 1160.49 [Japanese Study]

Study 1160.49 was a Japanese, multi-centred, open-label, randomised, parallel-group comparison Phase II study. The primary objective of this study was to evaluate the safety of dabigatran etexilate (DE) 110 mg and 150 mg bd compared with warfarin (WF), adjusted dose to target INR 2-3, for 12 weeks in Japanese patients with non-valvular atrial fibrillation. The primary endpoints were bleeding events, adverse events, discontinuations, and changes in laboratory test values. There were a number of secondary endpoints including efficacy, safety, pharmacodynamic and pharmacokinetic assessments. The primary analysis in this study was descriptive for safety. No statistical hypothesis was tested. The study estimated that a sample size of 50 patients would provide a probability of 0.89 to observe at least 5 bleeding events whose true rate was 15.0%. The study was not powered to assess efficacy. The study randomised 174 patients (166 treated), 53 to DE 110 mg bd (46 treated), 59 to DE 150 mg bd (58 treated), and 62 to WF (62 treated). The mean±SD age of the 166 treated patients was 68.4±years, and 88.0% (n=146) were male and 12.0% (n=20) were female. The study was undertaken in Japan from 10 November 2005 to 4 September 2006. The study report was dated 5 April 2007.

Safety Results (Bleeding)

The incidence rates of major bleeding events in the DE 110 mg bd, DE 150 mg bd, and WF groups were 0/46 (0%), 1/58 (1.7%), and 3.2% (2.62%), respectively. The corresponding results for major or clinically relevant bleeding were 4.3% (2/46), 8.6% (5/58) and 11.3% (7/62). The corresponding results for any bleeding were 21.7% (10/46), 34.5% (20/58), and 24.2% (15/62).

Comment

This study was primarily a 12-week, exploratory safety study in Japanese patients with AF. There were no thromboembolic events reported during the study in DE treated patients and one WF treated patient experienced an ischaemic stroke (coded as cerebral infarction). Ischaemic stroke coded as cerebral infarction was reported in one patient during the screening period and in one patient during the post treatment period in the DE 150 mg bd group. Major bleeding events and major or clinically relevant bleeding events occurred more commonly with WF than with DE 110 mg bd or DE 150 mg bd. All bleeding events occurred more commonly with DE 150 mg bd than with DE 110 mg bd.

Main Study – RE-LY [1160.26]

The pivotal Phase III, multinational, multicentred efficacy and safety study was RE-LY. The study was randomized, and open-label and was designed to evaluate whether DE 110 mg bd (DE110) and DE 150 mg bd (DE150) were non-inferior to adjusted dose WF (target INR of 2.0 to 3.0) for the prevention of stroke and systemic embolism in patients with non-valvular AF and at least one additional risk factor for stroke.

The study was conducted from 22 December 2005 to 15 March 2009. There were 1,044 sites in 44 countries and 951 sites randomized at least one patient. The participating countries included Australia, Canada, Netherlands, Singapore, Sweden, Switzerland, the UK and the USA. The median planned duration of treatment was 20 to 24 months, with a minimum of 12 months treatment after the last patient was randomized and a maximum of 3 years treatment. The total number of randomized patients was 18,113. Recruitment of 15,000 patients was completed in 1.5 years.

This study used the PROBE design [Hansson et al, 1992].[10] A central element of the PROBE design is the use of blinded adjudicators to reduce potential bias in the evaluation and classification of important outcome events. The study used the following methods to minimise adjudication bias: blinded adjudication of events by at least two independent adjudicators; database and data handling assigned to an academic group independent of the sponsor; blinding of sponsor and study management personnel to "by treatment" analyses during the study; oversight by a Data Safety Monitoring Board (DSMB); and Case Report Form (CRF) designed to elicit events based on investigations and other assessments performed by the site. In addition, the study used the following methods to minimise reporting bias: objective, clinically relevant outcomes; blinded dabigatran doses; categorization of all hospitalisations; patient stroke and bleeding questionnaires at each visit; blinded review of TIAs for possible under-reporting of strokes; review of adverse events for terms that suggested un-reported stroke or bleed; screening of haemoglobin changes in laboratory data for possible under-reporting of major bleeds; and evaluating reports of anaemia for possible bleeding events.

WF was chosen as the active comparator as it was considered that it would have been unethical to include a placebo comparator. WF treatment was administered open-label as the investigators considered that double-dummy INR monitoring would be complex and would have complicated patient and centre recruitment. The sponsor also considered that an open-label (PROBE) design would more closely approximate the usual clinical setting for treatment with DE and WF.

Comment

The objectives and design of the study are considered to be satisfactory. The use of the PROBE design is subject to bias due to open-label comparison of the treatments. However, the methods used in the study to minimise bias are considered to be satisfactory. The use of WF as an active control instead of the use of a placebo control is considered to be acceptable. AF predisposes to the formation of blood clots within the left atrium and particularly the left atrial appendage, and these may embolise to the systemic circulation [Medi et al., 2007].[11] Australian clinical guidelines relating to the management of non-valvular AF and stroke prevention recommend that "all patients with chronic AF should be considered for oral anticoagulant therapy, and the decision based on the balance between the risks of thromboembolism and bleeding" [Hankey GJ, 2001]. [12]

The inclusion criteria included patients aged ≥ 18 years with documented AF and one additional risk factor for stroke. The exclusion criteria included patients with prosthetic heart valves requiring anticoagulation per se, or with haemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study. The study also included criteria for handling removal of patients from therapy or assessment. The study included Vitamin K antagonist (VKA) experienced and naive patients. The study report referred to possible survivor bias relating to superior outcomes in VKA-experienced patients better able to tolerate WF treatment and requirements for regular INR testing. Consequently, the study recruited both VKA-experienced and VKA-naive patients and compared the results in both cohorts. In the first 12 months of the trial predominantly VKA-experienced patients were recruited (~80%). Consequently, a protocol amendment was made to ensure that balanced recruitment of the two VKA

[10] Hansson L et al. Prospective randomized open-blinded endpoint (PROBE) study. A novel design for intervention trials. Blood Pressure 1992;1: 113-119.
[11] Medi C et al. Clinical Update: Atrial Fibrillation. MJA 2007; 186: 197-202.
[12] Hankey GJ (on behalf of the National Blood Pressure Advisory Committee of the National Heart Foundation). Position Statement: on-valvular atrial fibrillation and stroke. MJA 2001; 174: 234-239.

cohorts occurred at randomization. The protocol amendment included expanding the definition of VKA-naive patients from 1 month to 2 months or less of lifetime VKA use in order to increase the inclusion of newly diagnosed VK-naive AF patients.

Comment

The division of patients into VKA-experienced and VKA-naive cohorts is acceptable. If DE is approved then it is likely to be used in both patient groups. The inclusion and exclusion criteria are acceptable. The criteria for documentation of AF are consistent with clinical practice. However, the inclusion criteria did not specify the duration of paroxysmal AF or persistent AF. Paroxysmal AF has been clinically defined as being self limiting and usually resolving within 24 hours, while persistent AF has been clinically defined as being sustained and lasting for > 7 days [Medi et al., 2007].[11] The additional risk factors for stroke in patients with AF are consistent with known risk factors. The study included only patients with AF with at least one additional risk factor for stroke, and this is considered to prevent extrapolation of the results to patients with AF without at least one additional risk for stroke. Of the patients in the study, 21.8% had valvular heart disease at baseline (predominantly mitral regurgitation). The initial protocol excluded patients with prosthetic valves or haemodynamically relevant valve disease. These exclusion criteria were subsequently amended to "patients with prosthetic heart disease requiring anti-coagulation per se, or with haemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study".

Patients were randomized (1:1:1) to DE110, DE150, or WF. DE was taken twice daily with or without food, and patients continued throughout the study on the dose to which they had been randomized. WF was taken once daily and titrated to maintain the INR at 2-3; a warfarin algorithm was provided for guidance but the protocol did not mandate its use. INR testing was usually undertaken at least once every 4 weeks. The doses of DE were blinded and WF was administered open-label. Randomization was via an interactive voice response system (IVRS) located at the central co-ordinating centre in Canada. Patients taking VKAs stopped on the day of randomization and began the assigned study drug when the INR fell to < 2.0 (if randomized to DE), or < 3.0 (if randomized to WF). Patients randomized to WF who had been taking WF prior to randomization continued on the same dose of study WF if the INR was < 3.0 on the day of treatment initiation. Patients randomized to WF who had been taking WF prior to randomization with an INR > 3 on the day of randomization had initiation of study WF delayed until the INR was in the target range of 2-3. Patients randomized to WF who had been taking other VKAs switched to WF according to a study algorithm. VKA-naive patients started study medication on the day of randomization.

The use of any additional drugs considered necessary for a patient's welfare were permitted during the study at the discretion of the investigator, subject to precautions regarding certain specified drugs. Details of all concomitant medication administered from the time of consent until completion of follow-up were recorded. The following medications were allowed during the study with a precaution that the combination of any of these agents with DE or warfarin might increase the risk of bleeding: ASA (≤ 100 mg/day); clopidogrel; ticlopidine; dipyridamole; aspirin/dipyridamole; and nonsteroidal anti-inflammatory drugs (NSAIDs). The following medications were allowed during the study only if the clinical necessity outweighed the increased bleeding risk: non study WF or other VKAs; ASA over the counter (OTC) medications; chronic systemic corticosteroids; heparin; and fibrinolytic agents. The use of the P-gp inhibitor quinidine was contraindicated during the treatment phase for patients taking DE following a protocol

amendment. This protocol amendment also included precautionary advice regarding the use of moderate to strong P-gp inhibitors with DE, but the use of P-gp inhibitors (other than quinidine) was not contraindicated. The study included no dietary of life style restrictions. The study included procedures to be undertaking relating to stopping (and restarting) study medication and instituting appropriate therapy in the event of minor bleeds, major bleeds, stroke or acute coronary syndromes. In addition, appropriate treatment procedures were specified for emergency surgery, elective surgery, coronary revascularization or cardioversion.

Comment

The strategies adopted for the use of concomitant medications are considered to be satisfactory. The specified procedures in the event of treatment having to be stopped were satisfactory. One of the disadvantages relating to DF compared with WF is the absence of a monitoring test. Consequently, the first sign of DE overdose might be a major bleed. There is no antidote able to reverse the anticoagulant effect of DE. Consequently, treatment of DE overdose is symptomatic. The treatment of DE overdose in the study was at the investigator's discretion and no specific treatment was mandated. Symptomatic treatment could include the administration of fresh frozen plasma or fresh whole blood. In case of excessive bleeding, measures to terminate bleeding such as concentrates of coagulation factors II, VII, IX, or X, or recombinant factor VII were permitted. The protocol stipulated that consideration could be given to the administration of platelet concentrates if thrombocytopenia was present.

Primary Efficacy Endpoint

The *primary efficacy endpoint* was a composite endpoint of time to first occurrence of stroke or systemic embolism (stroke/SEE). *Stroke* was defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death, and was categorised as ischaemic or haemorrhagic or cause unknown (based on CT scanning, MRI, or autopsy). Fatal stroke was defined as death from any cause within 30 days of stroke. Severity of stroke was assessed by the modified Rankin (mRS) score at discharge from hospital and 3 to 6 months after discharge. *Systemic embolism (SEE)* was defined as an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina, or grafts) documented by angiography, surgery, scintigraphy, or autopsy. SEE events excluded CNS embolic events.

Secondary Efficacy Endpoints, Other Efficacy Endpoints and Safety Endpoints

There were two composite secondary efficacy endpoints: time to first occurrence of stroke, systemic embolism, or all-cause death (stroke/SEE/all-cause death); and time to first occurrence of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular death (stroke/SEE/PE/MI/vascular death).

Stroke and systemic embolism were defined as for the primary efficacy endpoint. *Myocardial infarction (MI)* was defined differently depending on whether or not patients had undergone percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG). In *patients who did not undergo PCI or CABG*, at least two of the following three criteria had to be fulfilled: (i) typical prolonged severe chest pain or related symptoms or signs suggestive of MI (for example, ST changes of T-wave inversion in the ECG); (ii) elevation of troponin or CK-MB to more than the upper limit of normal (ULN) or if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level; and (iii) development of significant Q-waves in at least two adjacent ECG leads. In *patients who had under gone PCI (within 24 hours)* the criteria were elevation of troponin or CK-MB to more than 3xULN or if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of

significant Q-waves in at least two adjacent ECG leads.[13] In *patients who had undergone CABG within the previous 72 hours* the criteria were elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least two adjacent ECG leads. *Silent myocardial infarction* was retrospectively diagnosed by the appearance of significant new Q-waves between study visits. In such cases, the date of the event was recorded as the midpoint between the two study visits. MI may also have been demonstrated at autopsy. If CK-MB was not available then total CK could be assessed. Significant Q-waves were new Q-waves of at least 0.04 seconds duration and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least two adjacent leads. *Deaths* were classified as being vascular (including bleeding) or non-vascular, due to other specified causes (for example malignancy), or of unknown aetiology.

Other efficacy endpoints were: individual or composite occurrences of ischemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, acute myocardial infarction, transient ischaemic attacks (TIAs), vascular death (includes deaths from bleeding), all deaths, and hospitalizations; and Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all cause deaths, and major bleeds.

The *safety endpoints* were: bleeding events (major and minor), intracerebral haemorrhage, other intracranial haemorrhage (ICH), elevations in liver transaminase, bilirubin and hepatic dysfunction, and other AEs. *Minor bleeds* were clinical bleeds that did not fulfil the criteria for major bleeds. There was a *post hoc* analysis of major GI bleeds, life-threatening GI bleeds, and any GI bleeds.

Statistical Considerations

The primary endpoint was assessed as the time to the first occurrence of stroke or systemic embolism. The primary efficacy analysis was designed to test whether DE was non-inferior to WF using the Cox proportional hazard model and its 95% confidence interval (CI). DE was non-inferior to WE if the upper bound 95% CI of the Hazard Ratio (HR) (= risk ratio, stated in the protocol) [DE/WF] was less than the specified non-inferiority margin of 1.46. DE was not non-inferior to WF if the upper bound 95% CI of the HR [DE/WF] was equal to or greater than 1.46. The primary analysis was undertaken using the randomized data set (see below for definition). The null hypothesis was that the HR of dabigatran versus warfarin was larger than or equal to the specified non-inferiority margin of 1.46. The alternative hypothesis was that the HR of dabigatran versus warfarin was less than 1.46.

Since there were two comparisons of DE versus WF, the Hochberg procedure was used to adjust the significance level for multiple comparisons to maintain a non-inferiority α level of 0.05 (one-sided) for the hazard ratio [DE/WF]. Using this procedure, the DE dose with the largest HR versus WF was tested first for non-inferiority at an α=0.025 (one-sided) level. If non-inferiority was demonstrated for the first comparison at this significance level, then non-inferiority of DE versus warfarin for both DE dose could be claimed. If non-inferiority was not demonstrated for the first comparison at this significance level, then comparison between the DE dose with the lowest HR versus WF was tested for non-inferiority at an α=0.125 (one-sided) level. The protocol specified that if non-inferiority was established then superiority testing was to be performed to compare DE with WF for

[13] Creatine kinase (CK) is composed of two subunits, CK-M (muscle type) and CK-B (brain type), which are combined into three distinct isoenzymes: CK-MM, CK-MB, and CK-BB. CK-MB is a marker of myocardial injury - CK-MB levels become elevated in 4 to 6 hours, peak at 10 to 24 hours, and return to normal within 3 to 4 days after an acute myocardial infarction.

the primary endpoint. Although the non-inferiority testing was one-sided, two-sided 95% and 97.5% CIs of the hazard ratios were calculated.

The time to the occurrence of the primary endpoint event was computed as (event date minus randomization date) plus 1. Patients who did not have primary endpoint events during the trial period were considered to be censored. The time to censoring was computed as (study termination date minus randomization date) plus 1. For patients who had more than one primary endpoint event during the study, the time to the first occurrence of the primary endpoint event was used for the primary efficacy analysis. The primary analyses included yearly event rates, Kaplan-Meier estimates and Cox regression analyses.

There were four data sets used in the analysis: the randomized set, the safety set, the treated set, and the per-protocol set (PPS). The randomized set (n=18113) included all patients in the treatment groups to which they had been randomized, regardless of whether the patients took randomized study medication or not (that is, the intention-to-treat population). The safety set (n=18040) included all randomized patients who had taken at least one dose of study medication. The treated set (n=15266) included all randomized patients who took the randomized study medication for ≥ 70% of the time during the study or prior to the onset of a primary outcome event. The per-protocol set (n=14730) included all patients who were randomized and treated and did not have important protocol violations. The primary efficacy endpoint was analysed in the randomized set (primary analysis), treated set (sensitivity analysis), safety set (sensitivity analysis), and PPS (sensitivity analysis). The other efficacy endpoints were all analysed in the randomized set plus or minus the safety set.

Missing data were, in general, not imputed. Death of unknown cause was considered as vascular death. Other outcome events without supporting documentation were considered as refuted events. For the time-to-event analysis, if a patient could not be contacted, the patient was censored on the last day of available contact during the study. *Interim* analyses were included in the study. The DSMB conducted formal futility analyses at approximately 50% and 75% of expected primary endpoint events. No treatment arm was stopped for futility. The study also included formal rules for stopping if DE was found to be superior WF. The trial was not stopped for superiority.

Sample size was determined in the study as follows. The study assumed a yearly event rate of 1.6% for the primary efficacy endpoint for both DE and WF, with 5,000 patients per treatment group to be recruited in 2 years and followed up for 1 additional year to achieve 150 events per treatment group. Within these parameters, each comparison had approximately 90% power to establish the non-inferiority of DE to WF at a one-sided α=0.025 level (without adjusting for multiple comparisons) based on the non-inferiority margin of 1.46. With a total of 15,000 patients randomized to the two DE and WF treatment groups at a 1:1:1 ratio, to achieve a total of 450 events using the Hochberg procedure to compare each DE dose to WF, the study had approximately 84% power to establish the non-inferiority of both DE doses to WF using the non-inferiority margin of 1.46. A total of 18,113 patients were randomized meaning that if the actual event rate based on 15,000 patients was as planned then the statistical power would be > 84%.

Comment

The statistical methods and sample size calculations were considered to be satisfactory. The statistical analysis plan included a detailed description of the rationale for selecting the non-inferiority margin of 1.46. The statistical plan included a figure outlining the hypothetical outcomes of the study based on the inferiority margin for the HR of 1.46. The protocol explicitly indicated that the terms Hazard Ratio and Risk Ratio were identical in

this study ("hazard ratio (risk ratio)"). The yearly event rates for outcomes between treatments were compared using Hazard Ratios (Risk Ratios) with 95% CI.

The calculation of the non-inferiority margin was based on the 95%-95% method (that is, the first 95% refers to the CI used to choose the effect size from the historical data [WF vs placebo] and the second 95% refers to the CI used to reject the null hypothesis in the non-inferiority analysis [DE vs WF]). The non-inferiority margin of 1.46 was specified in the original protocol and not modified during the conduct or analysis of the study. It preserves 50% of WF's effect relative to placebo based on the confidence limits approach. The 95% CI chosen from the historical data was the upper limit of the HR [WF/placebo]based on a published meta-analysis [Hart et al 1999] which combined the summary statistics from six, small, published studies comparing WF with placebo for the prevention of stroke in patients with AF.[14] The published HR from the meta-analysis of these six studies was 0.38 [95%CI: 0.28, 0.52]: that is, a risk reduction of 62% [95%CI: 48%, 72%] observed with WF relative to placebo. In the published meta-analysis, WF reduced the absolute risk of stroke by 3.1% per year compared with placebo (no 95% CI provided in the study). The stroke/event rate for WF from these six studies ranged from 0.62% to 3.94% per year compared with 2.99% to 12.35% for placebo.

The non-inferiority margin of 1.46 preserved 50% of WF's effect on the incidence of stroke/SEE relative to placebo, based on the upper 95% CI (0.52) of the HR reported in the published meta-analysis. The non-inferiority margin was calculated as follows: δ (non-inferiority margin) = 1 + (1-50%)*(1/0.52 - 1) = 1.46. The obvious problem with statistical calculations of non-inferiority margins for HRs assessing serious clinical events with low event rates such as strokes/SEE is determining the clinical significance of these margins. In effect, the study accepted an increase in the risk of stroke/SEE of up to 46% with DE relative to WF as being evidence of non-inferiority (that is, DE preserved at least 50% of WF's effect relative to placebo on the risk of stroke/SEE). This appears to be a large relative increase but, as the results from the published meta-analysis showed, a 62% reduction in stroke observed with WF relative to placebo equated to only a 3.1% annual absolute risk difference (95% CI not provided). Overall, the non-inferiority margin of 1.46 for the HR [DE/WF] is considered to be clinically reasonable, given that stroke/SEE event rates were expected to be small. Interestingly, a smaller non-inferiority margin of 1.38, derived to preserve the effect of WF relative to placebo on a log scale, was recommended by the FDA. In any event, the smaller non-inferiority margin of 1.38 did not change the observed results based on the protocol specified, less conservative, non-inferiority margin of 1.46.

Patient Disposition

A total of 20,377 patients were enrolled, and 18,113 were randomized. Of the 2,264 patients enrolled but not randomized, 1,549 (68.4%) did not meet inclusion/exclusion criteria, 414 (18.3%) withdrew consent, and 301 (13.3%) were eligible but not randomized. The 18,113 randomized patients were equally distributed across the three treatment groups (DE110, n=6,015; DE150, n=6,076; WF, n=6,022). Of the total number of randomized patients (n=18113), 29.7% were from the USA, 25.7% from Western Europe, 15.4% from Asia, 11.7% from Central Europe, 6.3% from Canada, 5.9% from Australia, Israel, and South Africa and 5.3% from Latin America.

Of the 18,113 randomized patients, 18,040 were treated with at least one dose of the study medication, and 17,360 completed the study either on study medication (n=14086) or completed follow-up but had stopped study medication prematurely (n=3274). Of the 73

[14] Hart et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999; 131; 491-501.

randomized patients who had not been treated, 26 had completed follow-up and 47 had withdrawn consent or been lost to follow up. The percentages of treated patients who completed the study were 96.6% (5780/5983) for DE110, 96.1% (5824/6059) for DE150, and 96.0% (5756/5998) for WF. The percentages of treated patients who completed the study on study medication were 77.1% (4610/5983) for DE110, 76.4% (4627/6059) for DE150, 80.8% (4849/5998).

The mean (SD) *study duration* in the randomized set was 23.74 (7.09) months, 23.77 (7.06) months, and 23.5 (7.04) months, for DE110, DE 150 and WF, respectively. The total patient-years of exposure were 11899, 12033, and 11794 for the respective treatment groups.

Important protocol violations were defined prior to database lock as deviations that could potentially alter the analyses or put patients at risk. Of the randomized patients, only 8 had no documented AF but 546 (3.0%) had no additional risk factor, while 193 (1.1%) had a history of valve disorder (mitral stenosis). The distribution of protocol violations was similar for the treatment groups.

The percentages of randomized *patients excluded from the per-protocol set* were 19.9% (n=1194) for DE100, 21.1% (n=1279) for DE150, and 15.1% (n=910) for WF. The most frequent reason for exclusion from the randomized set was patient not on study medication for ≥ 70% of the time while in the study or prior to the onset of the primary endpoint: 17.0% (n=1020) DE110; 17.9% (n=1088) DE150; and 12.3% (n=739) for WF.

Overall, the baseline demographic characteristics of the randomized patients were well balanced across the three treatment groups. The mean (SD) age was 71.5 (8.7) years [range: 22-101], and 16.4% of randomized patients were aged < 65 years, 43.6% were aged ≥ 65 and < 75, and 40.0% were aged ≥ 75 years. Males comprised 63.6% of randomized patients. Caucasians comprised 70% of randomized patients, 16% were Asian, 1% were black, and 13% were other ethnic origin. The mean (SD) weight was 82.6 (19.6) kg, and on average, females weighed less than males (74.2 kg vs 87.5 kg, respectively).

The median CrCl was 68.4 mL/min in the total randomized population and was similar for the three treatment groups. Of the randomized patients (n=18113), 31.2% had a CrCl ≥ 80 mL/min, 45.8% had a CrCl ≥ 50 mL/min and < 80 mL/min, 18.5% had a CrCl ≥ 30 mL/min and < 50 mL/min, and 4.1% had a missing CrCl value. Patients with severe renal impairment (CrCl < 30 mL/min) were excluded, but 0.4% of randomized patients violated this inclusion criterion and were included in the study. The mean (SD) systolic and diastolic blood pressures of the randomized patients were 131.0 (17.5) mmHg [range: 70, 220] and 77.0 (10.6) mmHg [range: 30, 120], respectively. Approximately 31% of patients had new onset AF (diagnosed less than three months prior to randomization), 22% were diagnosed with AF between 3 months and 2 years prior to randomization, and 47% had AF diagnosed more than 2 years prior to the study. Approximately 32% of patients had persistent AF, 32.8% paroxysmal AF, and 35.2% permanent AF. Previous cardioversion had been used in 27.6% of patients, and 2.1% had been treated with AV nodal ablation, 10.7% with pacemaker, and 3.3% with an implantable defibrillator.

Additional protocol specified s*troke risk factors* at baseline were well balanced among the three treatment groups. The most common additional stroke risk factor in the three treatment groups (approximately 67% in each of the groups) was age ≥ 65 years and hypertension. In the total group, 31.1% of patients had one additional stroke risk factor, 33.1% had two additional factors, 20.4% had three additional factors, and 3.0% had no additional factors and should have been excluded from the study as this was a protocol violation.

The *mean $CHADS_2$ score* was 2.1 (median 2) for all treatment groups. Approximately one third of patients had $CHADS_2$ scores of ≥ 3. The $CHADS_2$ score is a commonly used method of assigning risk of ischaemic stroke in patients with AF. It is calculated by assigning 1 point each for congestive heart failure, hypertension, age ≥ 75 years, or diabetes mellitus, and 2 points for a history of stroke or TIA. For patients with valvular atrial fibrillation and $CHADS_2$ score ≥ 2, anti-coagulation with warfarin has been recommended (INR 2-3, or higher for mechanical valves) unless contraindicated or annual major bleeding risk > 3%, aspirin or warfarin has been recommended for a $CHADS_2$ score of 1, and aspirin (81-325 mg daily) has been recommended for a $CHADS_2$ score of 0 or if warfarin is contraindicated [Medi et al., 2007].[11]

Review of the *selected medical history* at baseline showed that 10.4% of the total number of randomized patients had a history of cancer with similar frequencies across the three treatment groups. Valvular heart disease (predominantly mitral regurgitation) was present in 21.8% of patients with similar frequencies across the three treatment groups. *Baseline medication* use prior to randomization was balanced across the treatment groups. The most commonly used medications at baseline were beta-blockers, calcium channel blockers and drugs used in AF (89.7%). The second most commonly used medications were anti-thrombotic agents (88.3%) and the most commonly used of these were oral anticoagulants (62.3%) followed by ASA (39.5%). Antihypertensive medications were used in 80.1% of randomized patients and the most commonly used were diuretics (44.9%) followed by ACE inhibitors (44.9%) and ARBs (23.9%). Statins were used in 44.5% of patients.

ASA at any time was used by 39.7% of patients and 100% of the time by 20.5% of patients. Clopidogrel at any time was used by 7.4% of patients and 100% of the time by 2.4% of patients. P-gp inhibitors, including amiodarone, verapamil, diltiazem and quinidine were used by 14.9%, 7.2%, 11.8% and 0.7% of patients, respectively, at anytime during the study. A small number of patients received quinidine prior to the protocol amendment and should have subsequently discontinued study medication. Proton pump inhibitors (PPIs) were used at least once during the study by 24% of patients, almost 10% more than at baseline. There was slightly more use of PPIs at least once during the study by patients in the DE groups than in the WF group: DE110 24.6%; DE150 24.7%; and WF 21.1%. Overall, concomitant medication use during the study was similar for the three treatment groups.

The baseline demographic characteristics of *VKA-experienced and VKA-naive groups* were generally comparable, apart from expected differences in AF duration. Baseline medication use was balanced across the three treatment groups for both VKA-naive and VKA-experienced patients. At baseline, more VKA-naive patients than VKA-experienced patients were receiving ASA (54.2% vs 24.6%, respectively), clopidogrel (7.9% vs 3.3% respectively) and ASA plus clopidogrel (5.2% vs 1.9%, respectively). Alternatively, more VKA-experienced than VKA-naive patients were receiving oral anticoagulants at baseline (91.7% vs 33.3%, respectively). Other baseline medication use was generally similar for VKA-naive and VKA-experienced patients. However, ASA was used at least once in 49.7% of all VKA-naive patients and 71.0% of all VKA-experienced patients and the respective figures for clopidogrel were 9.3% and 5.4%.

Comment

In the treated population, the percentage of patients who completed the study while on study medication was greater in the WF group than in both DE groups. The main identifiable reason for the difference between the treatment groups was the higher incidence of outcome events resulting in premature discontinuation of study medication in the DE groups than in the WF group. Serious adverse events not related to outcome events and adverse events resulting in premature discontinuation of study medication in the

treated population both occurred more commonly in the DE groups than in the WF group. The percentage of total randomized patients who were treated and completed the study (followed-up irrespective or whether continued study medication or discontinued study medication prematurely) was high (99.6%, 18040/18113).

Primary Endpoint Results

The primary endpoint was the time to the first occurrence of stroke or systemic embolism (stroke/SEE). All strokes were included in one of three categories of ischaemic stroke, haemorrhagic stroke, and strokes with uncertain classification (usually because no imaging results were available to categorise the event). Comparisons between treatment groups for stroke/SEE were performed using a Cox regression analysis with treatment in the model. Non-inferiority of both DE doses compared with WF was demonstrated (Hochberg procedure) in the randomized population (Table 8). The results showed that the upper bound 95% CI for both HRs [DE/QD] was less than the pre-specified non-inferiority margin of 1.46 ($p<0.0001$ for non-inferiority for both comparisons). DE110 and DE150 reduced the risk of stroke/SEE relative to WF by 10% ($p=0.2943$, non-superior) and 35% ($p=0.0001$, superior), respectively.

Table 8: RE-LY [re-analysis] - Hazard ratio and 95% CIs for stroke/SEE; randomized set.

Analysis	Parameter	DE 110 vs WF	DE 150 vs WF	DE 110 vs DE 150
Inferiority Analysis	Hazard ratio (SE)	0.90 (0.09)	0.65 (0.07)	1.39 (0.16)
	95% CI	0.74, 1.10	0.52, 0.81	1.11, 1.73
	p-value (non-inferiority using 1.46)	< 0.0001	< 0.0001	
Superiority Analysis	p-value (superiority)	0.2943	0.0001	

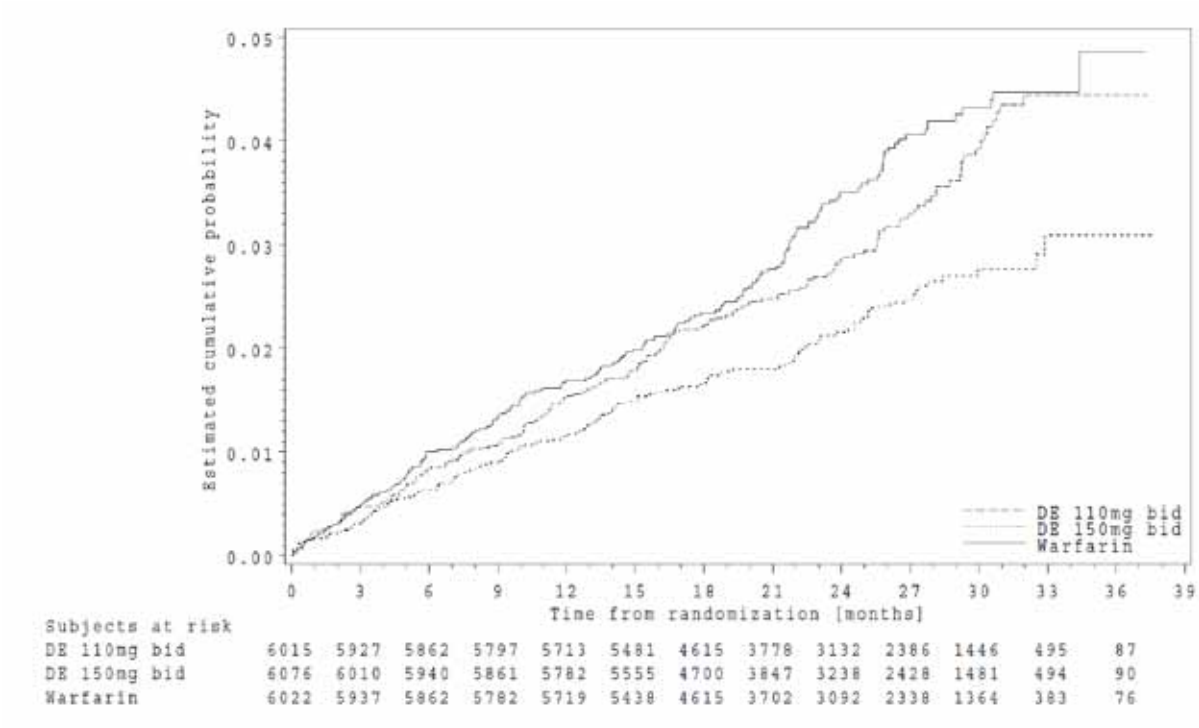
The frequency and yearly event rates for the primary endpoint of stroke/SEE in the randomized population are summarised in Table 9. The yearly event rate for stroke/SEE was lowest with DE150 (1.11%), followed by DE110 (1.54%) and WF (1.71%). The Kaplan-Meier estimates are shown in Figure 1. The DE150 curve began to diverge from the DE110 and WF curves at about 2 months after initiation of treatment and continued to diverge throughout the remainder of the study.

Table 9: RE-LY [re-analysis] – Frequency (n) and yearly event rate (%) for stroke/SEE.

	DE 110 mg bd, n (%)	DE 150 mg bd, n (%)	Warfarin, n (%)
Patients randomized	6015	6076	6022
Patient-years	11899	12033	11794
Patients with stroke/SEE	183 (1.54%)	134 (1.11%)	202 (1.71%)
Stroke	171 (1.44%)	122 (1.01%)	186 (1.58%)
Ischaemic stroke	152 (1.28%)	103 (0.86%)	134 (1.14%)
Haemorrhagic stroke	14 (0.12%)	12 (0.10%)	45 (0.38%)
Stroke of uncertain classifications	7 (0.06%)	9 (0.07%)	10 (0.08%)
SEE	15 (0.13%)	13 (0.11%)	21 (0.18%)

Each patient with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, the first event was considered. Patient-years = sum (date of study termination – date of randomization +1) of all randomized patients / 365.25. Yearly event rate (%) = [patients with event / patient-years] x 100.

Figure 1: RE-LY [Re-analysis] - Kaplan-Meier estimate of time to first stroke/SEE; randomized set.



Ischaemic stroke was the most commonly occurring individual component of the composite stroke/SEE endpoint for the three treatment groups. The yearly event rate for ischaemic stroke was highest in the DE110 group (1.28%) followed by the WF (1.14%) and DE150 (0.86%) groups. The hazard ratios for the three pairwise comparisons are summarised in Table 10.

Table 10: RE-LY [re-analysis] – Hazard ratios and 95% CIs for ischaemic stroke; randomized set.

Parameter	DE 110 vs WF	DE 150 vs WF	DE 110 vs DE 150
Hazard ratio (SE)	1.13 (0.13)	0.75 (0.10)	1.50 (0.19)
95% CI	0.89, 1.42	0.58, 0.97	1.17, 1.92
p-value	0.3139	0.0296	0.0015

The majority of strokes/SEEs in the three treatment groups (randomized population) occurred while patients were on the study drug or within six days of discontinuing the study drug compared with more than six days after discontinuing the study drug. The frequency of strokes/SEES occurring in patients while on the study drug was greater in the WF group (2.6%) compared with the DE110 (2.0%) and DE150 (1.4%) groups. The frequency of strokes/SEEs occurring in patients who had been off the study drug for more than six days was lower in the WF group (0.7%) compared with the DE110 (1.0%) and DE 150 (0.8%) groups.

Stroke severity was assessed by investigators using the modified Rankin Scale (mRS) score at hospital discharge and then at 3 to 6 months after discharge. A non-disabling stroke scored 0 to 2 and a disabling stroke scored 3 to 6, with 6 representing a fatal outcome. There were no statistically significant differences for the comparisons between DE110 and WF, and between DE150 and WF for mRS scores at hospital discharge or at 3

to 6 months after discharge. The number of patients with recurrent stroke (ischaemic stroke component) was 11 (10) in the DE110 group, 7 (6) in the DE150 group, and 7 (5) in the WF groups. There was only one patient in the study with a recurrent SEE and this patient was in the DE150 group.

The study included a number of sensitivity analyses of the primary efficacy endpoint which supported the results of the primary efficacy analysis. These analyses included the use of different data sets (safety, treated and per-protocol), and different statistical approaches (stratified analyses by VKA use, ASA use, stroke history).

Comment

The results showed that both DE110 and DE150 were non-inferior to WF as regards the composite endpoint of stroke/SEE, and DE150 was superior to WF. The comparison between DE110 and DE150 showed that the higher dose was associated with a statistically significantly better outcome as regards the primary efficacy endpoint. Stroke was the major component of the composite stroke/SEE endpoint for each of the three treatments and occurred more frequently with WF than with both DE110 and DE150. SEE events were low in the three treatment groups and occurred more commonly with WF compared with both DE110 and DE150. The major component of the stroke endpoint was ischaemic stroke. Relative to WF, the risk of ischaemic stroke was non-statistically significantly higher with DE110 and statistically significantly lower with DE150. Relative to WF, the risk of haemorrhagic stroke was statistically significantly lower with both DE110 and DE150.

The majority of strokes at hospital discharge were approximately evenly divided between non-disabling (mRS 0-2) and disabling (mRS 3-5). However, at 3-6 months after hospital discharge the number of fatal strokes (mRS 6) had notably increased in all three treatment groups with a small increase in the number of non-disabling strokes (mRS 0-2). The severity of stroke profiles at discharge and at 3-6 months after discharge was similar for the three treatment groups as assessed by the mRS.

The results and conclusions for the re-analysis of the primary efficacy endpoint remained unchanged from the original analysis. The yearly stroke/SEE event rates increased slightly in the re-analysis for DE110 from 1.53% (182 patients with event) to 1.54% (183 patients with event), for DE150 from 1.10% (133 patients with event) to 1.11% (134 patients with event), and for WF from 1.68% (198 patients) to 1.71% (202 patients with the event). The risk reductions for the composite stroke/SEE endpoint for DE110 relative to WF increased from 9% to 10% and for DE150 relative to WF increased from 34% to 35%. The statistical analyses of the pairwise comparisons between treatments were similar for the re-analysis and the original analysis.

Secondary Efficacy Endpoint – Stroke/SEE/Death

The frequency and yearly event rate for the components of the composite secondary efficacy endpoint of stroke/SEE/death are summarised in Table 11. The hazard ratios for the stroke/SEE/death composite endpoint are summarised in Table 12.

Table 11: RE-LY (re-analysis) – Frequency and yearly event rate (%) for stroke/SEE/death.

	DE 110 mg bd	DE 150 mg bd	Warfarin
Patients randomized	6015	6076	6022
Patient-years	11899	12033	11794
Patients with stroke/SEE/death	577 (4.85%)	520 (4.32%)	613 (5.20%)
Stroke	171 (1.44%)	122 (1.01%)	186 (1.58%)
SEE	15 (0.13%)	13 (0.11%)	21 (0.18%)
Death	446 (3.75%)	438 (3.64%)	487 (4.13%)
Vascular	289 (2.43%)	274 (2.28%)	317 (2.69%)
Sudden Cardiac	109 (0.92%)	93 (0.77%)	103 (0.87%)
Non-Sudden Cardiac	68 (0.57%)	68 (0.57%)	71 (0.60%)
Haemorrhagic	9 (0.08%)	13 (0.11%)	17 (0.14%)
Other vascular	46 (0.39%)	45 (0.37%)	58 (0.49%)
Unknown	57 (0.48%)	55 (0.46%)	68 (0.58%)
Non-Vascular	157 (1.32%)	164 (1.36%)	170 (1.44%)

Each patient with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, the first event was considered. Patient-years = sum (date of study termination – date of randomization +1) of all randomized patients / 365.25. Yearly event rate (%) = patients [with event / patient-years] x 100.

Table 12: RE-LY [re-analysis] - Hazard ratio and 95% CI for stroke/SEE/death; randomized set.

Parameter	DE 110 vs WF	DE 150 vs WF	DE 110 vs DE 150
Hazard ratio (SE)	0.93 (0.05)	0.83 (0.05)	1.13 (0.07)
95% CI	0.83, 1.04	0.74, 0.93	1.00, 1.27
p-value	0.2206	0.0015	0.0503

Comment

The yearly event rates for all outcomes were higher in the WF group than in both DE groups, apart from sudden cardiac death which was higher in the DE110 group than in the two other treatment groups. The pairwise comparisons for stroke/SEE/death showed that DE110 reduced the risk by 7% relative to WF (p=0.2206) and DE150 reduced the risk by 17% relative to WF (p=0.0015). The risk of stroke/SEE/death was 13% higher with DE110 relative DE150 (p=0.0503). The major contributor to the composite event endpoint of stroke/SEE/death in the three treatment groups was death and the most common cause of death was vascular. The re-analysis did not change the conclusions from the original analysis for stroke/SEE/death. The hazard ratios for DE110 vs WF and DE150 vs WF were unchanged and there were minimal changes in the p values. In the re-analysis, there were 2, 2, and 4 patients on DE110, DE150 and WF, respectively, with events added.

Secondary Efficacy Endpoint – Stroke/SEE/PE/MI/Vascular Death

The frequency and yearly event rate for the components of the composite endpoint of stroke/SEE/PE/MI/vascular death (re-analysis) are summarised below in Table 13.

Table 13: RE-LY (re-analysis) – Frequency and yearly event rate (%) for stroke/SEE/PE/MI (including silent MI) /vascular death.

	DE 110 mg bd	DE 150 mg bd	Warfarin
Patients randomized	6015	6076	6022
Patient-years	11899	12033	11794
Patients with Composite Endpoint	507 (4.26%)	443 (3.68%)	513 (4.35%)
Stroke	171 (1.44%)	122 (1.01%)	186 (1.58%)
SEE	15 (0.13%)	13 (0.11%)	21 (0.18%)
PE	14 (0.12%)	18 (0.15%)	12 (0.10%)
MI	87 (0.73%)	89 (0.74%)	66 (0.56%)
Silent MI	11 (0.09%)	8 (0.07%)	8 (0.08%)
Vascular Death	289 (2.43%)	274 (2.28%)	317 (2.69%)

Each patient with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, the first event was considered. Patient-years = sum (date of study termination – date of randomization +1) of all randomized patients / 365.25. Yearly event rate (%) = patients [with event / patient-years] x 100.

The HRs for the stroke/SEE/PE/MI/vascular death composite endpoint are summarised in Table 14. The re-analysis included analyses of the composite endpoint including and excluding silent MIs and the results for both of these analyses are also provided in Table 14.

Table 14: RE-LY [Re-analysis] - Hazard ratio and 95% CI for stroke/SEE/PE/MI/vascular death; randomized set.

	DE110 vs WF *	DE110 vs WF **	DE150 vs WF mg *	DE150 vs WF **
Hazard ratio (SE)	0.98 (0.06)	0.98 (0.06)	0.84 (0.06)	0.84 (0.05)
95% CI	0.86, 1.10	0.87, 1.11	0.74, 0.96	0.74, 0.96
p-value	0.6972	0.7508	0.0096	0.0093

* Excluding silent MIs. ** Including silent MIs.

Comment

The frequency of the composite endpoint of stroke/SEE/PE/MI/vascular death was similar for DE110 and WF and hazard ratios for the pairwise comparisons between the two treatments were not statistically significant for the composite endpoint including and excluding silent MIs. However, DE150 significantly reduced the risk of stroke/SEE/PE/MI/vascular relative to WF for the endpoints including and excluding silent MI. Stroke, SEE, and vascular death components of the composite endpoint all occurred more frequently with WF than with both doses of DE. However, both PE and MI occurred more frequently with both doses of DE than with WF, and silent MIs occurred more frequently with DE110 than with WF and DE150.

The re-analysis resulted in similar increases in the overall absolute event rates for the composite endpoint of stroke/SEE/PE/MI/vascular death in the three treatment groups, resulting in no substantive changes to the hazard ratios. The absolute event rate increased from 4.14% (493 patients with the event) to 4.26% (507 patients with the event) for DE110, from 3.60% (433 patients with the event) to 3.68% (443 patients with the event) with DE150, and 4.20% (496 patients with the event) to 4.35% (513 patients with the event) with WF. There were 14, 10, and 17 'new events' identified in the re-analysis for DE110, DE 150 and WF, respectively. The 'new' events consisted primarily of silent MI; 11, 8, and 9 silent MIs were added for DE110, DE150 and WF, respectively.

Other Efficacy Analyses

Other analyses included in the study were a composite outcome including ischaemic stroke/SEE/PE/MI/TIA/all-cause death or hospitalization, a composite outcome including stroke/SEE/PE/MI/death/major bleed representing net clinical benefit (NCB), and a *post-hoc* analysis of MI (discussed under safety).

The yearly event rates for the composite of ischaemic stroke/SEE/PE/MI (including silent MI)/TIA/all cause death or hospitalization were 20.83% (2479 patients with the event), 21.63% (2603 patients with the event) and 22.32% (2632 patients with the event) for DE110, DE 150 and WF, respectively. The composite endpoint was driven primarily by hospitalizations which accounted for about 93% of the composite total in the three treatment groups. The HRs for the composite were: 0.92 [95%CI: 0.87, 0.97], p=0.0025, for DE110 vs WF; and 0.97 [95%CI: 0.92, 1.03], p=0.3214, for DE150 vs WF.

The yearly event rates for net clinical benefit (NCB) consisting of the composite of stroke/SEE/PE/MI (including silent MI)/death/major bleed were 7.25% (863 patients with the event), 7.05% (848 patients with the event), and 7.84% (925 patients with the event) for DE110, DE 150 and WF, respectively. The major contributors to the composite endpoint were all cause death and major bleeding. The HRs for the composite were: 0.92 [95%CI: 0.84, 1.01], p=0.0852, for DE110 vs WF; and 0.90 [95%CI: 0.82, 0.99], p=0.0254, for DE150 vs WF.

Subgroup Analyses

There were a large number of subgroup analyses performed on the primary efficacy endpoint. The statistical model for the subgroup analysis was the Cox regression model in the randomized data set with factors for treatment, subgroup, and treatment by subgroup interaction. Overall, the primary efficacy endpoint (stroke/SEE) results in the re-analysis for DE110 and WF were similar for baseline demographic subgroups, while the results for DE 150 mg were generally superior compared with WF.

The subgroup re-analyses of the primary efficacy endpoint (stroke/SEE) for previous VKA use showed that there were no statistically significant differences between DE110 and WF in VKA-experienced and VK-naive patients, while DE 150 mg was statistically significantly superior to WF in both VKA-experienced and VKA-naive patients.

Concomitant medications of special interest were anti-platelet agents and P-gp inhibitors. The stroke/SEE event rates were higher for each of the three treatments when used at least once in the study with ASA, clopidogrel, ASA+clopidogrel, PPIs, statins, or other NSAIDs compared with never used in the study. The stroke/SEE event rate was higher with WF used at least once in the study with amiodarone, verapamil or diltiazem compared with never used in the study, while the stroke/SEE event rates for these three drugs was lower when used at least once in the study with DE110 compared with never used in the study, and lower for amiodarone and verapamil when used at least once in the study with DE150 compared with never used in the study.

Evaluator's Overall Conclusions on Clinical Efficacy

The pre-specified primary efficacy endpoint was time to first occurrence of stroke or non-CNS systemic embolism (stroke/SEE). The yearly event rates for stroke/SEE were 1.54%, 1.11%, and 1.71%, for DE110, DE 150 and WF, respectively. The primary non-inferiority analysis showed that both DE110 and DE 150 were non-inferior to WF as regards stroke/SEE. The secondary superiority analysis showed that DE150, but not DE110, was superior to WF. DE110 reduced the risk of stroke/SEE by 10% relative to WF (p=0.2943), and DE150 reduced the risk of stroke/SEE by 35% relative to WF (p=0.0001). The HR

[DE110/DE150] showed that the lower dose increased the risk of stroke/SEE by 39% [95CI%: 11%, 73%] relative to the higher dose.

Stroke was the predominant component of the composite stroke/SEE endpoint and contributed more than 90% of patients to the composite endpoint for each of the three treatments. The yearly event rates for stroke were 1.44%, 1.01%, and 1.58%, for DE110, DE 150 and WF, respectively. DE110 non-statistically significantly reduced the risk of stroke by 8% ([95%CI: -25%, +13%]; p=0.4269) relative to WF. DE150 statistically significantly reduced the risk of stroke by 35% ([95%CI: -48%, -19%]; p=0.0002) relative to WF. DE110 statistically significantly increased the risk of stroke by 42% ([95%CI: 13%, 78%]; p=0.0030) relative to DE150. Statistical analyses for the treatment comparisons for stroke could not be located in the re-analysis and, consequently, were calculated independently.

Ischaemic strokes were the most commonly occurring of the three stroke categories contributing to the composite stroke outcome (that is, ischaemic stroke, haemorrhagic stroke, and stroke of uncertain classification). The yearly event rates for ischaemic stroke were 1.28%, 0.86%, and 1.14%, for DE110, DE150 and WF, respectively. The HR for DE110 vs WF for ischaemic stroke was 1.13 ([95%CI: 0.89, 1.42], p=0.3139), and for DE150 vs WF was 0.75 ([95%CI: 0.58, 0.97], p=0.0296). DE110 increased the risk of ischaemic stroke by 50% ([95%CI: 17%, 92%], p=0.0015) relative to DE150.

The other significant stroke event was haemorrhagic stroke and this event occurred statistically significantly less frequently with both doses of DE compared with WF. The yearly event rates for haemorrhagic stroke were 0.12%, 0.10 %, and 0.38%, for DE110, DE150 and WF, respectively. The hazard ratio for haemorrhagic stroke for DE110 vs WF was 0.31 ([95%CI: 0.17, 0.56], p=0.0001) and for DE150 vs WF was 0.26 ([95%CI: 0.14, 0.49], p<0.0001).

The yearly event rates for SEE were 0.13%, 0.11%, and 0.18%, for DE110, DE 150 and WF, respectively. There were no statistically significant differences between DE110 vs WF (p=0.3206), DE150 vs WF (p=0.1657), and DE110 vs DE150 (p=0.6857).

There were two pre-specified secondary efficacy endpoints: (i) time to first occurrence of stroke, SEE and all cause death; and (ii) time to first occurrence of stroke, SEE, PE, MI (excluding silent MI) and vascular death. The yearly event rates for stroke/SEE/death were 4.85%, 4.32%, and 5.20%, for DE110, DE150 and WF, respectively. There were no statistically significant difference between DE110 and WF (p=0.2206) and DE110 and DE150 (p=0.0503), for stroke/SEE/death. However, the comparison between DE150 and WF for this event was statistically significant (p=0.0015). The yearly event rates for stroke/SEE/PE/MI (including silent MI)/vascular death were 4.26%, 3.68%, and 4.35%, for DE110, DE150 and WF, respectively. There were no statistically significant differences between DE110 and WF for the composite endpoint excluding silent MIs (p=0.06972) or including silent MIs (p=0.7508), while the comparison between DE150 and WF was statistically significant for analyses excluding and including silent MIs (p=0.0096 and p=0.0093, respectively).

Safety

Introduction

The evaluation of the safety of DE 110 mg and 150 mg bd compared with WF in this AusPAR focuses primarily on the RE-LY data. The safety data from the three, Phase II, exploratory, dose-ranging studies in patients with AF have been considered earlier in the AusPAR. The safety data in the Phase I studies were reviewed and give rise to no particular safety signals.

In RE-LY, stroke, MI, SEE, TIA, major and minor bleeds, PE and death were specified as outcome events. Outcome events were not reported as AEs or SAEs unless they were considered by the investigator to be drug-related. The safety data were summarised in the safety and randomized sets. Since the trial was not blinded to WF or DE, the assessment of an AE relationship to study drug may have been biased.

The evaluation of safety also includes a separate section on the RE-COVER study. This study included 6 month, double-blind, safety data in patients treated with DE 150 mg bd (n=1273) or WF (n=1266) to prevent recurrent VTE events and/or death due to VTE following acute VTE initially treated for 5-10 days with standard parenteral anti-coagulation therapy. The safety data from this study in patients with VTE has been evaluated separately from the safety data in patients with AF, in view of the difference in patient population and indication from those being proposed.

Exposure

In the four combined AF Phase II/III studies, a total of 18,710 patients received the study medication, with 12,579 receiving DE (50 mg qd to 300 mg bd) and 6,131 receiving WF. Exposure was highest in the DE110 (n=6030), DE150 (n=6473) and WF (n=6131) patient groups, which is the result of the majority of patients coming from RE-LY. Exposure occurred most frequently from 1 to < 2 years (42.0%) and from 2 to < 3 years (38.6%), again primarily due to exposure in RE-LY. The median total exposure to study medication was 1.8 years (range 0.0 to 5.1 years) with a total of 32,445 subject-years.

The RE-LY safety set included all patients treated with at least one dose of the study medication. The safety set included a total of 18,040 patients, with 5,983 patients in the DE110 group, 6,059 in the DE150 group and 5,998 in the WF group. The mean (SD) duration of exposure in the total patient population was 20.7 (9.4) months [range: 0.0, 37.0], and the total patient-years of exposure was 31,162.2 subject-years. The mean (SD) duration of exposure and the patient-years exposure for DE110, DE150 and WF were, respectively: 20.54 (9.62) months, and 10,229.2 subject-years; 20.32 (9.76) months, and 10,261.2 subject-years; and 21.33 (8.80) months, and 10,659.3 subject-years. The mean (SD) duration of exposure for the total number of patients in the safety set (re-analysis) was 19.4 (8.93) months in VKA-naive patients and 22.05 (9.70) months in VKA-experienced patients.

Of the total number of patients in the RE-LY safety set (n=18040), 51.9% (n=9371) had at least one interruption of study medication: 51.4% (n=3073), 52.5% (n=3178); and 52.0% (n=3120), for DE110, DE150 and WF, respectively. Temporary interruptions of ≤ 1 day and < 8 days occurred in 18.5% (n=3346) of the total population and the percentages were similar for the three treatment groups. Temporary interruptions of 8 ≤ and < 30 days occurred in 11.8% (n=2136) of the total population, and were higher in the WF group (14.6%, n=877) than in the DE110 (9.9%, n=590) and DE150 (11.0%, n=669) groups. Permanent interruptions occurred in 20.9% (n=3773) of the total population, with 22.0% (n=1318), 22.8% (n=1382), and 17.9% (n=1073), in the DE110, DE150 and WF populations, respectively. The most common identifiable reason for temporary interruption of the study drug in the total population in the safety set was procedure/surgery (36.6%), followed by adverse event (22.8%) and hospitalization (15.6%). The reasons for temporary interruption in the safety set were similar for the three treatment groups. The most common identifiable reason for permanent interruption of the study drug in the total population in the safety set was "patient did not want to take the study drug" (7.5%).

Permanent discontinuations by visit interval were higher with both doses of DE compared with WF for the first 9 months of treatment. After the first 9 months of treatment

permanent discontinuation rates by visit interval were generally similar for the three treatments. The Kaplan-Meier estimates showed that permanent discontinuation for both doses of DE were higher than for WF from almost immediately after the first drug intake and remained higher throughout the duration of the study. The reasons for permanent interruption in the safety set were similar for the three treatments.

Adverse Events

Overview

The reported incidence of adverse events (AEs) in patients in the safety set was higher in the DE110 (78.6%) and DE150 (78.3%) groups than in the WF group (75.9%) (Table 15). Treatment-emergent adverse effects (TEAEs) were defined as AEs that occurred between the first dose and within six days of the last dose of the study drug. Patients were counted once for each particular AE, regardless of the number of times an AE was reported. Patients in both DE groups had a higher incidence of AEs considered by the investigators to be related to treatment than patients in the WF group. Similarly, reported AEs leading to discontinuation were reported more commonly with DE than with WF. The overall incidence of serious adverse events (SAEs) was similar in the three treatment groups.

Table 15: RE-LY (re-analysis) - Adverse event summary; safety set

	DE 110 mg bd N (%)	DE 150 mg bd N (%)	Warfarin N (%)
Number of patients	5983 (100.0)	6059 (100.0)	5998 (100.0)
Patients with any AE	4703 (78.6)	4746 (78.3)	4551 (75.9)
Patients with severe AEs	1724 (28.8)	1749 (28.9)	1707 (28.5)
Patients with investigator defined drug-related AEs	1244 (20.8)	1335 (22.0)	950 (15.8)
Patients with other significant AEs (ICH E3)	775 (13.0)	875 (14.4)	586 (9.8)
Patients with AEs leading to discontinuation of trial drug	1138 (19.0)	1243 (20.5)	939 (15.7)
Patients with SAEs	1263 (21.1)	1290 (21.3)	1357 (22.6)
Fatal	107 (1.8)	100 (1.7)	122 (2.0)
Immediately life-threatening	50 (0.8)	46 (0.8)	64 (1.1)
Disability/incapacitating	575 (9.6)	5323 (8.8)	592 (9.9)
Required hospitalization	1073 (17.9)	1090 (18.0)	1178 (19.6)
Prolonged hospitalization	95 (1.6)	71 (1.2)	89 (1.5)
Other	215 (3.6)	252 (4.2)	230 (3.8)

A patient may be counted in more than one AE category.

There were numerous AEs in RE-LY. However, this was not unexpected as the population was elderly (mean age 71.5 years) and being treated with an anticoagulant for AF with at least one additional risk factor for stroke, and often having other medical conditions and taking concomitant medications. In addition, the mean exposure time to study medication in the total population in the safety set was 20.7 months which increases the likelihood of AEs being experienced and reported. Apart from gastrointestinal (GI) related AEs and anaemia, there did not appear to be any AEs reported with a greater frequency in the DE groups compared with the WF group. The incidence of AEs was generally similar for DE110 and DE150, with no obvious dose-response relationship being observed.

The System Organ Class (SOC) *Gastrointestinal Disorders* accounted for the highest incidence of AEs seen with both DE110 (34.6%) and DE150 (34.5%) and was higher in both DE groups compared with the WF group (24.1%). *Post-hoc* analysis of dyspepsia/gastritis related AEs showed that both dyspepsia and gastritis occurred about

twice as commonly with both doses of DE compared with WF, and that the there was no dose response between the two DE doses. The incidence of gastritis/dyspepsia was 16.4% (983/5893), 15.5% (940/6059) and 7.8% (470/4998) for DE110, DE150 and WF, respectively. *Post hoc* analysis of serious dyspepsia/gastritis related AEs showed that these events were reported uncommonly, and that there were no significant differences in frequency in the three treatment groups.

The incidence of drug-related adverse events was 20.8 % (1244/5983), 22.0% (1335/6059) and 15.8% (950/5998), for DE110, DE 150 and WF, respectively. As for AEs, drug-related AEs occurred more commonly with both doses of DE compared with WF. Drug-related AEs occurring with an incidence of ≥ 1% in one or more of the three treatment groups were, respectively, DE110, DE150 and WF: dyspepsia 3.1%, n=187; 2.9%, n=178; 0.1%, n=7; diarrhoea 1.2%, n=69; 1.1%, n=67; 0.2%, n=11; nausea 1.0%, n=58; 1.2%, n=73; 0.2%, n=12; abdominal pain upper 1.1%, n=65; 1.1%, n=69; 0.1%, n=8; epistaxis 1.1%, n=66; 1.1%, n=67; 1.8%, n=107; anaemia 0.8%, n=49; 1.1%, n=68; 0.8%, n=45; haematoma 0.4%, n=25; 0.5%, n=28; 1.0%, n=61; haematuria 0.8%, n=50; 1.0%, n=60; 1.1%, n=64; and contusion 0.7%, n=42; 0.7%, n=42; 1.1%, n=68.

Bleeding Events

All Bleeding Events

Major bleeding events were defined by one or more of the following criteria: bleeding associated with a reduction in haemoglobin levels of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells; or symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding). Major bleeds were further sub-classified as life-threatening if they met one or more of the following criteria: fatal; symptomatic intracranial bleed; reduction in haemoglobin levels of at least 50 g/L; transfusion of at least 4 units of blood or packed cells; hypotension requiring the use of intravenous inotropic agents; or necessitated surgical intervention.

The yearly event rates for bleeding events (re-analysis) and the hazard ratios in the randomized set are summarised below in Tables 16 and 17, respectively. The Kaplan-Meier estimates of time to first major bleed showed that the risk of experiencing a major bleed (WF > DE150 > DE110) began to diverge from about 3 months after initiation of treatment with differences remaining relatively constant from about 6 months to study end. The risk of experiencing a major bleed was consistently lower with DE110 than with DE150 and WF throughout the study.

Table 16: RE-LY (re-analysis) – Frequency and yearly rate (%) of major and other bleeding events; randomized set

	DE 110 mg bd N (%)	DE 150 mg bd N (%)	Warfarin N (%)
Number of patients	6015	6076	6022
Patient-years	11899	12033	11794
Major bleeds [a]	342 (2.87%)	399 (3.32%)	421 (3.57%)
Life threatening MBEs	147 (1.24%)	179 (1.49%)	218 (1.85%)
Other MBEs	218 (1.83%)	248 (2.06%)	226 (1.92%)
Intracranial Haemorrhage (ICH) [a, b]	27 (0.23%)	38 (0.32%)	90 (0.76%)
Minor bleeds [c]	*1566 (13.16%)*	*1787 (14.85%)*	*1931 (16.37%)*
Any bleeds [c]	*1754 (14.74%)*	*1993 (16.56%)*	*2166 (18.37%)*

In case of recurrent event of the same category, the first event was considered. Patient-years = sum (date of study termination - date of randomization +1) of all randomized patients / 365.25. Yearly event rate (%) = number of patients with event / patient-years x 100

[a] Adjudicated major bleeds and ICH.

[b] ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.

[c] Investigator-reported bleeding events (all other bleeding events were adjudicated).

Table 17: RE-LY (re-analysis) - Bleeding events, hazard ratios (HR) and 95% confidence intervals; randomized set

Event	DE 110 mg bd vs WF	DE 150 mg bd vs WF	DE 110 mg bd vs DE 150 mg bd
Major bleeds *	0.80 [95%CI: 0.70, 93] p=0.0026	0.93 [95%CI: 0.81, 1.07] p=0.3146	0.86 [95%CI: 0.75, 1.00] p=0.0429
Life-threatening bleeds *	0.67 [95%CI: 0.54, 0.82] p=0.0001	0.80 [95%CI: 0.66, 0.98] p=0.0305	0.83 [95%CI: 0.67, 1.03] p=0.0915
Intracranial haemorrhage *	0.30 [95%CI: 0.19, 0.45] p<0.0001	0.41 [95%CI: 0.28, 0.60] p<0.0001	0.72 [95%CI: 0.44, 1.18] p=0.1875
Haemorrhagic strokes *	0.31 [95%CI: 0.17, 0.56] p=0.0001	0.26 [95%CI: 0.14, 0.49] p<0.0001	1.18 [95%CI: 0.55, 2.55] p=0.6750
Reported major bleeds **	0.78 [95%CI: 0.68, 0.90] p=0.0006	0.94 [95%CI:, 0.82, 1.07] p=0.3234	0.84 [95%CI: 0.73, 0.96] p=0.0134
Reported symptomatic ** intracranial bleeds	0.29 [95%CI: 0.19, 0.44] p<0.0001	0.47 [95%CI: 0.33, 0.67] p<0.0001	0.62 [95%CI: 0.38, 1.00] p=0.0502
Reported any bleeds **	0.78 [95%CI: 0.73, 0.83] p<0.0001	0.91 [95%CI: 0.85, 0.96] p=0.0016	0.86 [95%CI: 0.81, 0.92] p<0.0001

* Adjudicated events (major bleed, life-threatening major bleeds, haemorrhagic strokes, intracranial haemorrhage)

** Investigator reported (reported major bleeds, reported symptomatic intracranial bleeds, and reported any bleeds).

The total number of randomized patients with one or major bleed during the study was 1162 (1378 major bleeds), with the respective numbers for DE110, DE150 and WF being 342 patients (406 major bleeds), 399 patients (489 major bleeds), and 421 patients (483 major bleeds). The total number of patients with 1, 2, and ≥ 3 major bleeds were 993, 131, and 38, respectively. The corresponding number of patients with respective number of occurrences were 291, 38, and 13 with DE110; 355, 44, and 20 with DE150; and 367, 49,

and 5 with WF. The majority of patients in the three treatment groups had only one major bleed.

The total number of adjudicated major bleeds in the randomized patients was 397, 487 and 477, for DE110, DE 150 and WF, respectively. The most common reason for a bleed being categorised as major was "hospitalization for the event" (72.0% [286 bleeds], 75.7% [368 bleeds] and 76.3% [364 bleeds], for DE110, DE 150 and WF, respectively). The next two most common reasons were "drop in haemoglobin of ≥ 20 g/L" (67.0% [266 bleeds], 67.9% [330 bleeds] and 59.1% [282 bleeds], for DE110, DE 150 and WF, respectively), and "required transfusion ≥ 2 units" (58.9% [234 bleeds], 64.8% [315 bleeds] and 51.6% [246 bleeds] for DE110, DE 150 and WF, respectively). The most common site of a major bleed was GI (38.8% [154 bleeds], 44.9%, [218 bleeds] and 29.1% [139 bleeds], for DE110, DE 150 and WF, respectively). This was followed by "symptomatic intracranial" major bleeds (7.8% [31 bleeds], 7.8% [38 bleeds] and 18.4% [88 bleeds], for DE110, DE 150 and WF, respectively). Fatal bleeding events represented 6.3% (25 deaths), 5.8% (28 deaths) and 8.4% (40 deaths) of all major bleeds for DE110, DE 150 and WF, respectively.

The only baseline demographic factor significantly influencing the relative risk of major bleeding was age ($p<0.0001$). With increasing baseline age, the higher was the yearly event rate for a major bleed. This was consistent for the three treatment groups. For patients aged < 75 years, both DE110 and DE150 reduced the risk of a major bleed relative to WF, while for patients aged ≥ 75 years DE150 increased the risk of a major bleed by 18% (non-statistically significant) relative to WF.

The risk of major bleeding was statistically significantly lower (31%) with DE 110 relative to WF in patients with the baseline risk factor of stroke/SEE/TIA; HR = 0.69 [95%CI: 0.51, 0.93]. The risk of major bleeding with DE110 relative to WF was not statistically significant for all other additional stroke risk factors. The risk of major bleeding with DE150 relative to WF was not statistically significant for all additional stroke risk factors. The risk of major bleeding in the DE110 group was statistically significantly lower relative to DE150 mg in patients with the baseline risk factor of stroke/SEE/TIA (HR=0.65 [95%CI: 0.48, 0.87]) and in patients with the baseline risk factor of age ≥ 65 years with hypertension (HR=0.80 [95%CI: 0.68, 0.94]).

The yearly event rate for major bleeds increased with increasing $CHADS_2$ score in each of the three treatment groups. Relative to WF, the risk of major bleeding in patients with $CHADS_2$ scores of 1 was significantly lower with DE110 compared with WF: HR=0.65 [95%CI: 0.48, 0.88]. The risk of major bleeding in patients with $CHADS_2$ scores of +3 was significantly lower with DE110 compared with DE150: HR=0.77 [95%CI: 0.62, 0.96]. For AF type, the respective yearly event rates for major bleeding for DE110, DE 150 and WF, were: persistent AF, 2.9%, 3.1%% and 3.9%; paroxysmal AF, 3.1%, 3.7%, 3.9%; and permanent AF, 2.7%, 3.1% and 3.0%.

Minor bleeding events were defined by exclusion as all bleeding events not defined as major bleeding events. Minor bleeding events were not centrally adjudicated but were investigator reported. The yearly rates for minor and any bleeding events in randomized patients were both higher with WF than with both DE doses.

Comment

Relative to WF, the risk of major bleed was reduced by 20% with DE110 (p=0.0026) and 7% (p=0.3146) with DE150. The major bleed rate for DE110 was statistically significantly 15% lower relative to DE150 (p=0.0429). Relative to WF, the risk of life threatening major bleed was statistically significantly lower with both DE110 (33%, p=0.0001) and DE150 (20%, p=0.0305). Intracranial haemorrhage yearly rates were 0.27% (27 patients), 0.32% (38 patients) and 0.76% (90 patients), for DE110, DE 150 and WF, respectively. Relative to

WF, the risk of intracranial haemorrhage was statistically significantly lower with both DE110 (70%, p<0.0001) and DE150 (59%, p<0.0001).

Gastrointestinal Bleeding Events

RE-LY included a *post hoc* analysis in randomized patients of major GI bleeds (adjudicated), life-threatening GI bleeds (adjudicated) and any GI bleeds (adjudicated plus investigator reported). Of the total number of major bleeds in each treatment group, GI major bleeds contributed 38.8% (154/397), 44.9% (218/486) and 29.1% (139/477) in the DE110, DE 150 and WF groups, respectively. The yearly event rates for major GI bleeds, life-threatening GI major bleeds and any GI bleeds were higher in both DE groups compared with WF (Table 18), and the hazard ratios are provided in Table 19.

Table 18: RE-LY (re-analysis) - Frequency and yearly event rate of GI bleeding events; randomized set

	DE 110 mg bd N (%)	DE 150 mg bd N (%)	Warfarin N (%)
Number of patients	6015	6076	6022
GI Major Bleeds	134 (1.14%)	186 (1.57%)	125 (1.07%)
GI life-threatening major bleeds	67 (0.57%)	94 (0.79%)	55 (0.49%)
Any GI Bleed [a]	600 (5.41%)	681 (6.13%)	452 (4.02%)

In case of recurrent event of the same category, the first event was considered. Minor bleeds were not adjudicated.
For patients with event, patient-years= (first onset date - date of randomization + 1) / 365.25. For patients without event, patient-years= (study termination date - date of randomization + 1)/365.25. Yearly event rate (%) = # of patients with event / patient-years * 100.
[a] Any GI bleeds included adjudicated major GI bleeds and non-adjudicated minor GI bleeds.

Table 19: RE-LY (re-analysis) - Hazard ratio (HR) and 95% CI for gastrointestinal (GI) bleeds; randomized set

Event	DE 110 mg bd vs WF	DE 150 mg bd vs WF	DE 110 mg bd vs DE 150 mg bd
GI Major bleeds *	1.07 [95%CI: 0.84, 1.36] p= 0.6002	1.47 [95%CI: 1.17, 1.85] p=0.0008	0.73 [95%CI: 0.58, 0.91 p=0.0046
GI life-threatening bleeds *	1.17 [95%CI: 0.82, 1.67] p=0.3839	1.62 [95%CI: 1.17, 2.26] p=0.0038	0.72 [95%CI: 0.53, 0.99] p=0.0400
Any GI bleeds **	1.35 [95%CI: 1.19, 1.53] p<0.0001	1.52 [95%CI: 1.35, 1.72] p<0.0001	0.89 [95%CI: 0.79, 0.99] p=0.0298

* Adjudicated events (GI major bleed, GI life-threatening major bleed)
** Adjudicated reported plus investigator reported (any GI bleed).

Comment

GI major bleeds were the most commonly occurring symptomatic major bleeds in critical areas/organs. There were only minor differences in the GI major bleeding data between the original analysis and the re-analysis. In the re-analysis, there were 2/0/0, 5/3/1 and 7/1/3 additional patients identified with GI major bleeds / GI life-threatening major bleeds/ any GI bleeds in the DE110, DE 150 and WF groups, respectively.

Serious Adverse Events and Deaths

Deaths

The yearly event rate of death in randomized patients was 3.75% (446 patients), 3.64% (438 patients) and 4.13% (487 patients) with DE110, DE 150 and WF, respectively. The majority of deaths were adjudicated as vascular (including deaths from bleeding). The

yearly event rates for vascular death were 2.43% (289 patients), 2.28% (274 patients), and 2.69% (317 patients) with DE110, DE 150 and WF. The most common causes of vascular death were considered to be sudden cardiac death and non-sudden cardiac death. The respective yearly event rates for sudden cardiac and non-sudden cardiac death were 0.92% (109 patients) and 0.57% (68 patients) for DE110, 0.77% (93 patients) and 0.57% (68 patients) for DE150 and 0.87% (103 patients) for 0.60% (71 patients) for WF. The majority of deaths in the three treatment groups occurred while patients were receiving the study drug or within 6 days. The HRs of all-cause and vascular deaths are summarised in Table 20. The Kaplan-Meier curves for all cause death showed that the DE curves began to diverge from WF curve at approximately 16 months after randomization.

Table 20: RE-LY (re-analysis) – Hazard Ratios for all-cause and vascular deaths; randomized set

	All Cause Death – Hazard Ratios			Vascular Death – Hazard Ratios		
Event	DE110 vs WF	DE150 vs WF	DE110 vs DE150	DE110 vs WF	DE150 vs WF	DE110 vs DE150
Hazard ratio (SE)	0.91 (0.06)	0.88 (0.06)	1.03 (0.07)	0.90 (0.07)	0.85 (0.07)	1.07 (0.09)
95% CI	0.80, 1.03	0.77, 1.00	0.90, 1.17	0.77, 1.06	0.72, 0.99	0.90, 1.26
p-value	p=0.1308	p=0.0517	p=0.6655	0.2081	0.0430	0.4441

Other SAEs

The incidence of SAEs in the safety set was similar in the three treatment groups: 21.1% (1263 patients), 21.3% (1290 patients), 22.6% (1357 patients), for DE110, DE 150, and WF, respectively. The SAEs in the three treatment groups are summarised in Table 21. The SAEs patterns were generally similar in the three treatment groups.

Table 21: RE-LY (re-analysis) – Serious adverse events; safety set

Event	DE 110 mg bd N (%)	DE 150 mg bd N (%)	Warfarin N (%)
Number of patients exposed	5983 (100%)	6059 (100%)	5988 (100%)
Total Serious Adverse Events	1263 (21.1%)	1290 (21.3%)	1357 (22.6%)
Fatal	107 (1.8%)	100 (1.7%)	122 (2.0%)
Immediately life-threatening	50 (0.8%)	46 (0.8%)	64 (1.1%)
Disabling/incapacitating	575 (9.6%)	532 (8.8%)	592 (9.9%)
Required hospitalization	1073 (17.9%)	1090 (18.0%)	1178 (19.6%)
Prolonged hospitalization	95 (1.6%)	71 (1.2%)	89 (1.5%)
Congenital anomaly	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	215 (3.6%)	252 (4.2%)	230 (3.8%)

Cardiac Disorders were the source of the most commonly reported SAEs in the three treatment groups: 5.2% (310 patients), 4.8% (291 patients) and 5.4% (321 patients), for DE110, DE 150 and WF, respectively. The three most commonly occurring SAE *Cardiac Disorders* were cardiac failure congestive, atrial fibrillation and cardiac failure. The second and third most commonly sources of SAE were, respectively, *Infections and Infestations* and *Gastrointestinal Disorders*. The SAE patterns were similar for the three treatment groups, and nearly all SAEs occurred with an incidence of < 1.0%.

Myocardial Infarction

RE-LY included a *post hoc* analysis of the incidence of MI in the three treatment groups. The yearly event rates for MI (clinical + silent) in the randomized set are summarised in Table 22. The total number of MIs for each treatment group, clinical + silent, were 87+11 (n=98), 89+8 (n=97) and 66+9 (n=75), for DE110, DE 150 and WF, respectively. The Kaplan-Meier estimates of time to first MI (including silent MI) showed that the curves began to separate within the first 1-2 months after randomization and remained separated for the duration of the study.

Table 22: MI (clinical + silent) – Frequency and yearly event rate (%); randomized set

	DE 110 mg bd N (%)	DE 150 mg bd N (%)	Warfarin N (%)
Number of patients	6015	6076	6022
Patient-years	11899	6076	11794
MI + Silent MI	98 (0.82%)	97 (0.81%)	75 (0.64%)

The HRs for the re-analyses for MIs are summarised below in Table 23. The HRs showed that the risk of MI was greater with both doses of DE relative to WF but the increased risks were not statistically significant.

Table 23: RE-LY (re-analysis) – Hazard ratio for MI; randomized set

	DE110 vs WF		DE150 vs WF		DE110 vs DE150	
	Clinical only	Clinical + Silent	Clinical only	Clinical + Silent	Clinical only	Clinical + Silent
Hazard Ratio	1.30 (0.21)	1.29 (0.20)	1.32 (0.21)	1.27 (0.19)	0.99 (0.15)	1.02 (0.15)
95% CI	0.95, 1.80	0.96, 1.75	0.96, 1.81	0.94, 1.71	0.74, 1.33	0.77, 1.35
p-value	0.1037	0.0929	0.0877	0.1240	0.9376	0.8816

There was no interaction between treatment and baseline demographic factors (age, gender, ethnicity, region, BMI or CrCl) on MI (including silent MI). There were no statistically significant interactions between treatment and any of the protocol specified additional baseline risk factors for stroke on MI (including silent MI). There was no statistically significant interaction between treatment and $CHADS_2$ score at study entry on MI. The yearly event rates for MI were higher in patients in the DE groups who had taken ASA, clopidogrel or ASA+clopidogrel at least once during the study. There were no other significant associations between concomitant medications and treatment on the frequency of MI during the study. Overall, the results for the various analyses were similar for MI (including silent MI) and MI (excluding silent MI).

Comment

The *post hoc* re-analysis showed that the relative risk of MI (including and excluding silent MIs) was increased with both doses of DE compared with WF, with the increased risks being not statistically significant. The potential risk factors for MI appeared to be well balanced between the three treatment groups. While the imbalance in MI outcomes between WF and DE might be due to chance, it was concerning that the increased risk was similar for both doses of DE relative to WF, despite there being no dose response.

Clinical Laboratory Values, Vital Signs and ECG Changes

Liver Function

Liver function tests (LFTs) were a pre-specified secondary safety endpoint, and were measured monthly during the first year of treatment and then every 4 months. Overall, there were no marked differences between treatments in LFT elevations no matter how

the elevation was defined. The incidence of alanine transaminase (ALT)/aspartate transaminase (AST) > 3x ULN and total bilirubin > 2x ULN (that is, potential Hy's law cases) was 0.2% (11 patients), 0.3% (16 patients) and 0.4% (21 patients), for DE110, DE 150 and WF, respectively. The HRs for potential Hy's law cases were statistically non-significantly < 1 for the DE110 vs WF (HR=0.55 [95%CI: 0.26, 1.13], p=0.1032), and DE150 vs WF comparisons (HR=0.69 [95%CI: 0.35, 1.36], p=0.2846). Potential Hy's law cases were discontinued from treatment immediately and evaluated for a clinical cause. There were 4 cases for which no identifiable cause could be identified (2 with DE, 2 with WF).

Haematology

The percentages of patients with possible clinically significant changes in haematology parameters were similar for the three treatment groups. Similarly, changes in other blood cell parameters were unremarkable for all three treatments.

Other Biochemical Parameters

Overall, there were no marked differences among the three treatments in possible clinically significant changes in laboratory chemistry parameters.

Vital Signs and ECG Changes

Mean reductions in systolic and diastolic blood pressure of 1-2 mmHg from baseline occurred in the three treatments over 36 months and there were no notable differences among the treatments. The majority of patients had AF at baseline on 12-lead ECG: 73.9% (4421 patients), 73.0% (4423 patients) and 72.1% (4326 patients), with DE110, DE 150 and WF, respectively. At study end, or final follow-up, AF was present in 67.5% (4040 patients), 66.9% (4035 patients) and 66.0% (3949 patients), with DE110, DE 150 and WF, respectively.

Safety in Special Groups

Re-LY included an analysis of the interaction between treatment and baseline demographic subgroup on the incidence of major bleeding events. The HR and interaction p-values were calculated from a Cox regression model with all three treatment groups and each specified demographic subgroup variable in the model. There was a significant interaction between treatment and age on major bleeding ($p<0.0001$). In patients aged ≥ 75 years, there was a 1% increased risk [95%CI: -17%, +23%] of major bleeding with DE110 mg relative to WF and an 18% increased risk [95%CI: -2%, +43%] with DE150 relative to WF. The risk of major bleeding was 14% lower [95%CI: -29%, +3%] in patients aged < 75 years treated with DE110 relative to DE150. Apart from age the only other demographically statistically significant interaction was between treatment and ethnicity. There were no statistically significant interactions between treatment and baseline demographic factors of gender, weight, BMI, CrCl or region.

Safety Related to Drug-Drug Interactions and Other Interactions

In RE-LY, the yearly event rates for major bleeding were analysed in patients taking various medications in combination with DE during the study. The use of ASA during the study nearly doubled the rate of major bleeds in each of the three treatment groups. The yearly event rates for major bleeds with ASA (used at least once) versus without ASA (never used) during the study were, respectively, 4.0% vs 2.1% for DE110, 4.7% vs 2.4% for DE150 and 5.1% vs 2.6% for WF. Similarly, the yearly event rates for major bleeds for each of the three treatments were about two-fold high with clopidogrel used at least once versus clopidogrel never used, and for ASA+clopidogrel used at least once versus never used.

The yearly event rates for major bleeding with COX2-inhibitors and with other NSAIDs were higher for patients who had taken the drugs at least once compared with patients who had not taken the drugs during the study. The yearly event rates for major bleeds in patients taking concomitant COX2-inhibitors were 4.6%, 5.2% and 6.3% for DE110, DE 150 and WF, respectively. These major bleeding event rates were 1.7, 1.6 and 1.8 fold higher than the respective rates for patients who had not taken concomitant COX2-inhibitors. The yearly event rates for major bleeds in patients taking concomitant other NSAIDs were 4.1%, 4.3% and 5.0%, for DE110, DE 150 and WF, respectively. These major bleeding event rates were 1.5, 1.4 and 1.5 fold higher than the respective rates for patients who had not taken concomitant other NSAIDs.

The yearly event rates for major bleeding with proton pump inhibitors (PPIs) and H_2-blockers were higher in patients who used the drugs at least once compared with patients who had never used the drugs during the study. The major bleeding event rates for concomitant PPI use were 5.3%, 7.2% and 7.1%, for DE110, DE 150 and WF, respectively. These major bleeding event rates were 2.6, 3.4 and 2.7 fold high than the respective rates for patients who had not taken concomitant PPIs. The major bleeding event rates for concomitant H_2 blocker use were 6.6%, 6.9% and 7.6% for DE110, DE 150 and WF, respectively. These major bleeding event rates were 2.6, 2.3 and 1.4 fold higher than the respective rates for patients who had not taken concomitant H_2 blockers.

The yearly event rates for major bleeding with the P-gp inhibitor verapamil were higher in patients who had used the drug at least in once compared with patients who had not taken the drug during the study. The respective with verapamil and without verapamil yearly event rates for major bleeds were 1.3% vs 1.2% for DE110, 1.6% vs 1.5% for DE150 and 2.4% vs 1.8% for WF. The respective increases for the three treatments were 1.04, 1.1 and 1.3 fold. Similar patterns were seen with the P-gp inhibitors diltiazem and amiodarone. The rates for quinidine could not be meaningfully interpreted as numbers were small for patients who had taken quinidine at least once.

Discontinuations Due to Adverse Events

Adverse events leading to permanent treatment discontinuation in the safety set occurred more frequently with DE110 (19.0%, 1138/5984) and DE150 (20.5%, 1243/6059) than with WF (15.7%, 935/5998). GI disorders were the most common cause of permanent treatment discontinuations in the three treatment groups: 6.5% (387 patients), 7.0% (422 patients) and 3.9% (232 patients), for DE110, DE 150 and WF, respectively. The most common GI disorder leading to discontinuation (DE110; DE150; WF) was dyspepsia (1.0%, n=57; 0.9%, n=57; < 0.05%, n=2), followed by GI haemorrhage (0.7%, n=29; 0.9%, n=55; 0.6%, n=37), nausea (0.7%, n=41; 0.7%, n=42; 0.3%, n=20), upper abdominal pain (0.5%, n=31; 0.6%, n=36; 0.1%, n=7), diarrhoea (0.6%, n=36; 0.6%; n=36; 0.3%, n=20) and rectal haemorrhage (0.3%, n=20; 0.5%, n=39; 0.3%, n=20). There were a large number of other GI AEs leading to treatment discontinuation and most occurred more commonly in DE treated patients than in WF treated patients. Other AEs of note leading to permanent treatment discontinuation (DE110; DE150; WF) were: anaemia (0.7%, n=43; 1.0%, n=61; 0.7%, n=39); pneumonia (0.6%, n=33; 0.4%, n=24; 0.4%; n=22); dyspnoea (0.6%, n=37; 0.7%, n=43; 0.6%, n=33); cardiac failure congestive (0.5%, n=29; 0.3%, n=20; 0.4%, n=25); and dizziness (0.5%, n=32; 0.4%; n=27; 0.2%, n=14).

RE-COVER [Study 1160.53/U09-1400-01] – VTE

Overview

RE-COVER was a recently completed, Phase III, multi-national, multi-centred, randomized, controlled study which compared dabigatran etexilate 150 mg bd (DE) with warfarin (WF) for 6 months for the prevention of recurrent venous thromboembolism (VTE) in

patients with an acute VTE initially treated (5-10 days) with standard parenteral anti-coagulant therapy. The patient population in this study is not directly relevant to the proposed target population and the indication differs from that being proposed. Nevertheless, the study included 6 month comparative safety on DE150 and WF and for this reason the safety data has been reviewed.

The study took place in 231 centres in 29 countries (Europe, North America, South America, South Africa, Australia, New Zealand, India, Israel, and Turkey). It ran from 7 April 2006 to 22 May 2009. The study was carried out in compliance with IEC/IRB approval of the protocol, the Declaration of Helsinki (1996), the ICH Guideline for Good Clinical Practice (GCP), and applicable national regulatory requirements relating to clinical trials.

Treatments

Patients were initially treated for 5 to 10 days with parenteral anticoagulant therapy (unblinded) approved for the treatment of acute VTE in combination with single-dummy blinded WF (those patients randomized to WF warfarin) or placebo (those patients randomized to DE). During this initial single-dummy period no patients received active DE. The double-dummy period (blinded oral therapy only) started as soon as a patient had received at least 5 days of parenteral therapy and had an INR value ≥ 2 for WF treated patients, or sham INR value ≥ 2 for placebo treated patients, on two separate occasions. The double-dummy period lasted for 6 months with patients being treated with either active DE or active WF. During the double-dummy period, WF treated patients had the dose adjusted by INR level (2.0-3.0) while DE treated patients underwent sham INR procedures. Patients who required anticoagulation beyond the planned treatment duration of 6 months could be switched to standard anticoagulation therapy after the last intake of trial drug.

Efficacy Endpoints, Statistical Methods, and Sample Size

The primary efficacy endpoint was the composite of recurrent symptomatic VTE and death related to VTE. VTE was defined as the composite of DVT and PE. All suspected recurrent symptomatic VTEs were objectively verified using standard diagnostic techniques. All events contributing to the primary endpoint were centrally adjudicated by an independent committee blinded to treatment allocation and adjudicated results were used in the analyses. In addition, all deaths were reviewed for evidence of fatal PE or bleeding. Statistical analysis of the primary endpoint aimed to demonstrate non-inferiority of dabigatran compared with warfarin. If non-inferiority was demonstrated, then statistical analysis was undertaken to demonstrate superiority of DE over WF. The analysis of the primary endpoint was based on the full analysis set (FAS), with allocation of patients to treatment groups as randomised. The secondary efficacy endpoints included composite of recurrent symptomatic VTE and all deaths, symptomatic DVT, symptomatic PE, deaths related to VTE, and all deaths.

HRs were calculated on the times to first occurrence of any of the components of the composite primary endpoint using a proportional hazards model (Cox regression). Risk differences were calculated using stratified Kaplan-Meier (KM) estimates of the cumulative risk at 6 months after randomization (Day 180). The non-inferiority margins were 2.75 for the HR, and 3.6% for the risk difference. The 95% CIs were calculated for both the HR and risk difference and non-inferiority was concluded if the upper bound of the 95% CI was less than the pre-specified non-inferiority margin. The study included a reasonable justification for the chosen non-inferiority margins based on the results of previous VTE clinical trials. The study (1275 patients in each treatment group) had a power of at least 90% to demonstrate non-inferiority of DE compared with WF, meeting

simultaneously the predefined non-inferiority margins for HR and risk difference, assuming a DE event rate for VTE over 6 months of at least 2% and an overall drop out rate of 20%.

Safety Endpoints

The safety endpoints included: bleeding events (major bleeding events [MBEs], MBEs and clinically relevant bleeding events [CRBEs], and any bleeding event including MBEs, CRBEs, and nuisance bleeding events); AEs; treatment discontinuation due to AEs; laboratory results; acute coronary syndrome (ACS); ECG and vital signs. All safety endpoints were assessed during treatment, including the 6 days following the last dose of study drug. In addition, safety data were collected for 30 days following the last study drug dose. Definitions of bleeding events were similar to those used in RE-LY.

Patient Demographics and Disposition

The inclusion criteria included male and female patients aged at least 18 years with acute symptomatic unilateral or bilateral DVT involving proximal leg veins, and/or PE confirmed by definitive objective clinical test for who at least 6 months of anticoagulant therapy was considered appropriate by the investigator. The inclusion and exclusion criteria have been examined and are considered to be satisfactory, as were the criteria for stopping treatment.

The study randomized 2564 patients to either DE (n=1280) or WF (n=1284). Randomisation of patients was stratified by active cancer at baseline and symptomatic PE at baseline (both cancer and initial PE were considered to be risk factors for the recurrence of VTE). Overall, 122 of the randomised patients had active cancer at baseline and 2442 patients had no active cancer, and 807 of the randomized patients had symptomatic PE at baseline and 1757 patients had no symptomatic PE at baseline. Of the 2564 randomized patients, 25 were not treated with study drug medication (DE=7; WF=18), including 3 patients who withdrew consent, 2 patients who refused to participate or to continue the intake of study medication and were lost to follow-up, 18 patients who were non-compliant with the study protocol and 2 patients with 'other' reasons.

The two treatment groups were well balanced with regard to baseline demographics. The study included more male than female patients (58.4% vs 41.6%, respectively), the mean (SD) age of the total population was 54.7 (16.0) years, and nearly all patients were white (94.8%). The baseline index VTE event was symptomatic DVT alone in 68.9% of patients (the majority), and symptomatic PE alone in 21.3% of patients. The baseline index VTE events were both symptomatic PE and DVT in 9.6% of patients. The baseline index VTE index events as identified by the investigators were well balanced between the two treatment groups in the treated set. The rate of central confirmation (the ratio of centrally confirmed index events to locally suspected index events) was in the range from 97% to 99%. The most frequent risk factors were VTE prior to the index event (25.6% overall), a history of venous insufficiency (19.4%), surgery / trauma (19.1%), prolonged immobilisation (15.6%) and recent systemic use of oestrogens (10.8%). Active cancer at any time was present in 6.9% of patients (active cancer at baseline was 4.8%, active cancer diagnosed during the study was 2.2%).

Of the 2539 treated patients, 387 patients (15.2%) prematurely discontinued study drug (16.0% in the DE group and 14.5% in the WF group). Discontinuations of the study drug were due to AEs in 9.9% of patients in the DE group and 8.1% of patients in the WF group. The difference in the discontinuation rate between the two groups (DE vs WF) was mostly due to increased rates in the DE group of other AEs (6.0% vs 5.1%) and worsening of the disease under study (2.7% vs 2.0%), although there were less discontinuations due to bleeding in the DE group than in the WF group (1.1% vs 1.7%). Worsening of the disease

referred to symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

The time from randomisation to the end of study participation was comparable for the DE and WF treatment groups (mean: 191 vs 189 days, and median: 193 vs 191 days). The median exposure to active study drug was 174 days for DE (double-dummy period) and 180 days for WF (single-dummy plus double-dummy period). Interruptions of any study drug were reported in 11.2% of DE treated patients and 13.7% of WF treated patients. Patients were exposed for a median of 9 days to initial parenteral therapy.

Primary Efficacy Endpoint Results

The HR [DE/WF] of the primary endpoint of composite recurrent symptomatic VTE and death related to VTE based on centrally adjudicated events in the full analysis set (FAS) was 1.05 [95%CI: 0.65, 1.70]: Cox-regression adjusted for the baseline factors of active cancer, symptomatic PE, and the interaction between active cancer and symptomatic PE at baseline. The upper limit of the 95% CI of the hazard ratio was below the pre-defined non-inferiority margin of 2.75, and the p-value for the test for non-inferiority was <0.0001. Consequently, it can be concluded that DE is non-inferior to WF based on the hazard ratio. The p-value for superiority of DE compared with WF was p=0.8508 (two-sided), indicating that DE was not superior to WF. There were 34 out of 1274 DE treated patients with an event and 32 out of 1265 WF treated patients with an event.

The cumulative risk for the primary endpoint at 6 months was 2.4% in the DE group and 2.2% in the WF group. The risk difference based on the estimated cumulative risk at 6 months using stratified KM estimates was 0.4% [95% CI: −0.8%, 1.5%]. The upper limit of the 95% CI of the risk difference was below the pre-defined non-inferiority margin of 3.6%, and the p-value for the test for non-inferiority was <0.0001. Consequently, it can be concluded that DE is non-inferior to WF based on the risk difference. The p-value for superiority of DE compared with WF was p=0.5026 (two-sided), indicating that DE was not superior to WF. In the DE group there were 30 out of 1274 patients with an event at 6 months (estimated cumulative risk 2.4% using KM estimate without stratification) compared with 27 out of 1265 patients in the WF group (estimated cumulative risk 2.2% using KM estimate without stratification).

Safety Results

Overall Adverse Events

This safety review of AEs and bleeding events focused on the period of any study drug intake (that is, DE/placebo, WF/placebo). In general, this was the time from the first intake of study drug to 6 days after the last intake of study drug. The median exposure to DE (double-dummy period only) was 174 days compared with a longer exposure of 180 days to WF (single-dummy plus double-dummy period). To avoid confounding of the safety analyses by bleeding events occurring due to open-label anticoagulants being administered during the 6 day washout period after the last intake of the study drug, a censoring rule was pre-specified for the 6 day washout period. This rule specified that the washout period would stop when a patient started an open-label anticoagulant. The results described in this review are based on application of the censoring rule for the 6 day washout period.

In total, 2539 patients received at least one dose of study medication (that is, DE/placebo or WF/placebo). These 2539 patients formed the treated set (1273 DE treated patients and 1266 WF treated patients). The overall AE incidence was similar in the DE (66.3%) and WF (65.2%) groups. However, AEs leading to discontinuation occurred more

commonly in the DE group than in the WF group (9.0% vs 6.8%, respectively), as did SAEs (13.0% vs 11.8%, respectively).

The most frequently reported AEs in the total safety population were *Gastrointestinal Disorders*, and these occurred more frequently in the DE group than in WF group (25.1% vs 19.2%, respectively). *Respiratory, Thoracic, and Mediastinal Disorders* were reported less frequently in the DE group than in the WF group (12.6% vs 16.5%, respectively). AEs following *Investigations* were reported less frequently in the DE group than in the WF group (4.2% vs 6.2%, respectively), mostly due to increased INR in the WF group compared with the DE group (0% vs 1.2%, respectively). Of the SOCs with an incidence below 5% per treatment group, *Cardiac Disorders* affected 3.5% of DE treated patients and 3.6% of WF treated patients. *Hepatobiliary Disorders* were reported in 2.5% of DE treated patients and 1.9% of WF treated patients, with cholelithiasis (0.6% DE vs 0.4% WF) and hepatic steatosis (0.5% DE vs 0.5% WF) being the most frequently reported preferred term AE hepatobiliary disorders.

There were three AEs with an incidence of at least 5% in either treatment group (DE vs WF): headache (6.2% vs 7.0%); pain in extremity (5.0% vs 5.6%), and epistaxis (2.8% vs 6.3%). Discontinuations due to AEs were reported more frequently in the DE group (9.0%) than in the WF group (6.8%) The AEs most frequently resulting in discontinuation (DE vs WF) were PE (1.2% vs 0.6%) and DVT (1.3% vs 1.1%). The AEs assessed by investigators as drug-related were reported more frequently in the WF group (18.1%) than in the DE group (15.3%).

Deaths and Serious Adverse Events (SAEs)

During the treatment period, SAEs (including fatal events) were reported in 13.0% (165/1273) of patients in the DE group and 11.8% (150/1266) in the WF group. The most frequently reported SAEs (DE vs WF) were PE (1.1% vs 0.6%), DVT (0.8% vs 0.7%), dyspnoea (0.4% vs 0.8%), pneumonia (0.4% vs 0.6%) and haematuria (0.3% vs 0.7%).

SAEs resulting in hospitalisation occurred in 11.2% (n=143) of patients in the DE group and 9.8% (n=124) of patients in the WF group. Of all patients in the treated set, 44 patients (3.5%) in the DE group and 32 patients (2.5%) in the warfarin group were hospitalised for MBEs and/or recurrent VTEs. Among these hospitalisations (DE vs WF), MBE was most frequently recorded as reason (1.4% [n=18] vs 1.3% [n=16]), followed by PE (1.2% [n=15] vs 0.7% [n=9]) and DVT (1.0% [n=13] vs 0.9% [n=12]. The mean [range] duration of hospitalisation in the 44 DE treated patients was 10.3 [range: 1-31] days and 13.5 [range: 2-60] days in the 32 WF treated patients.

Immediately life threatening SAEs were reported in 0.9% (n=11) of patients in the DE group and 0.5% (n=6) in the WF group. The immediately life threatening SAEs in the 11 DE treated patients were: PE in 2 patients; MI; ischaemic stroke; angina pectoris and atrial fibrillation; oesophageal haemorrhage and haemorrhagic shock; gastrointestinal haemorrhage; small intestinal haemorrhage; ruptured vascular pseudoaneurysm; angioedema; and road traffic accident and multiple injuries. The immediately life threatening SAEs in the 6 WF treated patients were: thrombosis; intracranial haemorrhage; gastrointestinal haemorrhage; haemoptysis; arrhythmia; and renal neoplasm.

SAEs that caused disability and/or incapacity occurred in 0.6% (n=8) of patients in the DE group and 0.2% (n=3) of patients in the WF group. The SAEs causing disability and/or incapacity in the 8 DE treated patients were: iliac artery thrombosis; post-thrombotic syndrome and erythema nodosum; ischaemic stroke; hepatic cirrhosis; hip fracture; and various malignant neoplasms in 3 patients. The SAEs causing disability and/or incapacity in the 3 WF treated patients were: arrhythmia; lung infiltration; and chest pain.

During the study, 27 DE treated patients died (2.1%) compared with 29 WF treated patients (2.3%). Of the 27 DE treated patients, 14 (1.1%) had a fatal AE during intake of active study drug, 11 (0.9%) had a fatal AE after stopping the active drug, and 2 (0.2%) had a fatal AE without any intake of active study drug. Of the 29 WF treated patients, 19 (1.5%) patients had fatal AEs during intake of active study drug and 10 (0.8%) had a fatal AE after stopping the active study drug. In patients with fatal AEs during treatment with active study drug (14 DE vs 19 WF), the most frequent SOC was *Benign, Malignant, and Unspecified Neoplasms* (7 in each group), followed by *Respiratory, Thoracic, and Mediastinal Disorders* (4 DE vs 5 WF), *Infections and Infestations* (3 DE vs 1 WF) and *General Disorders and Administration Site Conditions* (2 in each group). The most frequently reported AEs with a fatal outcome were PE (1 DE vs WF 3), liver metastases (2 DE vs 0 WF), respiratory failure (2 DE vs 0 WF), metastatic neoplasm (1 in each group), pancreatic carcinoma (1 in each group), "death" (1 in each group), and multi-organ failure (1 in each group). Three deaths were due to AE bleeding events assessed as drug-related by the investigator: 1 in the DE group due to oesophageal haemorrhage; and 2 in the WF group (1x cerebellar haemorrhage and 1x intracranial haemorrhage).

Bleeding Events

The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis. In general, a bleeding event was categorised as an MBE if it was fatal, was symptomatic bleeding into a critical area or organ, or caused a fall in the haemoglobin level of ≥20 g/L (≥1.24 mmol/L), or led to transfusion of ≥2 units of whole blood or red blood cells.

MBEs (centrally adjudicated) were reported in 1.6% (20/1273) of DE treated patients (22 events), and 1.9% (24/1266) of WF treated patients (25 events). Of the total number of treated patients, two MBEs were reported in 2 DE treated patients and 1 WF treated patient. The HR [DE/WF] for MBEs was 0.82 [95%CI: 0.45, 1.48], indicating no statistically significant difference in the risk of MBEs between DE and WF. The cumulative risk for MBEs at 6 months was 1.7% in the DE group and 2.0% in the WF group and the non statistically significant risk difference was -0.4% [95%CI: -1.3%, 0.6%]. MBEs and/or CREs were reported in 71 (5.6%) DE treated patients (83 events) and 111 (8.8%) WF treated patients (122 events). Any bleeding events were reported in 207 (16.3%) DE treated patients (303 events) and 280 (22.1%) WF treated patients (482 events).

Of the 22 MBEs reported in the DE treatment group, 1 was fatal, 1 was categorised as symptomatic bleeding in a critical area or organ and 20 were categorised as bleeding causing a fall in haemoglobin or leading to transfusion. Of the 25 MBEs in the WF treatment group, 1 was fatal, 9 were categorised as symptomatic bleeding in a critical area or organ and 18 were categorised as bleeding causing a fall in haemoglobin or leading to transfusion. The MBEs categorised as symptomatic bleeding in a critical area or organ were haemarthroses (1/1 for DE; 5/9 for WF), intracranial haemorrhage (2/9 for WF; 0/1 for DE), cerebellar haemorrhage (1/9 for WF; 0/1 for DE) and haemoptysis (1/9 for WF; 0/1 for DE). Overall, there were 3 intracranial haemorrhages in the WF group and 0 in the DE group. Of the 47 bleeding events centrally adjudicated as MBEs (22 DE vs 25 WF), the most frequent events were gastrointestinal bleeds (9 vs 5 events), followed by urogenital bleeds (5 vs 6 events), intraarticular bleeds (1 vs 4), intramuscular bleeds (1 vs 3 events), intracranial bleeds (0 vs 3 events) and other bleeding location not previously mentioned (and not intraspinal, intraocular, retroperitoneal, pericardial or nasal (6 vs 4)).

Any bleeding events were reported in 16.3% (207/1273) of DE treated patients and 22.1% (280/1266) of WF treated patients. The HR [DE/WF] for any bleeds was 0.71 [95%CI: 0.59, 0.85], indicating that the risk of any bleeding was significantly 29% lower in DE treated patients relative to WF treated patients. The cumulative risk for any bleeding

events at 6 months was 17.3% in the DE group and 23.3% in the WF group, with a risk difference of −6.0% [95% CI −9.3%, −2.8%]. Of the 303 bleeding events in the DE group and 482 bleeding events in the WF group, the most frequent bleeds were urogenital bleeds (53 DE vs 95 WF) followed by non major nasal bleeds (40 DE vs 107 WF). Gastrointestinal bleeds were reported 53 times in the DE group and 35 times in the WF group. Intramuscular bleeding events were reported 7 times in the DE group and 22 times in the WF group. Blood transfusions (at least 1) were received by 18/1226 (1.5%) DE treated patients and 14/1266 (1.1%) WF treated patients. The number of patients transfused due to a AE was 11 (0.9%) in the DE group and 8 (0.6%) in the WF group

Acute Coronary Syndrome (ACS)

All suspected ACS events occurring during the study were centrally adjudicated and treatment blinded. The adjudication committee received ECGs, results of relevant laboratory analyses, results of imaging techniques if available (such as coronary angiograms) and other information (for example information on concomitant diseases and medication, SAE forms and narratives). ACS events were stated to be of particular interest in the study because of the possibility of a "rebound effect" after stopping anti-coagulant therapy. There were 49 suspected ACS events and 14 of these ACS events were considered to be definite (that is, occurred during or after the period of active study drug intake). These 14 definite ACS events (12 MIs; 2 ischaemia/unstable angina) occurred in 9 (0.7%) patients randomized to DE and 5 (0.4%) randomized to WF. In the 14 patients with a definite ACS event (9 DE and 5 WF), 8 patients experienced the event while on the study drug (5 DE vs 3 WF) and 6 patients experienced the event after stopping the study drug (4 DE vs 2 WF).

In the 9 DE treated patients with a definite ACS event, 8 experienced an MI and 1 experienced unstable angina and there were no deaths due to a definite ACS event. However, 1 DE treated patient who had an MI rated as a definite ACS with an onset 14 days after last intake of DE died later from another MI. This second MI was adjudicated as a likely ACS events (likely MI and likely cardiac death). In the DE treated group there were an additional 2 patients who both experienced an MI before receiving the active drug. In the 5 WF treated patients with a definite ACS event, 4 experienced an MI (1 additionally categorised as cardiac death) and 1 experienced unstable angina. There were 8/1273 (0.6%) DE treated patients with a definite MI (0.6%) compared with 4/1266 (0.3%) WF treated patients. There were 11 (0.9%) patients in the DE treated group who experienced a definite or likely ACS compared with 5 (0.4%) patients in the WF treated group.

Laboratory Tests, Vital Signs and ECGs

The analyses of mean changes from baseline to the last value on treatment and of transitions relative to the reference ranges did not reveal any notable differences between the treatment groups for any of the parameters. In particular, there were no notable differences between the two treatment groups (DE vs WF) in liver function tests of ALT ≥ 3 x ULN (2.2% vs 3.2%), AST ≥ 3 x ULN (1.7% vs 1.8%), alkaline phosphatase ≥ 2 x ULN (1.3% vs 1.7%), and total bilirubin ≥ 2 mg/dL (0.6% vs 1.1%). There were no notable differences between the two treatment groups in vital sign and /or ECG changes.

Comments

This was a good quality study. It showed that DE 150 mg bd was non-inferior to WF as regards the primary endpoint of recurrent VTE events or death due to VTE following 6 months treatment of patients with an acute VTE event treated initially for 5-10 days with standard parenteral anti-coagulant therapy. The safety profiles of the two treatments differed with MBEs, any bleeds and overall AEs occurring more frequently with WF than with DE 150 mg bd, while SAEs (including fatal events), AEs resulting in discontinuation,

blood transfusions due to AEs, and ACS events occurring more frequently with DE 150 mg bd than with WF. Overall, the safety profiles of both DE 150 mg bd and WF are considered to be acceptable in this patient population. While MBEs occurred more commonly in the WF group than in the DE 150 mg bd group the absolute difference in the cumulative risk at 6 months was only -0.4% [95%CI: -1.3%, 0.6%] in favour of DE. However, any bleeding events occurred statistically significantly more frequently in the WF group than in the DE 150 mg bd group (23.3% vs 17.3% cumulative risk at 6 months); risk difference -6.0% [95%CI: -9.3%, -2.3%] in favour of DE. Despite the increased risk of bleeding in the DE 150 mg bd group compared with the WF group the number of patients requiring a blood transfusion due to AEs was greater in the DE group than in the WF group (11 [0.9%] vs 8 [0.6%], respectively. ACS events (including MI) occurred more commonly in the DE 150 mg bd group than in the WF group, although the absolute number of events was small. The pattern of MIs occurring more frequently with DE 150 mg bd than with WF observed in RE-COVER is consistent with the patterns observed in RE-LY for both DE 110 mg bd vs WF and DE 150 mg bd vs WF.

Evaluator's Overall Conclusions on Safety

The safety conclusions relating to the use of DE in patients with AF are based on the data from RE-LY. The major safety concern associated with the use of DE compared with WF is GI bleeding. Other GI disorders associated more commonly with DE compared with WF included dyspepsia/gastritis related adverse events. The high incidence of GI adverse events observed with DE might be due to the tartaric acid included in the capsules as an excipient, presumably to increase the solubility of the drug. The other adverse event of concern was MI with the yearly event rate for this event being non-statistically significantly higher with both DE doses relative to WF. Permanent treatment discontinuation rates due to AEs (any) were higher with both DE110 (19.8%) and DE150 (20.0%) compared with WF (15.2%) in patients who completed the study (complete follow-up data available).

The yearly event rates for a major bleed were lower with both DE110, and DE150, compared with WF: 2.87%, 3.32% and 3.57%, respectively. Relative to WF, the risk of a major bleed was 20% lower (p=0.0026) with DE110 and 7% lower (p=0.3146) with DE150. The risk of a major bleed was 14% lower (p=0.0429) with DE110 relative to DE150. The yearly event rates for a life-threatening major bleed were lower with both DE110 and DE150 compared with WF: 1.24%, 1.49% and 1.85%, respectively. Relative to WF, the risk of a life-threatening major bleed was 33% lower (p<0.0001) with DE110 and 20% lower (p=0.0305) with DE150. The risk of a life-threatening major bleed was 17% lower (p=0.0915) with DE110 relative to DE150. The yearly event rates for intracranial haemorrhage were lower with both DE110, and DE150, compared with WF: 0.23%, 0.32% and 0.76%, respectively. Relative to WF, the risk of an intracranial haemorrhage was 70% lower (p<0.0001) with DE110 and 59% lower (p<0.0001) with DE150. The risk of an intracranial haemorrhage was 28% lower (p=0.1875) with DE110 relative to DE150. The yearly event rates for haemorrhagic stroke were lower with both DE110 and DE150 compared with WF: 0.12%, 0.10% and 0.38%. Relative to WF, the risk of a haemorrhagic stroke was 69% lower (p=0.0001) with DE110 and 74% lower (p<0.0001) with DE150. However, the risk of a haemorrhagic stroke was 18% higher (p=0.6750) with DE110 relative to DE150.

The risks of investigator reported major bleeds, symptomatic intracranial bleeds and any bleeds were statistically significantly lower for both doses of DE relative to WF, apart from reported major bleeds which were non-statistically significantly lower with DE150 relative to WF. The risks of investigator reported bleeding events were all reduced with DE110 relative to DE150, with the reductions being 16% (p=0.0134) for reported major

bleeds, 38% (p=0.0502) for reported symptomatic intracranial bleeds and 14% (p<0.0001) for reported any bleeds.

Of the total number of adjudicated major bleeds in each treatment group, GI major bleeds contributed 38.8% (154/397), 44.9% (218/486) and 29.1% (139/477) in the DE110, DE 150 and WF groups, respectively. The GI tract was the most common site of symptomatic bleeding in critical areas/organs. The yearly event rates for adjudicated GI major bleeds were 1.14%, 1.57% and 1.07% for DE110, DE 150 and WF, respectively. Relative to WF, the risk of a major GI bleed was 7% higher (p=0.6002) with DE110, and 47% higher (p=0.0006) with DE150. The risk of a GI major bleed was 27% lower (p=0.0046) with DE110 relative to DE150. The risk patterns between treatment for life-threatening major bleeds (a subset of GI major bleeds) was consistent with those for GI major bleeds. Relative to WF, the frequency of any GI bleed (adjudicated plus investigator reported) was 35% higher (p<0.0001) with DE110 and 52% higher (p<0.001) with DE150. The risk of any GI bleed was 11% lower (p=0.0298) with DE110 relative to DE150.

The study included an analysis of the interaction between treatment and demographic subgroup on the incidence of major bleeding events. There was a significant interaction between treatment and age on major bleeding rates (p<0.0001). The risk of major bleeding increased with age in all three treatment groups. Apart from age and ethnicity there were no other statistically significant interactions between treatment and baseline demographic factors (gender, region, BMI or CrCl).

The main difference in the reported adverse events for the three treatments related to the higher incidence of GI disorders with DE compared with WF. Both dyspepsia and gastritis like related AEs occurred about twice as frequently with both doses of DE compared with WF. The incidence of serious adverse events (any) was similar in the three treatment groups. Serious dyspepsia and gastritis like adverse event were infrequent in the three treatment groups. Relative to WF, the risk of all cause death was non-statistically significantly lower with DE110 and DE150, while the risk of vascular death was non-statistically significantly lower with DE110 and statistically significantly lower with DE150.

There was about a 2-fold increased risk of major bleeding in all three treatment groups in patients who used concomitant ASA at least once compared with patients who never used the drug during the study. There was about a 1.6-fold to 1.8-fold increased risk of a major bleed in the three treatment groups in patients who had used concomitant COX-2 inhibitors at least once in the study compared with patients who never used the drugs. There was about a 2.6-fold to 3.7-fold increased risk of a major bleed in the treatment groups in patients who had used concomitant PPIs at least once compared with patients who had never used the drugs during the study. There was similar, relatively small increased risk of a major bleed in all three treatment groups for patients who had used concomitant P-gp inhibitors at least once compared with patients who had never used the drugs during the study. Overall, where concomitant use of a drug during the study increased the risk of a major bleed the increased risk did not differ significantly between DE and WF.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated. The following questions were submitted to the sponsor:

Does the sponsor have any data on the effects of DE on platelet function? The increase in gMean urinary 11-dehydrothromboxane B_2 concentrations observed with DE compared with WF is a signal that increased platelet aggregation might be occurring with DE

compared with WF. The effects of DE on platelet function should be further investigated given that there was an non-statistically significantly increased risk of MI observed in patients treated with both DE110 and DE150 compared with WF in RE-LY.

Does the sponsor intend undertaking any clinical studies with DE specifically in patients with AF at risk of cardiovascular disease in order to further assess the association between DE and MI?

Does the sponsor intend undertaking any epidemiological studies based on post-marketing utilisation data to investigate the association between DE and MI?

How does the sponsor reconcile the apparent inconsistency in the PI between dosage recommendations for DE in orthopaedic surgical patients and atrial fibrillation patients with moderate renal impairment (CrCl 30-50 mL/min): that is, 75 mg bd and 110 mg bd, respectively?

Clinical Summary and Conclusions

Clinical Aspects

The discussion relates to the relevant efficacy and safety data from the re-analysis of RE-LY. The initial FDA review of individual patient records from RE-LY identified a number of inconsistencies in the original data. This resulted in the sponsor re-checking the original outcome data. The sponsor identified 80 patients with an additional 81 outcome events directly related to the efficacy and safety evaluations. Of these 80 patients, the majority (85%, n=68) were identified as experiencing a major bleed. The sponsor also identified an additional 28 patients with silent MIs. The re-analysis of the efficacy and safety data using the newly identified outcome data, and additional outcome data identified after the data lock, did not significantly change the outcome measures derived from the original analysis or the conclusions based on the results of this analysis. The increased number of major bleeds resulted in the absolute yearly event rate increasing by about 0.2% per year in each of the three treatment groups. As the increases were similar for the three treatment groups, the effect on the relative risk of major bleeding in the pairwise treatment comparisons was minimal. Overall, the similar distribution of newly identified outcomes in the three treatment groups suggests that failure to identify the events was the result of random error. However, it was of concern that such a large number of major bleeds were not initially identified in the original study and this suggests a significant problem with initial quality control and/or auditing of the study.

The submission included one, multinational, multicentred, pivotal Phase III efficacy and safety study [RE-LY]. The submission also included three, Phase II supportive safety studies but none of these studies were powered to assess efficacy and the number of patients allocated to the two DE doses of interest was small. The pivotal study was a PROBE design. As PROBE designs are open-label rather than double-blind they are subject to bias. However, bias was satisfactorily mitigated in the pivotal study by a number of acceptable methods aimed at blinding outcome assessments. The pivotal study used an active WF control, dose adjusted to INR 2-3, rather than a placebo-control. This is considered acceptable but the lack of a placebo control makes interpretation of some of the outcomes difficult (for example, increased yearly event rates for MI seen with DE compared with WF; significance of differences between DE and WF yearly event rates for all cause death and vascular death).

The pivotal efficacy study randomised a total of 18113 patients with non-valvular AF and at least one additional risk factor for stroke to treatment with DE 110 mg bd (n=6015), DE150 mg bd (n=6076) or WF (n=6022). The mean (SD) duration of treatment in the 18,113 randomized patients was 23.67 (7.07) months and there were 35,727 patient-

years of exposure. The respective exposure figures for DE110, DE 150 and WF were 23.74 (7.09) months and 11,899 patient-years, 23.77 (7.06) months and 12,033 patient-years, and 23.5 (7.04) months and 11,794 patient-years. The duration of exposure was similar for the three treatment groups. Of the 18,113 randomized patients, 18,040 (96.2%) received at least one dose of study medication with the respective figures for DE110, DE 150 and WF being 5,780 (96.6%), 5,824 (96.1%), and 5,756 (96.0%). The percentage of randomized patients who were treated and completed the study on study medication was higher in the WF group than in the DE110 and DE150 groups, with the respective figures being 80.8% (n=4849), 77.1% (n=4610) and 76.4% (n=4627). The completed on study medication figures suggest that, overall, WF was better tolerated than DE.

The mean (SD) age of the 18,113 randomized patients was 71.5 (8.7) years [range: 22-101]. Of the randomized patients, 16.5% (n=2981) were aged < 65 years, 43.6% (n=7894) aged ≥ 65 to < 75 years and 40.0% (n=7238) aged ≥ 75 years. The majority of the 18,113 randomized patients were male (63.6%) and white (70.0%). The mean age, age distribution, sex distribution and ethnicity were similar for the three treatment groups. Of the 18,113 randomized patients, 50.4% were VKA-naive and 49.6% were VKA-experienced and the distribution between the two VKA groups was similar for the three treatment groups. The baseline AF characteristics in the total randomized population (n=18113) were persistent (32.0%), paroxysmal (32.8%) and permanent (35.2%), and this pattern was similar for the three treatment groups. In the total randomized population (n=18113), protocol specified baseline risk factors for stroke in addition to AF were 21.8% (n=2953) stroke/SEE/TIA, 10.7% (n=3953) LVEF ≤ 40%, 27.1% (n=4904) heart failure NYHA ≥ 2, 40.0% (n=7238) aged ≥ 75 years, 19.3% (n=3496) aged ≥ 65 years with diabetes mellitus, 24.2% (n=4377) aged ≥ 65 years with CAD, 67.3% (n=12190) aged ≥ 65 years with hypertension, and 3.0% (n=547) none of the preceding (protocol violation). The population also appears to have significant risk factors for haemorrhagic stroke (age, hypertension) in addition to ischaemic stroke. Overall, the distribution of demographic factors and additional stroke factors was well balanced across the three treatment groups. The population in the pivotal study appears similar to elderly Australian patients with AF likely to be considered for anti-thrombotic treatment.

The pre-specified primary efficacy endpoint was a composite endpoint of time to first occurrence of stroke or non-CNS systemic embolism (stroke/SEE), and the major contributor to the composite endpoint was time to first occurrence of stroke The stroke endpoint was itself a composite consisting of ischaemic stroke, haemorrhagic stroke and stroke of uncertain origin. The sponsor proposed that DE be approved for the prevention of stroke, systemic embolism and vascular mortality in patients with atrial fibrillation. It could be argued that the indication should specifically refer to “ischaemic stroke” rather than “stroke” as the purpose of treatment is to prevent ischaemic stroke associated with AF while avoiding haemorrhagic stroke associated with the medication. Furthermore, the relevant indication for warfarin is “prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation”. However, on balance it was considered that the proposed term (stroke) is acceptable as it is commonly used in clinical practice when treating patients with AF with warfarin.

The proposed indication includes prevention of systemic embolism (SEE). The time to first occurrence of SEE was a minor contributor to the composite primary efficacy endpoint of stroke/SEE. The yearly event rate of SEE was lower for both doses of DE compared with WF. However, the yearly event rate of PE (not included in the SEE composite) was higher with both doses of DE than for WF, although event rates were low for the three treatments. The inconsistency between SEE and PE is unexplained. It was considered reasonable to include prevention of SEE in the indication even though event rates were low.

The proposed indication includes reduction of vascular mortality. Vascular death was a component of one of the composite secondary efficacy endpoints of time to first occurrence of stroke/SEE/PE/MI/vascular death. The yearly event rate for vascular death was greater than those of the other components of the composite endpoint for the three treatments. The yearly event rate for vascular death was higher for WF than for both DE110 and DE150: 2.69%; 2.43%; and 2.28%; respectively. However, WF is not approved for the reduction of vascular mortality, and the absence of a placebo control makes meaningful interpretation of the yearly event rates for vascular death difficult. Consequently, it was recommended that "reduction of vascular mortality" not be included in the approved indication.

In RE-LY, patients were required to have non-valvular AF with at least one additional risk factor for stroke. However, the proposed indication relates to AF without conditions. Consequently, it was recommended that the indication should be amended to include patients "with non-valvular atrial fibrillation with at least one additional risk factor for stroke".

Benefit Risk Assessment

Benefits

The pivotal study established that both DE110 and DE150 were non-inferior compared with WF for the composite primary efficacy endpoint of time to first occurrence of stroke/SEE (primary analysis) and that DE150 but not DE110 was statistically significantly superior to WF for this endpoint (secondary analysis). Comparison between the two DE doses showed that the higher dose was statistically significantly superior compared with the lower dose as regards the primary efficacy endpoint. The pivotal study also established that the differences between DE110 and WF were non-statistically significant as regards both the secondary efficacy endpoints of time to first occurrence of ischaemic stroke/SEE/all-cause death and time to first occurrence of stroke/SEE/PE/MI (excluding silent MI)/vascular death. In contrast, DE150 mg was statistically significantly superior compared with WF for both of the secondary efficacy endpoints. Comparison between DE150 and DE110 showed that the results for the higher dose were better for both secondary efficacy endpoints. Overall, it was considered that the primary and safety endpoints analyses showed that DE110 and WF were non-inferior, while DE150 was superior to both WF and DE110.

The major contributor to the composite primary efficacy endpoint of stroke/SEE endpoint was stroke. Stroke contributed more than 90% of patients to the total number of patients with the composite endpoint for each of the three treatments. Relative to WF, the risk of stroke was lower with both DE110 (statistically non-significant) and DE150 (statistically significant). The risk of stroke was statistically significantly higher with DE110 relative to DE150. The minor contributor to the composite primary efficacy endpoint of stroke/SEE was SEE. The frequency of SEE events was small in each of the three treatment groups, and the relevant pairwise comparisons were non-statistically significant.

Ischaemic strokes were the most commonly occurring of the three stroke categories contributing to the composite stroke outcome (ischaemic stroke, haemorrhagic stroke, and stroke of uncertain classification). Relative to WF, the risk of ischaemic stroke was non-statistically significantly higher with DE110 and statistically significantly lower with DE150.

Risks

The most significant potential risk of treatment with DE and WF for the prevention of thromboembolic events in patients with AF is the risk of bleeding. Major bleeds

(adjudicated), life-threatening major bleeds (adjudicated), intracranial haemorrhage (adjudicated), and haemorrhagic stroke (adjudicated) all occurred less frequently with both doses of DE compared with WF. The frequency of each of these events (apart from haemorrhagic stroke) was lower with DE110 compared with DE150. The risks of all four of these adjudicated bleeding events were statistically significantly lower with DE110 relative to WF. The risks of three of these adjudicated bleeding events (life-threatening bleeds, intracranial haemorrhage, haemorrhagic strokes) were statistically significantly lower with DE150 relative to WF, while the risk of the adjudicated event (major bleeds) was non-statistically significantly lower with DE150 relative to WF. The comparisons between DE110 and DE150 showed that the lower dose statistically significantly reduced the risk of major bleed relative to the higher dose, non-significantly reduced the risk of adjudicated life-threatening major bleed and adjudicated intracranial haemorrhage, and non-statistically significantly increased the risk of adjudicated haemorrhagic stroke.

The most common symptomatic adjudicated major bleeds in critical areas/organs were GI bleeds followed by symptomatic intracranial bleeds. Of the total number of major bleeds in each of the three treatment groups, GI major bleeds accounted for 38.8% (154 bleeds), 44.9% (218 bleeds) and 29.1% (139 bleeds), for DE110, DE 150 and WF, respectively. The corresponding figures for symptomatic intracranial bleeds were 7.8% (31 bleeds), 7.8% (38 bleeds) and 18.4% (88 bleeds), DE110, DE 150 and WF, respectively. The risk of GI major bleed was lower with WF relative to DE110 (non-statistically significant) and DE150 (statistically significant) and the risk was statistically significantly lower with DE110 relative to DE150. Relative to WF, the risks of a major GI bleed and a life-threatening GI major bleed were both higher with DE110 (non-statistically significant) and DE150 (statistically significant). The risks of both of these GI bleeding events were statistically significantly lower with DE110 compared with DE150. The risks of any GI bleeds (adjudicated plus investigator reported) were statistically significantly higher for both doses of DE compared with WF and the risk was statistically significantly lower for DE110 compared with DE150.

Adverse events occurred frequently in all three treatment groups which is unsurprising given the characteristics of the patient population. The main difference in the reported adverse events for the three treatments related to the higher incidence of gastro-intestinal disorders with both DE110 (34.6%) and DE150 (34.5%) compared with WF (24.1%). Both dyspepsia and gastritis like related adverse events occurred about twice as frequently with both doses of DE compared with WF. The incidence of serious adverse events was similar in the three treatment groups, including dyspepsia and gastritis like effects. Relative to WF, the risk of all cause death was non-statistically significantly lower with DE110 and DE150, while the risk of vascular death was non-statistically significantly lower with DE110 and statistically significantly lower with DE150. The risk of MI was non-statistically significantly higher with both doses of DE relative to WF. The imbalance in the yearly event rate between DE and WF in MI was unexpected and requires further investigation.

There was about a 2-fold increased risk of major bleeding in all three treatment groups in patients who used concomitant ASA at least once during the study compared with patients who never used the drug during the study. There was about a 1.6-fold to 1.8-fold increased risk of a major bleed in the three treatment groups in patients who had used concomitant COX-2 inhibitors at least once during the study compared with patients who never used the drugs during the study. There was about a 2.6-fold to 3.7-fold increased risk of a major bleed in the treatment groups in patients who had used concomitant PPIs at least once during the study compared with patients who had never used the drugs during the study. There was similar, relatively small increased risk of a major bleed in all three treatment groups for patients who had used concomitant P-gp inhibitors at least once during the

study compared with patients who had never used the drugs during the study. Overall, where concomitant use of a drug during the study increased the risk of a major bleed the increased risk did not differ significantly between DE and WF.

There was a statistically significant interaction between treatment and age on the risk of major bleeding. In each of the three treatment groups the risk of major bleeding increased with age with the risks being lower with both doses of DE compared with WF in both the < 65 years and ≥ 65 to < 75 years age groups and greater for DE150 (5.12%) compared with both DE110 (4.44%) and WF (4.39%) in ≥ 75 years age group. There was a statistically significant interaction between treatment and ethnicity on the risk of major bleeding suggesting that the risk of major bleeding was lower with DE relative to WF in patients of Black, Asian and Other ethnicity, while the risks were similar in patients of White ethnicity. There were no statistically significant interactions between treatment and other assessed baseline factors on major bleeding (sex, region, Hispanic or Latino ethnicity, weight, BMI or CrCL).

The most concerning unexpected adverse event reported with DE compared with WF was MI. The event rates for MI (clinical + silent) were higher with both DE110 and DE150 compared with WF: 0.82% (98 patients); 0.81% (97 patients); and 0.64% (75 patients); respectively. Relative to WF, the risks of MI (clinical + silent) were non-significantly higher with both DE110 and DE150: 29% [95%CI: -4%, +75%], p=0.0929, and 27% [95%CI: -6%, +71%], p=0.1240, respectively. The corresponding risks for clinical MIs were marginally higher than for clinical plus silent MIs for both doses of DE relative to WF but the increased risks remained non-statistically significant. The yearly event rate for sudden cardiac death was greater with DE110 (0.92%, 109 patients with the event) compared with both WF (0.87%, 103 patients with the event) and with DE150 (0.77%, 93 patients with the event). It was considered that further investigation of the relationship should be undertaken but the increased risk of MI observed with DE relative to WF should not preclude registration.

Balance

The pivotal study established that both DE110 and DE150 were non-inferior compared with WF as regards the composite primary efficacy endpoint of time to first occurrence of stroke/SEE (primary analysis) and that DE150 was statistically significantly superior to WF for this endpoint (secondary analysis). These results were supported by the secondary efficacy endpoints analyses. The yearly event rates for the primary efficacy endpoint of stroke/SEE were 1.54% (183 patients with event), 1.11% (134 patients with event) and 1.71% (202 patients with event), for DE110, DE 150 and WF, respectively. The risk of this endpoint was 10% lower [95%CI: -26%, +10%] with DE110 relative to WF and the absolute risk was 0.17% lower with DE110. The risk of this endpoint was 35% lower [95%CI: -48%, -19%] with DE150 relative to WF and the absolute risk was 0.60% lower with DE150. The risk of this endpoint was 39% higher [95%CI: +11%, +73%] with DE110 relative to DE150 and the absolute risk was 0.43% higher with DE110.

The risks of adjudicated life-threatening major bleed, intracranial haemorrhage and haemorrhagic stroke were significantly lower for DE150 relative to WF (20% [95%CI: -34%, -2%]; 59% [95%CI: -72%, -40%]; and 74% [95%CI: -86%, -51%]; respectively), while the risk of adjudicated major bleed was non-significantly lower with DE150 relative to WF (7% [95%CI: -19%, +7%]). The risks of adjudicated GI major bleeds (the most commonly occurring site of major bleeding) and adjudicated life-threatening GI major bleeds were both significantly higher with DE150 relative to WF (47% [95%CI: +17%, +85%] and 62% [95%CI: +17%, +126%], respectively), as was the risk of any GI bleed investigator reported plus adjudicated (52% [95%CI: +35%, +72%]). The absolute risk differences in the yearly event rates (DE150 compared with WF) were 0.25% in favour of

DE150 for adjudicated major bleeds, 0.36% in favour of DE150 for adjudicated life-threatening major bleeds, 0.50% in favour of WF for GI major bleeds, and 0.30% in favour of WF for life-threatening GI major bleeds.

The risk of all cause death was non-significantly lower with DE150 relative to WF (12% [95%CI: -23%, 0%]), while the risk of vascular death was significantly lower (15% [95%CI: -28%, -1%]). The frequency of SAEs was similar for DE150 and WF (21.3% and 22.6%, respectively). The risk of myocardial infarction (clinical plus silent) was non-significantly higher with DE150 relative to WF (27% [95%CI: -6%, +71%]) and the absolute risk was 0.17% higher with DE150. Discontinuations due to adverse events occurred more frequently with DE150 than with WF (20.5% and 15.7%, respectively).

It was considered that the risk-benefit balance for DE150 relative to WF is neutral. It was considered that the overall risks associated with DE150 are greater than those associated with WF but these are balanced by the greater overall benefits associated with DE150 compared with those associated with WF.

The risks of the following major adjudicated bleeding events were all significantly lower with DE110 relative to WF: major bleed (20% [95%CI: -30%, -7%]); life-threatening major bleed (33% [95%CI: -46%, -18%]); intracranial haemorrhage (70% [95%CI: -81%, -55%]); and haemorrhagic stroke (69% [95%CI: -83%, -44%]). Similarly, the risk of investigator reported any bleeds was significantly lower with DE110 relative to WF (22% [95%CI: -27%, -17%]). The risks of adjudicated GI major bleeds and adjudicated life-threatening GI major bleeds were both non-significantly higher with DE110 relative to WF (7% [95%CI: -16%, +36%], and 17% [95%CI: -18%, +67%], respectively), while the risk of any GI bleed investigator reported plus adjudicated was significantly higher with DE110 relative to WF (35% [95%CI: +19%, +53%]). The absolute risk differences in the yearly event rates (DE110 compared with WF) were 0.45% in favour of DE110 for adjudicated major bleeds, 0.25% in favour of DE110 for adjudicated life-threatening major bleeds, 0.07% in favour of WF for GI major bleed and 0.08% in favour of WF for life-threatening GI major bleed.

The risks of all cause death and vascular death were non-significantly lower with DE110 relative to WF (9% [95%CI: -20%, +3%] and 10% [95%CI: -23%, +6%], respectively). The frequency of other SAEs was similar for DE110 and WF (21.1% and 22.6%, respectively). The risk of myocardial infarction (clinical plus silent) was non-significantly higher greater with DE110 relative to WF (29% [95%CI: -4%, +75%] and absolute risk was 0.18% higher with DE110. Permanent discontinuations due to adverse events occurred more frequently with DE110 than with WF (19.0% and 15.7%, respectively).

It was considered that the risk-benefit balance favours DE110 relative to WF. It was considered that the overall risks associated WF are greater than those associated with DE110, while the overall benefits associated with DE110 are similar to those associated with WF.

The sponsor proposed that both the DE110 and DE150 treatment regimens be approved, with the higher dose regimen (150 mg bd) being the recommended dose. The sponsor proposed that the lower dose regimen (110 mg bd) be reserved for patients with a "potentially higher risk of major bleeding". However, the pivotal study did not stratify patients on the basis of the risk of bleeding. Furthermore, the patient population in the pivotal study can be considered to have been not only at a high risk of stroke but also at a high risk of bleeding (for example, mean age 71.5 years; 40% of patients aged ≥ 75 years; 67.3% of patients aged ≥ 65 years and with a history of hypertension; 20.5% of patients taking concomitant acetylsalicylic acid throughout the study; and 32.4% of patients having a $CHADS_2$ score of 3+ at entry). The risk of major bleeding in the DE110 group was

statistically significantly lower relative to DE150 mg in patients with the baseline risk factor of stroke/SEE/TIA (HR=0.65 [95%CI: 0.48, 0.87]) and in patients with the baseline risk factor of age ≥ 65 years with hypertension (HR=0.80 [95%CI: 0.68, 0.94]).

The risk of stroke/SEE was 39% significantly higher [95%CI: +11%, +73%] with DE110 relative to DE150, and the absolute risk was 0.43% higher with DE110. The risk of adjudicated major bleed was significantly lower with DE110 relative to DE150 (14% [95%CI: -25%, 0%], p=0.0429) and the risks of life-threatening major bleeds and intracranial haemorrhage were both non-significantly lower with DE110 relative to DE150 (17% [95%CI: -33%, +3%], p=0.0915 and 28% [95%CI: -56%, +18%], p=0.1875). However, the risk of haemorrhagic stroke was non-significantly higher with DE110 relative to DE150 (18% [95%CI: -45%, +155%], p=0.6750). The risk of investigator reported any bleeds was significantly lower with DE110 relative to DE150 (14% [95%CI: -19%, -8%], p<0.0001). The risks of adjudicated GI major bleeds and adjudicated life-threatening GI major bleed were both significantly lower with DE110 relative to DE150 (27% [95%CI: -42%, -9%], p=0.0046 and 28% [95%CI: -47%, -1%], p=0.0400, respectively), as was the risk of any GI bleed investigator reported plus adjudicated (11% [95%CI: -21%, -1%], p=0.0298). The absolute risk in the yearly event rates were all lower with DE110 compared with DE150 for adjudicated major bleeds (0.45%), life-threatening major bleeds (0.25%), GI major bleeds (0.43%) and life-threatening GI major bleeds (22%).

The risks of all cause death and vascular death were non-significantly higher with DE110 relative to DE150 (3%, p=0.6655 and 7%, p=0.4441, respectively). The frequency of SAEs was similar for DE110 and DE150 (21.1% and 22.6%, respectively). The risk of MI (clinical and silent) was non-significantly higher with DE110 relative to DE150 (2%, p=0.8816), and the absolute risk was 0.01% higher with DE110. The frequency of permanent discontinuations due to AEs was similar for DE110 and DE150 (19.0% and 20.5%, respectively).

It was considered that the risk-balance favours DE110 relative to DE150. It was considered that the risks associated with DE150 are greater than those associated with DE110 as are the benefits. However, it was considered that that the risks of DE150 compared with DE110 outweigh the benefits. Consequently, this shifts the risk-balance towards DE110 relative to DE150.

The sponsor calculated a composite net clinical benefit (NCB) endpoint consisting of time to first occurrence of stroke / SEE /PE /MI (including silent MI) /death (all cause) / major bleeds. In the randomized patients, the NCB yearly event rate was similar for DE110, DE150 and WF, being 7.34% (873 patients with event), 7.11% (855 patients with event) and 7.91% (933 patients with event). The NCB was statistically significantly better with DE150 compared with WF (p=0.0246) and non-statistically significantly better with DE110 compared with WF (p=0.0968). The absolute difference between DE150 and DE110 was 0.23% in favour of the higher dose.

Conclusions

It was recommended that Pradaxa (dabigatran etexilate) be approved

for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke.

It was recommended that the approved dose be 110 mg twice daily.

It was recommended that 150 mg twice daily not be approved as the risk-balance of this dose is considered to be unfavourable relative to 110 mg twice daily. The greater benefit of 150 mg twice daily as regards stroke/SEE prevention compared with 110 mg twice

daily was considered to be outweighed by the greater risk of bleeding with the higher dose compared with the lower dose.

As a condition of registration, the sponsor should undertake the following:

- a study assessing the effects of DE on platelet function.
- a clinical safety study comparing DE with WF in patients with AF with risk factors for coronary artery disease.
- a post-marketing epidemiological study investigating the effect of DE in patients with AF with coronary artery disease.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Important identified risk	Bleeding
Important potential risk	Hepatotoxicity (proposed to be deleted)

The clinical evaluator recommended that the use of DE in AF be contraindicated in patients with the following: history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding; history of gastrointestinal haemorrhage; and history of endoscopically documented gastroduodenal ulcer disease in the previous 30 days. It was considered that these contraindications will reduce the risks of major bleeding associated with DE treatment.

It was also recommended that treatment with DE be initiated and supervised by a cardiologist. The risk-benefit balance for DE in individual patients will be critical and will require careful assessment of cardiovascular status and risk factors for bleeding.

The OPR reviewer recommended that the summary of ongoing safety concerns be updated to include 'increased risk of bleeding with concomitant administration of aspirin, COX-2 inhibitors, PPIs and P-gp inhibitors' and 'increased risk of myocardial infarction' as important identified risks and 'increased risk of platelet aggregation' and 'effects on the ovaries' as important potential risks.

It was also recommended that the sponsor include 'use in patients < 18 years of age' and 'use in pregnant or lactating women' as important missing information.

Furthermore, based on the available evidence, and given that the proposed AF indication will lead to a prolonged exposure, it was not recommended that the sponsor delete hepatotoxicity from the important potential risks.

Proposed pharmacovigilance activities

The sponsor stated that routine pharmacovigilance (PhV) practices will be undertaken to monitor the specified important identified risk: 'bleeding' and the important potential risk: 'hepatotoxicity'.[15] Additional PhV activities proposed for the important potential risk: 'hepatotoxicity' included the continued safety assessment of the on-going clinical trials REMEDY 1160.47 and RECOVER 1160.53:

In principle, the OPR reviewer had no objection to the sponsor implementing the proposed application of routine and additional PhV activities for the ongoing safety concerns as detailed above. However, the specified studies were not considered to be a part of the planned clinical studies in the PhV plan and therefore the related study protocols have not been reviewed. The sponsor should also provide details of the planned PhV activities for the additional safety concerns identified by the reviewer.

Furthermore, it was recommended that the sponsor be required to update the information on routine PhV practices to reflect the practices the sponsor will undertake for drugs marketed in Australia.

In the RMP, the sponsor has included details of two additional ongoing studies (protocols 1160.84 and 1160.85). It was not clear why these studies have been included in these summary tables as the sponsor has not made any reference to either study in the pharmacovigilance plan. It was recommended that the sponsor be required to update the pharmacovigilance plan to include these studies.

Given the proposed extension to the indication will result in prolonged exposure to DE in a population that potentially use many other medications, many of which have not been adequately excluded as having a potential interaction with DE, it was recommended that the sponsor be required to undertake a post-authorisation study to fully investigate all potential interactions with medicinal products including, prescription and OTC medicines and herbal and food products.

In light of the potential signal that increased platelet aggregation might be occurring with DE compared with WF and that there was an increased risk of myocardial infarction observed in patients treated with DE compared with WF in the pivotal efficacy and safety study, it was also recommended that the sponsor be required to undertake further studies to investigate these signals.

Evaluation of the Need for Risk Minimisation Activities

The sponsor has stated that there is currently no need for a Risk Minimisation Plan and that routine risk minimisation activities are sufficient.[16]

However, the sponsor has proposed a number of additional risk minimisation activities such as a kit for thrombin time coagulation assays. The sponsor has also proposed routine risk minimisation including the addition of a special warning in the European Summary of Product Characteristics (SmPC) "Patients with elevated liver enzymes > 2 ULN were

[15] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[16] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

excluded in controlled clinical trials in primary VTE prevention. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation."

The OPR reviewer did not consider this to be acceptable. The sponsor has stated there is no need for a risk minimisation plan; however, they have identified a number of proposed risk minimisation activities such as conveying information through the SmPC. Routine risk minimisation activities are considered to be a part of the risk minimisation plan and therefore there is a need for a risk minimisation plan. Furthermore, there are inconsistencies in the RMP with regards to the proposed risk minimisation activities.

The sponsor has proposed measuring ALT as part of the standard pre-operative evaluation for the primary VTE indication however has not made any comment regarding this in relation to the proposed AF indication. It was recommended that the sponsor be required to comment on how this proposed risk minimisation activity applies to long term use associated with the proposed AF indication, including, addressing if LFTs are required prior to prescribing and if LFTs need to be measured regularly.

It was recommended that the sponsor be required to update the RMP to:

- state the need for a risk minimisation plan;
- refer specifically to the proposed routine and additional risk minimisation activities; and
- remove internal inconsistencies regarding the proposed risk minimisation activities.

The sponsor should also be required to incorporate the recommendations made by the clinical evaluator as risk minimisation activities or provide a justification of their decision not to do so.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator recommended approval of the 150 mg capsules with respect to chemistry, manufacturing and controls and also has no objections to the proposed changes to the active ingredient and currently registered 75 mg and 110 mg capsules. The evaluator concluded that the three strengths of the capsules are bioequivalent at equal dose and the new 75 mg and 110 mg capsules are bioequivalent to the currently registered capsules. Changes proposed to the drug substance were acceptable. The sponsor proposed changes to the manufacturing method of the 75 mg and 110 mg capsules to a second generation process such that they will be direct scales of the proposed 150 mg capsule. The data to support this change were dissolution data and a bioequivalence study comparing a 150 mg capsule made using the current generation process and a 150 mg capsule made using the new generation process. This bioequivalence study showed strict bioequivalence was not demonstrated using scaled average bioequivalence analysis with a C_{max} 113.3%, 90%CI 101.6-126.3% and AUC_{0-t} 112.5%, 90%CI 101.6-124.6%. However when this was re-analysed by the TGA evaluator as a two sequence, two period ANOVA the results were C_{max} 113.3% (90%CI 102.5-125.1%) and AUC_{0-t} 112.5% (90%CI 102.2-123.8%). The evaluator concluded these two formulations were bioequivalent. A food study showed that when the capsules were sprinkled over food or given as an oral solution then the bioavailability increases (55-75% for average AUC_{0-t}).

Nonclinical

The nonclinical evaluator had no objections to approval of this indication based on the nonclinical data but requested the RMP address the issue of potential adverse effects on the ovaries which should be monitored in patients. The dose proposed for DE in this indication is 36.4% higher than recommended for the current indication and usage is now potentially life-long. New pharmacodynamic, pharmacokinetic, genotoxicity and phototoxicity data have been submitted. Data in rats suggested recombinant factor VIIa or activated prothrombin complex concentrate might be useful to treat dabigatran induced bleeding, for example, overdosage. Dabigatran was not genotoxic however carcinogenicity studies in rats showed an increase in ovarian tumours at 3-8 times the clinical exposure. A study in rhesus monkeys did not show an effect for up to 52 weeks exposure but this nevertheless remains a concern for potentially indefinite use in this indication that the evaluator recommended monitoring in the RMP. Phototoxicity data indicated a weak effect that is not expected to be clinically significant.

Clinical

Clinical Evaluation

The clinical evaluator recommended approval of the 110 mg twice daily dose but recommended rejection of the 150 mg twice daily dose as the risk-balance of this dose was considered to be unfavourable relative to 110 mg twice daily. The greater benefit of 150 mg twice daily as regards stroke/SEE prevention compared with 110 mg twice daily was considered to be outweighed by the greater risk of gastrointestinal bleeding with the higher dose compared with the lower dose. The concerns noted by the evaluator in this submission included:

- Major gastrointestinal bleeding and life threatening GI major bleeds higher on DE than WF
- Myocardial infarction higher on both doses of DE than WF

Pharmacology

The following comments were noted from the clinical evaluator:

Two pivotal BE studies satisfactorily established the bioequivalence of the proposed DE 150 mg formulation and the currently marketed formulation as regards polymorphs and manufacturing processes [1160.66, 1160.70]. The submission did not include relevant BE studies for the proposed DE 75 mg and 110 mg formulations, however an acceptable justification was provided.

Capsules should not be chewed or opened, as the relative $AUC_{0-\infty}$ and C_{max} values increased by 75% and 87%, respectively, for the pellets compared with the capsules [1160.87].

In a repeat dose study, exposure to total and free dabigatran as assessed by the AUC and C_{max} increased by about 1.73 fold and 1.45 fold, respectively, following repeat DE doses (150 mg bd) in healthy Caucasian subjects [1160.61].

With respect to potential interactions, the clinical evaluator noted the following:

Quinidine

DE did not significantly affect the bioavailability of quinidine sulfate and co-administration did not result in a fall in systolic blood pressure compared with DE alone suggesting they can be co-administered with caution.

Verapamil

The PK drug-drug interaction study between DE and the P-gp inhibitor verapamil showed that the effects of co-administration were complex and depended on whether DE was co-administered with steady state or single dose verapamil, and the time relationship between DE and verapamil administration.

Ketoconazole

The data suggest that co-administration of DE and ketoconazole should be contraindicated.

Clarithromycin

The data suggest DE and the P-gp inhibitor clarithromycin can be co-administered with caution.

Rifampicin

The data suggest that co-administration of DE and the P-gp inducer rifampicin should be avoided.

Enoxaparin

The PK and PD data suggest that switching to DE can occur 24 hours after the last dose of EN.

Clopidogrel

Overall, the PK and PD data suggest that the two drugs can be co-administered, but caution is required when initiating treatment with a clopidogrel loading dose of 600 mg.

The following observations were made from [1160.26; sub-study RE-LY]:

- Dose proportionality in dabigatran concentrations was seen in patients taking DE 110 mg bd and DE 150 mg bd.
- Dabigatran concentrations were 30% higher in female compared with male patients
- Dabigatran concentrations increased with age, with patients aged ≥ 75 years having concentrations 30% higher than patients aged ≥ 65 to < 75 years, and 68% higher than patients aged < 65 years and similar trends were seen for 2-hour post-dose concentrations.
- Dabigatran concentrations increased with decreasing body weight.
- Dabigatran concentrations increased with decreasing CrCl.
    - Concentration in patients with moderate renal impairment (CrCl 30-50 mL/min) was 2.3 fold higher than in patients with normal renal function (CrCl ≥ 80 mL/min)
    - Trough and 2-hour post-dose concentrations were 1.5 and 1.3 fold higher, in patients with mild renal impairment (CrCl 50-80 mL/min) compared with normal renal function.
- No differences in concentrations in patients with and without the primary efficacy endpoint.
- Increased trough (57%) and 2-hour post-dose (37%) dabigatran plasma concentrations were observed in patients experiencing a major bleed compared with patients without a major bleed.

- Increased trough concentrations of 1.02 to 1.16 fold and increased 2-hour post-dose concentrations of <0 to 1.20 fold were observed with concomitant DE and P-gp inhibitors
- No significant changes in dabigatran concentration with concomitant ASA or PPIs.

Platelet aggregation

In patients with AF, increased gMean urinary 11-dehydrothromboxane B_2 concentrations were observed with DE compared with WF [1160.20]. This increase is a signal that increased platelet aggregation might be occurring with DE compared with WF. The effects of DE on platelet function should be further investigated given that there was an increased risk of myocardial infarction DE patients compared with WF in the pivotal study.

Population PK study [U09-1399-02]

Increasing renal impairment increased dabigatran exposure; apparent total body clearance (CL/F) linearly declined by about 0.64% for one unit decrease in CrCl below 120 mL/min; apparent total body clearance (CL/F) changed by 0.66% for every year above (decrease) and below (increase) the age of 68 years; females had a 12.5% lower apparent body clearance (CL/F) than males; dabigatran bioavailability increased by 15% in patients receiving concomitant P-gp inhibitors and decreased by 14% in patients receiving concomitant PPIs.

Efficacy

Four clinical studies were submitted, including the pivotal RE-LY trial.

PETRO

This was a small unpowered exploratory Phase II with no primary efficacy endpoint. It was primarily a safety study to investigate the effect of DE 150 mg bd alone (n=91) and in combination with ASA 81 mg qd (n=34) and ASA 300 mg qd (n=33) on bleeding in patients with chronic AF. No major bleeds were observed with DE alone and in combination with ASA (both doses). However, major plus clinically relevant bleeds occurred with DE alone and in combination with ASA (both doses) with any bleeds being higher on DE when combined with ASA (both doses) compared with DE alone. There was no obvious dose response relationship. The study included no data on DE 110 mg bd.

PETRO-EX

This uncontrolled extension study indicated bleeding at 300 mg bd is too high for safe use. The yearly event rate for major bleeding for 150 mg bd was 3.1% (range 0% with 50 mg qd and bd to 7.3% with 300 mg bd). The yearly event rate for any bleeding for 150 mg bd was 14.1% which puts it in the range 0% (lowest with 50 mg qd) to 58.5% (highest with 300 mg bd).

Japanese Study

This exploratory safety study in Japanese patients with AF showed no thromboembolic events during the study in DE treated patients and 1 WF treated patient experienced an ischaemic stroke. Major bleeding events occurred more commonly with WF than with DE 110 mg bd or 150 mg bd. All bleeding events occurred more commonly with DE 110 mg bd than with DE 150 mg bd.

RE-LY

This was a pivotal Phase III, multinational, multicentre, randomised, open label, blinded assessment, non-inferiority trial comparing DE 110 mg bd, DE 150 mg bd and WF (INR 2-3, naïve and experienced cohorts) in 18,113 patients with AF (47% for >2 years, 31% new

onset, approximately a third each with persistent, paroxysmal and permanent AF) and one additional risk factor for stroke (67% age≥65 years and hypertension; mean $CHADS_2$ score of 2.1) for a median 24 months (pre-specified 20-24 months) of treatment (12-36 months range). The primary efficacy endpoint which was a composite of time to first occurrence of stroke or systemic embolism (SEE) showed both doses of DE were statistically significantly non-inferior to WF with DE 110 mg bd reducing the risk of stroke by 10% compared to WF and DE 150 mg bd reducing the risk of stroke by 35% compared to WF ($p<0.0001$) (Table 9, Table 8, Figure 1)). DE 150 mg bd also demonstrated superiority compared to warfarin ($p<0.0001$) but DE 110 mg bd was not superior to WF ($p=0.2943$). The yearly event rate for stroke/SEE was lowest with DE150 (1.11%), followed by DE110 (1.54%) and WF (1.71%) which was primarily driven by ischaemic stroke. The yearly event rates for SEE alone were 0.13% (DE110), 0.11% (DE150) and 0.18% (WF) respectively.

Subgroup analyses for the primary endpoint indicated no significant differences in regards to whether patients were WF naïve or experienced. The primary endpoint was higher in all groups exposed to ASA, clopidogrel, PPIs, statins or NSAIDs and varied for those exposed to amiodarone, verapamil or diltiazem.

The secondary efficacy endpoints included two composites:

The first which was the time to first occurrence of stroke, systemic embolism or all cause death showed DE110 reduced the risk by 7% relative to WF ($p=0.2206$) and DE150 reduced the risk by 17% relative to WF ($p=0.0015$). The risk of stroke/SEE/death was 13% higher with DE110 relative DE150 ($p=0.0503$) (Table 13). The major contributor to the composite event endpoint of stroke/SEE/death in the three treatment groups was death and the most common cause of death was vascular. The yearly event rates for all outcomes were higher in the WF group than in both DE groups, apart from sudden cardiac death which was higher in the DE110 group than in the two other treatment groups.

The second which was time to first occurrence of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction or vascular death showed the frequency was similar for DE110 and WF, with hazard ratios not statistically significant for the composite endpoint including and excluding silent MIs (Table 15). However, DE150 significantly reduced the risk relative to WF for the endpoints including and excluding silent MI. Stroke, SEE, and vascular death components of the composite endpoint all occurred more frequently with WF than with both doses of DE. However, both PE and MI occurred more frequently with both doses of DE than with WF and silent MIs occurred more frequently with DE110 than with WF and DE150. The re-analysis showed similar increases across all groups with mostly silent MIs increasing.

Other endpoints were examined in the clinical evaluation report and notably a net clinical benefit endpoint of stroke/SEE/PE/MI (including silent MI)/death/major bleed had results of 7.25% for DE110, 7.05% for DE150 and 7.84% for WF.

Safety

Exposure across the four clinical studies was a total of 18,710 patients with 12,579 receiving exposure to a dabigatran dose (6030 for DE110 and 6473 for DE150). The median duration of exposure in RE-LY was 22 months. Approximately half of RE-LY patients had an interruption of study medication with about 22% having permanent interruptions across the three groups. The reasons included surgery/procedure in 37%, adverse event in 23% and hospitalisation in 16% and were similar in all three groups. Adverse events were slightly higher on DE (78%) than WF (76%) but severe adverse events were similar (29% each). AEs leading to discontinuation were higher on DE (19-21% vs 16% on WF) with GI disorders the main reason and adverse reactions were also

higher on DE (21-22% vs 16% on WF). AEs were generally similar between DE doses and WF but greater on DE than WF for gastrointestinal related (35% vs 24% on WF). Dyspepsia/gastritis was doubled on DE (16%) than WF (8%) but no dose response and a *post hoc* analysis showed no differences in frequency of serious dyspepsia/gastritis between the three groups. All cause mortality was less on DE (9-12% less) than WF with the majority of deaths being vascular (10-15% less on DE). Serious AEs were similar in all groups and LFT measurement showed potential Hy's law cases to be similar (0.2% on DE110, 0.3% on DE150 and 0.4% on WF). Haematology and chemistry parameters were similar between the groups. Clinically significant decreases in haemoglobin were reported in 7.8% on DE110, 8.5% on DE150 and 7.5% on WF. Vital sign changes were not notably different.

Bleeding

Any bleeds, minor bleeds, intracranial haemorrhage and major bleeds occurred more frequently on WF than DE150, with the least on DE110 (Table 17). Compared to WF, DE150 was statistically significantly less for life threatening bleeds, intracranial haemorrhage, haemorrhagic strokes, symptomatic intracranial bleeds and any bleeds (Table 18). Compared to WF, DE110 was statistically significantly less for all of the above bleed types and also major bleeds. Major bleeds were mostly hospitalisation for bleeds, drop in haemoglobin of ≥20g/L and required transfusion of ≥2 units. A major bleed was mostly GI (38.8% for DE110, 44.9% for DE150 and 29.1% for WF) which was higher on DE (1.14% on DE110, 1.57% on DE150 and 1.07% on WF) followed by symptomatic intracranial bleeds which were lower on DE. A *post hoc* analysis of GI bleeds showed the greater risk for the DE150 group occurred soon after treatment whereas DE110 remained similar to WF (Table 19). Fatal bleeds were also lower on DE (6.3% on DE110, 5.8% on DE150 and 8.4% on WF). Age significantly influenced major bleeds with increasing risk with age. For those <75 years, both DE doses reduced the risk vs WF, but for those >75 years, DE110 was similar to WF (+1%) whereas DE150 increased the risk vs WF by 18%.

Concomitant medications showed increased major bleeding with ASA (nearly double), clopidogrel (double), Cox-2 inhibitors (60-80% higher), NSAIDs (40-50% higher), PPIs (2.6-3.4 fold higher) and verapamil (4-30% higher) across the three groups. The exposures for quinidine were too small. The evaluator noted that where concomitant use of a drug during the study increased the risk of a major bleed the increased risk did not differ significantly between DE and WF.

Myocardial Infarction

MIs were non-significantly higher on both dose of DE by 27-29% compared to WF with differences appearing after 1-2 months (Tables 23, 24). There were no differences in potential risk factors for MI across the groups.

RECOVER

This study in VTE prevention for 6 months used DE 150 mg bd vs WF and provided some safety data. The safety profiles of the two treatments differed with major bleeds, any bleeds and overall AEs occurring more frequently with WF than with DE 150 mg bd, while SAEs (including fatal events), AEs resulting in discontinuation, blood transfusions due to AEs, and ACS events occurring more frequently with DE 150 mg bd than with WF. Overall, the safety profiles of both DE 150 mg bd and WF were considered to be acceptable in this patient population by the evaluator. MIs were more frequent with DE 150 mg bd (0.7%) than with WF (0.4%) which is consistent with the patterns observed in RE-LY.

Risk Management Plan

The Office of Product Review raised a number of concerns regarding the RMP (RMP version 5.0, dated 4 November 2009) for dabigatran with which the sponsor has disagreed.

The following matters need inclusion in the RMP as recommended by the OPR evaluator:

- The summary of ongoing safety concerns updated with increased risks of bleeding with aspirin, cox-2 inhibitors, PPIs and P-glycoprotein inhibitors; increased risk of myocardial infarction; increased risk of platelet aggregation and effects on the ovaries.
- The pharmacovigilance plan updated for the risk of myocardial infarction and platelet aggregation.
- A risk minimisation plan.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

The RE-LY trial used a PROBE design which has potential for bias but was considered acceptable in this circumstance given the use of a warfarin active control. The results of RE-LY are considered generalisable to the Australian population and although an initial broader indication was requested by the sponsor, subsequent to the clinical evaluation report, an amended indication reflective of the RE-LY trial population was agreed. RE-LY showed that both DE110 and DE150 were non-inferior to WF as regards the composite endpoint of stroke/SEE, and DE150 was superior to WF. DE110 reduced the risk of stroke/SEE by 10% relative to WF (p=0.2943), and DE150 reduced the risk of stroke/SEE by 35% relative to WF (p=0.0001). DE150 was associated with a statistically significantly better outcome as regards the primary efficacy endpoint compared to DE110. Stroke (mainly ischaemic) contributed 90% of the composite stroke/SEE endpoint for each of the three treatments and occurred more frequently with WF than with both DE110 and DE150. Systemic embolism event rates were low in the three treatment groups and occurred slightly more commonly with WF than both DE110 and DE150. The risk of ischaemic stroke was non-statistically significantly higher with DE110 (1.28%) and statistically significantly lower with DE150 (0.86%) compared to WF (1.14%). Relative to WF (0.38%), the risk of haemorrhagic stroke was statistically significantly lower with both DE110 (0.12%) and DE150 (0.10%). The two composite secondary endpoints showed DE110 was similar to warfarin but DE150 was superior to warfarin. Sudden cardiac death was slightly lower on DE150 and pulmonary embolism was slightly higher on DE compared to WF. Myocardial infarction was higher in both DE doses (0.73-0.74% vs 0.56% on WF).

Safety and RMP

The RE-LY trial had pre-specified outcome events of interest however these were only reported as adverse events if deemed related by the investigator. Since the trial was open label, then the safety results may be affected by bias. AEs were high in RE-LY but not unexpected for the population and study duration. RE-LY had good exposure for DE and WF with AEs being similar between the groups except for slightly higher discontinuations due to AEs. The data indicated concern with greater GI events on DE. Bleeding was less on both doses of DE than WF for all categories being significantly less on both doses of DE than WF except for major bleeds on DE150 which was non-significantly less than WF. The risk of a major bleed was reduced by 20% with DE110 (p=0.0026) and 7% (p=0.3146)

with DE150 compared to WF. The risk of life threatening major bleed was statistically significantly lower with both DE110 (33%, p=0.0001) and DE150 (20%, p=0.0305) compared to WF. The risk of intracranial haemorrhage was statistically significantly lower with both DE110 (70%, p<0.0001) and DE150 (59%, p<0.0001) compared to WF. Major bleeds was driven by GI bleeds which were higher on DE than WF and intracranial bleeds which were lower on DE than WF. The risk of a major GI bleed was 7% higher (p=0.6002) with DE110 and 47% higher (p=0.0006) with DE150 compared to WF. GI bleeding remains a significant concern for DE and it has been postulated that it may be related to the tartaric acid in the capsules which are designed to increase solubility of dabigatran. Appropriate warnings are needed in the PI. Fatal bleeds were less on both doses of DE compared to WF. For those >75 years, DE150 increased the risk of major bleeds therefore the lower dose might be considered given its rate of bleeding was similar to warfarin (4.44% vs 4.39%).

Myocardial Infarction was higher on both DE doses compared to WF

Myocardial infarction was higher in both DE doses at 0.73% on DE110 and 0.74% on DE150 vs 0.56% on WF. This finding was unexpected for an anticoagulant and unclear on the mechanism of action. It does not appear to be dose-related however it has appeared in both DE doses and is therefore less likely to be a chance finding. Patients had similar baseline cardiovascular risk factors across the groups and similar use of antiplatelet and anticoagulant medicines. The sponsor has compared MI rates in trials of other antiplatelet/anticoagulants and noted comparable rates (Table 24). However, an increase in MI was also seen in the RECOVER study. Further investigation is required in relation to this finding and this should be specifically examined in other long term ongoing studies with dabigatran. An effect on platelets may be possible. MI should be included in the RMP.

Table 24: MI rates in AF trials (event rate per 100 subject-years

Trial	N	Warfarin	DE	Ximelagatran	Clopidogrel/ ASA	ASA	Idraparinux	Apixaban
ACTIVE-W	6,706	0.55			0.86			
ACTIVE-A	7,554				0.70	0.90		
AMADEUS	4,576	0.6					0.8	
SPORTIF III	3,410	0.6		1.1				
SPORTIF V	3,922	1.4		1.0				
RE-LY	18,113	0.64	0.82, 0.81					
BAFTA	973	1.2						
AFFIRM*	4,060	0.99				1.2		
AVERROES	5,600					0.8		0.7

*140 MIs, mean exposure 3.5 years, estimated crude rate=0.99%/year

Bioequivalence between the current generation and new generation capsules is borderline

The data submitted by the sponsor for bioequivalence between the current first generation capsules and new second generation of capsules shows borderline bioequivalence. If based solely on the sponsor's results, then the C_{max} and AUC_{0-t} have increased exposure with the new capsules by an average 13% with a 90% CI up to 126.3% for C_{max} total dabigatran and 124.6% for AUC_{0-t}. When reanalysed by the evaluator, the average increase is 13% with a 90% CI up to 125.1% for C_{max} free dabigatran and 123.8% for AUC_{0-t}. The clinical evaluator did not have clinical concerns with these results. However, it should be noted that the results were borderline for concluding

bioequivalence, all confidence intervals were on one side of unity with an average 13% increase in C_{max} and AUC, and it may be worth considering if the bioequivalence limits for an anticoagulant drug like dabigatran should have narrower confidence limits applied to it in order to conclude bioequivalence. An effect of food was noted if the capsules were opened and sprinkled over food or placed in solution and the sponsor has addressed this in the PI by recommending against opening the capsules.

Significant drug interactions

The PK/PD data indicate a number of interactions with dabigatran including with P-glycoprotein inhibitors. The clinical evaluator has provided an extensive review of the studies and noted the complexity with prescribing verapamil and dabigatran. The sponsor has proposed that contraindications for verapamil only apply to the VTE indication however it is not clear why it should not be applied to both indications. It was noted that the contraindication in relation to strong p-glycoprotein inhibitors (for example quinidine) has been replaced with a precaution based on the new drug interaction study and ketoconazole has been specifically mentioned as a contraindication in its place. The RE-LY trial allowed for P-glycoprotein use (amiodarone, verapamil, diltiazem and quinidine, were used by 14.9%, 7.2%, 11.8% and 0.7% of patients, respectively). The long term use of dabigatran proposed in this indication could make managing drug interactions more difficult for the prescriber. Bleeding was higher with ASA, clopidogrel, Cox-2 inhibitors, NSAIDs, PPIs and verapamil and appropriate precautions are needed in the PI. The RMP evaluator has noted that further interaction studies should be conducted with drugs, food and herbal products and the sponsor should provide an overview of its intended plan in this regard.

Non-inferiority margin was wide

The non-inferiority margin of 1.46 for the pivotal trial was based on a preservation of 50% of warfarin's effect on the incidence of stroke/systemic embolism relative to placebo, based on the upper 95% CI of the hazard ratio reported in a meta-analysis of warfarin vs placebo in six trials in AF patients for stroke prevention. The effect of this is that the RE-LY study accepted an increase in the risk of stroke/SEE of up to 46% with DE relative to WF as being evidence of non-inferiority which is rather generous however the clinical evaluator having considered the evidence to support this deemed this to be clinically reasonable, given that stroke/SEE event rates were expected to be small. Interestingly, a smaller non-inferiority margin of 1.38, derived to preserve the effect of WF relative to placebo on a log scale, was recommended by the FDA. In any event, the smaller non-inferiority margin of 1.38 did not change the observed results, given that the 95% CI upper limit for the primary endpoint hazard ratios were within the non-inferiority margin.

Renal impairment dosing

Increasing renal impairment is associated with decreased dabigatran clearance (that is, increased dabigatran exposure) as seen in the RE-LY substudy where those with moderate renal impairment had dabigatran concentrations 2.3 fold higher than those with normal renal function and those with mild renal impairment had concentrations 1.3-1.5 fold higher. Patients with severe renal impairment were excluded and the PI contraindicates severe renal impairment. For VTE patients, the dose of dabigatran was reduced from 220 mg daily to 150 mg daily in moderate renal impairment based on an increased risk of bleeding. For this new indication the sponsor is not proposing to reduce the dose in moderate renal impairment however then also states that in those at potentially higher risk of bleeding (for example moderate renal impairment), a reduced dose may be considered of 110 mg bd. This should be clarified in the PI. The sponsor has indicated that those with renal impairment dosed at 150 mg bd did not have an additional bleeding

risk compared to 110 mg bd but if given 110 mg bd there was reduced efficacy, thus supporting the use of the standard dose in moderate renal impairment. The advice of the Advisory Committee on Prescription Medicines (ACPM) was requested on this matter. There have been previous concerns about the dose of dabigatran in renally impaired patients.

Overdose

One of the disadvantages relating to DE compared with WF is the absence of a monitoring test if needed. Consequently, the first sign of DE overdose might be a major bleed and there is no antidote available to reverse its anti-coagulant effect. The treatment of DE overdose is symptomatic and in RE-LY the treatment was at the investigator's discretion and no specific treatment was mandated. Doses beyond 150 mg bd expose the patient to an increased risk of bleeding. Symptomatic treatment was as per the Overdosage section of the PI: discontinuation, maintaining diuresis, blood volume replacement, whole blood, fresh frozen plasma, dialysis, activated prothrombin complexes (for example Feiba), recombinant factor VIIa or coagulation factor (factors II, VII, IX, or X) or platelet concentrates.

Data Integrity problem

The inconsistencies in the data identified by the FDA and brought to the TGA's attention by the sponsor raise concerns about the initial quality control and/or auditing of the study. Although there was a similar distribution of these new outcomes in the three treatment groups which suggests random error being the cause, it was nevertheless concerning that such a large number of major bleeds were not initially identified in the original study.

Summary

This submission, whose pivotal trial is the RE-LY trial, has demonstrated that in patients with atrial fibrillation and at least one additional risk factor for stroke, dabigatran 110 mg bd reduces the risk of developing a stroke or systemic embolism by 10% compared to warfarin (non-inferior) or by 35% compared to warfarin for those on the higher dose of 150 mg bd (superior). The yearly event rate for stroke/SEE was lowest with DE150 (1.11%), followed by DE110 (1.54%) and warfarin (1.71%). The majority (90%) of strokes were ischaemic which when analysed showed that only DE 150 mg bd reduced this risk compared to warfarin and DE 110 mg bd had a higher event rate than warfarin. Importantly, haemorrhagic stroke was reduced on both doses of dabigatran compared to warfarin.

Dabigatran showed reduced major bleeding on 110 mg bd (2.87%) and a slightly less rate of major bleeding on DE 150 mg bd (3.32%) compared to warfarin (3.57%). Life threatening bleeds, intracranial haemorrhages and haemorrhagic strokes were all significantly reduced on both doses of DE compared to warfarin and fatal bleeds was non-significantly reduced on both doses of dabigatran compared to warfarin. However, major bleeds was driven by GI bleeds which were higher on dabigatran than warfarin with a yearly event rate of 1.14% on DE110, 1.57% on DE150 and 1.07% on warfarin. Added to this is an unexpected finding of increased risk of myocardial infarction on dabigatran at 0.73% on DE110 and 0.74% on DE150 vs 0.56% on warfarin. Drug interactions remain a concern for clinical practice and lack of a specific antidote or monitoring test for degree of anticoagulation in overdose are also of concern. The benefits of dabigatran in reduced stroke and reduced major bleeding overall including reduced haemorrhagic stroke need to be balanced against the increased risk of GI bleeding and myocardial infarction. In trying to balance the benefits with the risks, a net clinical benefit endpoint of stroke/SEE/PE/MI(including silent MI)/death/major bleed was used which demonstrated that both doses of dabigatran had similar results to warfarin (7.25% for DE110, 7.05% for

DE150 and 7.84% for WF). The net clinical benefit was actually statistically significantly better with DE150 compared with warfarin (p=0.0246) and non-statistically significantly better with DE110 compared with warfarin (p=0.0968). On balance, the Delegate was inclined to view these results as supportive of the registration of both doses of dabigatran, which the prescriber could choose between depending upon the clinical situation (for example, history of GI bleeding and those >75 years).

The Delegate proposed to approve this submission to extend the indications for Pradaxa (dabigatran) and to vary the currently approved capsules as follows:

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one other additional risk factor for stroke.

The sponsor should address the following issues in the Pre-ACPM response:

- Why was the 110 mg dose not approved in the USA?
- Provision of a table outlining the ongoing and planned interaction studies with dabigatran with respect to medicines, food and herbal products.
- Provision of a summary table of yearly rates of events and number needed to treat for the major benefits of dabigatran and number needed to harm in relation to major safety concerns (for example, major bleeding including GI bleeds, myocardial infarction).
- Comment on the potential platelet aggregation effects of dabigatran, following the demonstrated urinary excretion of thromboxane and increased rates of myocardial infarction. Also required was an outline what further investigations are being conducted to address these concerns.
- Summary of how the sponsor intends to manage the risks of GI major bleeds and myocardial infarction in the PI/CMI, RMP and post-marketing?
- Provision of a summary of the risk of bleeding in patients with varying grades of renal impairment from the RE-LY trial.

The Delegate also addressed the following question to the ACPM:

- Should both proposed strengths of dabigatran be approved, that is, 150 mg twice daily and 110 mg twice daily?
- Are the findings in relation to myocardial infarction and GI major bleeds of sufficient concern to not support approval of this indication?
- Should dabigatran only be prescribed under the supervision of a cardiologist?
- Should the dose of dabigatran in moderate renal impairment be reduced?
- Are the bioequivalence results and standard 90% confidence intervals of 80-125% clinically acceptable for dabigatran to conclude bioequivalence between the current and proposed new generation 75 mg and 110 mg capsules?
- Should the contraindication in relation to verapamil apply to both the VTE and AF indications, as the sponsor is only proposing it apply to VTE?
- Should conditions of registration be applied in relation to further study into the effects of dabigatran on platelet function and myocardial infarction risk?

Response from Sponsor

The sponsor expressed its agreement with the Delegate's proposed action to approve the submission to extend the indications and to vary the currently approved capsules. The sponsor addressed the concerns of the Delegate as follows:

Why was the 110 mg dose not approved in the USA?

For regulatory submissions worldwide, the 110 mg bd dose is proposed for patients older than 80 years or those at a higher bleeding risk. The rationale is to provide an alternative dose to the treating physician in patients where bleeding may be of special concern.

The FDA decided not to approve the 110 mg bd dose at this point in time because of concerns that the 110 mg bd dose may be used by patients and physicians instead of the 150 mg bd dose when the clinical data suggest that the 150 mg bd dose is superior. They believe that the sponsor has not identified a specific population for whom there is compelling evidence that the net benefit of the 110 mg bd dose exceeds that of the 150 mg bd dose, balancing the risk and harm of stroke with the risk and harm of bleeding. However, the efficacy of the 110 mg bd dose has been acknowledged in the approved US label. Communication with the FDA is still ongoing.

Health Canada has recently approved the 150 mg bd dose as the standard recommended dose for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The 110 mg bd dose was also approved by Health Canada for use in specific patient populations such as patients older than 80 years and patients at higher risk of bleeding.

Provision of a table outlining ongoing and planned interaction studies with dabigatran with respect to medicines, food and herbal products.

The following future interaction studies are currently in a planning phase:

- An *in vitro* study profiling dabigatran as a substrate or inhibitor of a panel of drug Solute Carrier transporters (OATPs, OATs, OCTs).
- An *in vitro* study of the effects of amiodarone and dronedarone on active transport of dabigatran.
- An *in vivo* interaction study with dronedarone.

Provision of a summary table of yearly rates of events and number needed to treat (NNT) for the major benefits of dabigatran and number needed to harm (NNH) in relation to major safety concerns (for example, major bleeding including GI bleeds, myocardial infarction).

The sponsor provided a table of annualised rates of key outcomes and absolute differences by treatment. The NNT for dabigatran etexilate 150 mg bd over warfarin for the primary endpoint of stroke/SEE is 167. As the RE-LY study was not powered to demonstrate differences in secondary outcomes, the sponsor considered it inappropriate to provide NNT or NNH for these outcome events, especially for those occurring at low incidence rates (for example PE and MI).

Comment on the potential platelet aggregation effects of dabigatran, following the demonstrated urinary excretion of thromboxane and increased rates of myocardial infarction. Also outline what further investigations are being conducted to address these concerns.

Dabigatran has been investigated for its effects on platelet aggregation *in vitro* with human platelets. It potently inhibits thrombin-induced platelet aggregation and has not demonstrated any hyper-reactivity with platelets. It also inhibited thrombosis in a

platelet-driven arterial thrombosis model, both in the presence and absence of aspirin, and showed no evidence of platelet activation in this model

The elevated urinary thromboxane results observed in the PETRO study are not understood and not consistent with preclinical mechanistic data. PETRO was a Phase II dose ranging study which did not evaluate clinical outcomes such as myocardial infarction. Therefore a definitive correlation between elevated urinary thromboxane levels and increased rates of myocardial infarction cannot be established without further investigation.

The following further investigations are ongoing:

- *In vitro* study investigating whether dabigatran can bind directly to PAR-1 and PAR-4 on the human platelet surface to theoretically activate platelets independently of thrombin - completion was expected towards the end of 2010
- Evaluation of a platelet function substudy of RE-LY that also measured serum and urine thromboxane - completion was expected in mid 2011
- Platelet function will be measured in a subset of patients in RELYABLE. Outcome parameters include platelet aggregation, platelet activation markers like P-selectin and serum and urinary thromboxane measurements - completion was expected in mid 2011

Provision of a summary of how the sponsor intends to manage the risks of GI major bleeds and myocardial infarction in the PI/CMI, RMP and post-marketing?

The sponsor described the inclusions in the PI and the Consumer Medicines Information (CMI) with respect to these risks.

In the Risk Management Plan "haemorrhage" is described as an identified risk. Haemorrhagic events including gastrointestinal haemorrhage are closely monitored. It was considered that these routine pharmacovigilance procedures are sufficient to cover this risk.

In view of this non-statistically significant imbalance in the occurrence of myocardial infarction, as part of the Risk Management Plan, myocardial infarction has been included as a monitoring topic and routine pharmacovigilance measures including monitoring of all events associated with coronary artery disease and myocardial infarction is considered sufficient.

Provision of a summary of risk of bleeding in patients with varying grades of renal impairment from the RE-LY trial.

The sponsor provided a table of annualised rates of major bleeding by baseline renal function.

Questions to the ACPM

The sponsor also noted that the Delegate was seeking ACPM's advice on a number of issues.

The sponsor believed that both the 150 mg bd dose and 110 mg bd dose should be approved. The 150 mg bd dose is clearly superior to warfarin in terms of reducing the risk of stroke and systemic embolism with comparable rates of major bleeding and is recommended as the standard dose. The 110 mg bd dose is non-inferior to warfarin in terms of reducing the risk of stroke and systemic embolism with lower rates of major bleeding and is recommended in specific patient populations where bleeding may be of special concern.

The increased numeric imbalance in myocardial infarction events and the higher frequency of GI bleeding in subjects treated with dabigatran compared to warfarin should be considered in the overall context of the risk/benefit ratio of dabigatran for the proposed indication. The benefits of dabigatran on ischaemic and hemorrhagic stroke and the benefits in intracranial bleeding and life-threatening bleeding far outweigh the increased risk of myocardial infarction and gastrointestinal bleeding in these patients.

The sponsor strongly disagreed that dabigatran should only be initiated by or continued under the supervision of a cardiologist. This restriction does not apply to warfarin, which is a much more difficult drug to manage, with a narrow therapeutic index requiring at least monthly monitoring of INRs, dose adjustments, and multiple food and drug interactions. Dabigatran has been demonstrated to be safer and more efficacious than warfarin, with a predictable and consistent anticoagulant effect, no food interactions and minimal drug interactions.

Based on the data from the RE-LY study the sponsor did not believe that a dose reduction for dabigatran is warranted in patients with moderate renal impairment. Pharmacokinetic data as well as clinical results from RE-LY (over 2000 patients treated with dabigatran had moderate renal impairment) indicate that patients with moderate renal impairment will especially benefit from the 150 mg bd dose without additional bleeding risk.

The sponsor did not believe that the contraindication in relation to verapamil should apply to the atrial fibrillation (AF) indication. The results of the RE-LY study confirm this view as the overall effect of verapamil co administration was substantially smaller than observed in the controlled Phase I studies which were aimed to evaluate a worst case scenario. RE-LY patients who were on concomitant verapamil had on average a 16% higher trough dabigatran plasma concentration and a 20% higher 2 hours post-dose dabigatran plasma concentration, compared to patients who were not on concomitant verapamil. Accordingly, the yearly event rates of major and any bleeding were comparable for dabigatran-treated patients in comparison to warfarin-treated patients when verapamil was concomitantly administered for various time intervals from at least once to always.

At least 6000 cardioembolic ischaemic strokes occur among an estimated 150 000 Australians with AF. These numbers are expected to rise substantially with the ageing of the Australian population and associated increase in the prevalence of AF. Furthermore, AF is associated with worse outcomes following ischaemic stroke. Bearing in mind that patients with non-valvular AF are at fivefold increased risk for embolic stroke and that a recent study showed that a third of patients with AF were on no treatment at the time of stroke, a third were on antiplatelet treatment and a quarter were on warfarin with sub therapeutic INR – only 1/8th were on adequate warfarin at the time of the stroke, demonstrating a clear unmet medical need for an alternative to warfarin.[11]

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval for the indication:

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

In making this recommendation the ACPM advised that although efficacy was demonstrated, there were acknowledged significant safety risks associated with this product in the proposed population group. The safety risks identified were attributed to the absence of clinical means to monitor coagulation levels or to administer an antidote to reverse the effects.

In addition, the ACPM advised that although the increased bioavailability of the new formula was acceptable, there were increased risks associated with the large 150 mg capsule being opened before consumption and the absence of comparative data on lean versus full body mass.

There was a concern that the impact of concomitant therapies on bleeding risks was not satisfactorily included in the PI. However, despite these concerns the ACPM considered that the overall risk benefit profile was appropriate and did not warrant limiting prescribing to the direct supervision of a cardiologist.

The specific conditions of registration should include:

- Further post marketing follow up in regards to Myocardial Infarction (MI).

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pradaxa containing dabigatran etexilate (as mesilate) for the new indication:

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

TGA also approved the registration of the additional strength of Pradaxa capsules containing dabigatran etexilate (as mesilate) 150 mg and the manufacturing changes relating to the existing strengths of Pradaxa capsules.

Among specific conditions of registration were the following:

- The implementation in Australia of the dabigatran Risk Management Plan (RMP), version 9 including Annex XI, dated 26 January 2011 and any subsequent revisions, as agreed with the TGA and its Office of Product Review OPR).
- Submission of the three studies investigating the effects of dabigatran on platelet aggregation when completed.
- The sponsor should undertake further studies that examine the effects of dabigatran on the risk of myocardial infarction and submit these studies to the TGA for evaluation. A plan outlining the studies/investigations to be undertaken should be submitted to the TGA within 6 months of this approval. The results of the ongoing RE-LYABLE and VTE prevention studies, that will examine the risk of myocardial infarction, should also be submitted when completed.
- There should be continued close pharmacovigilance monitoring of hepatic adverse events, particularly of possible and confirmed cases of Hy's Law and of serious hepatic adverse events, in all patients exposed to dabigatran, whether in the clinical trial database or in the database relating to the post-marketing experience. If there are any occurrences of very serious or life-threatening hepatic adverse events, for example cases involving fulminant hepatitis or hepatic failure, suspected of being caused by dabigatran, the sponsor is required to inform the TGA without delay.
- The sponsor was required to submit to the TGA, on an ongoing basis, information summarising the rates of all confirmed Hy's Law cases, suspected of being related to dabigatran. The rates are to be expressed according to a meaningful, consistent denominator or according to a standard measure of patient exposure such as per patient-year and versus any relevant comparator-drug data, if available. The first such information is to be reported to the TGA three months after the date of approval of this application and then at 3-monthly intervals for the first 12 months following the date of approval and then at 6-monthly intervals for the next 24

months. The information was requested in the form of a short summary document of at most a few pages. This requirement was in addition to the normal, ongoing PSUR requirements. The information requested is to be submitted to both the clinical unit responsible for dabigatran and to the OPR.

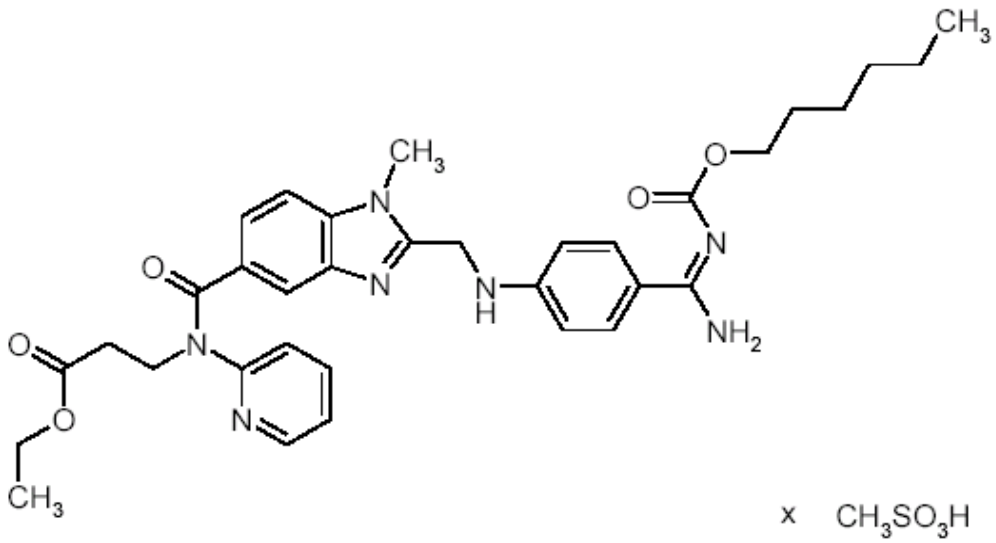
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRADAXA®
(dabigatran etexilate)

NAME OF THE MEDICINE

Dabigatran etexilate mesilate is Ethyl N-{[2-({[4-((E)-amino{[hexyloxy)carbonyl]imino}methyl) phenyl]amino}methyl)-1-methyl-1H-benzimidazol-5-yl]carbonyl}-N-pyridin-2-yl-β-alaninate methanesulfonate.



Molecular Formula: $C_{35}H_{45}N_7O_8S$

Molecular Weight: 627.75 (free base)

723.86 (mesilate salt)

CAS Registry Number: 211915-06-9 (free base)

593282-20-3 (mesilate)

DESCRIPTION

Dabigatran etexilate mesilate is a yellow-white to yellow crystalline powder; the crystals have a rod-like habit. It contains two weak basic centers with pKa-values of 4.0 ± 0.1 (benzimidazol moiety) and 6.7 ± 0.1 (carbamic acid hexyl ester moiety). Its solubility in water is strongly pH dependent with rather high solubility in acidic media (>50 mg/mL in 0.1 N HCl) and very poor solubility in neutral and basic media (0.003 mg/mL at pH 7.4). The solubility in water is 1.8 mg/mL (0.18%). In its neutral form it is very lipophilic (log P = 3.8, determined in different mixtures of aqueous solution and n-octanol).

75 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75.

110 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110.

150 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R150.

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimeticone 350, talc, hydroxypropylcellulose

HPMC capsule shell: Carrageenan, potassium chloride, titanium dioxide, sunset yellow FCF CI15985, indigo carmine CI73015, hypromellose, water - purified

Printing ink: Shellac, tert-butyl alcohol, isopropyl alcohol, methylated spirit - industrial, iron oxide black CI77499, water - purifed, propylene glycol.

PHARMACOLOGY

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a competitive (K_i = 4.5 nM) and reversible direct thrombin inhibitor and is the main metabolite of dabigatran etexilate in plasma.

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and *ex-vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of venous thrombosis.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as INR) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT) and Thrombin Time (TT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher dabigatran concentrations (see

Precautions, Effect on laboratory tests). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of dabigatran etexilate administration relative to time of blood sampling (see Pharmacokinetics, Absorption).

In patients undergoing elective hip replacement surgery, greater test variability with aPTT and ECT was observed. The mechanisms for this variability immediately after surgery are unclear and aPTT and ECT levels measured in the first 2-3 days following surgery should be interpreted with caution.

PHARMACOKINETICS

Absorption

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12–14 hours in elderly healthy volunteers and 14–17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 1.

Table 1: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

Glomerular filtration rate (CrCL) [mL/min]	gMean (gCV%; range) half-life [h]
>80	13.4 (25.7%; 11.0–21.6)
>50–≤80	15.3 (42.7%; 11.7–34.1)
>30–≤50	18.4 (18.5%; 13.3–23.0)
≤30	27.2 (15.3%; 21.6–35.0)

gMean – Geometric mean
gCV% - Geometric coefficient of variation

Upon administration of the dabigatran etexilate HPMC capsules together with a high fat, high caloric breakfast, the average total exposure (AUC) of dabigatran increased by 27% and the maximum exposure on average by 8.5%. The time to peak plasma concentrations was delayed by 2 hours. The relative increase of bioavailability was considered of no clinical relevance.

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5%.

The oral bioavailability was increased by 75% compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the

integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and take the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery. It is noted however that contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

Distribution

Low (34-35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60–70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Metabolism and elimination

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabelled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88–94% of the administered dose by 168 hours post dose. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods.

Special populations

<u>Renal impairment</u>

An open, parallel-group single-centre study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a

single dose of dabigatran etexilate 150 mg. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 2). Similar findings were observed in the RE-LY study (see Precautions, Renal Insufficiency and Dosage and Administration).

Table 2: Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCL (mL/min)	Increase in AUC	Increase in Cmax	$t_{1/2}$ (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

In a small number of volunteers with severe renal insufficiency (CrCL 10–30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see Dosage and Administration and Contraindications).

Elderly patients

The $AUC_{T,ss}$ and $C_{max,ss}$ in male and female elderly subjects (>65 years) were approximately 1.9 fold and 1.6 fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18-40 years of age.

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance. The effect by age on exposure to dabigatran was confirmed in the RE-LY study: Compared with subjects aged <65 years, dabigatran trough concentrations were 28% higher in subjects aged between 65 and 75 years and 68% higher in subjects aged ≥75 years. (see Precautions, Use in the elderly and Dosage and Administration).

Hepatic insufficiency

No change in dabigatran exposure was seen in 12 subjects in a phase 1 study with moderate hepatic insufficiency (Child-Pugh B) compared to 12 controls.

- *Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery:* Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes≥2 X Upper Limit Normal (ULN) were excluded in clinical trials.

- *Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:* Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥2 X ULN or hepatitis A, B or C were excluded in clinical trials.

Body weight

The dabigatran trough concentrations were about 20% lower in subjects with a body weight >100 kg compared with subjects of 50–100 kg. The dabigatran trough concentrations were about 20% higher in subjects with a body weight <50 kg compared with subjects of 50-100 kg. Comparing the extremes, <50 kg versus >100 kg, the median dabigatran trough concentrations differed by 53%. The majority (80.8%) of the subjects were in the ≥50 kg and <100 kg category with no clear difference detected.

Gender

Drug exposure in the primary VTE prevention studies was about 40% to 50% higher in female patients. In atrial fibrillation, female patients had on average 30% higher trough and post-dose concentrations. This finding had no clinical relevance.

Ethnic origin

The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

CLINICAL TRIALS

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery

In 2 large randomised, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1–4 hours of surgery followed by 150 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and once daily thereafter.

Both trials were performed in centres of countries located on 3 continents (Africa, Australia and Europe).

In the RE-MODEL trial (knee replacement) treatment was for 6–10 days and in the RE-NOVATE trial (hip replacement) for 28–35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

Enrolled patients were scheduled to have total knee or hip replacement surgery; 18 years of age or older and weighing at least 40 kg. Patients were excluded if there was a history of bleeding diathesis; coagulation disorders; major surgery or trauma (e.g. hip fracture) within the last 3 months; recent unstable cardiovascular disease or history of myocardial infarction within the last 3 months; greater than 3 attempts or traumatic placement for spinal or epidural anaesthesia; history of haemorrhagic stroke or intracranial pathology such as bleeding, neoplasm, AV malformation or aneurysm; history of VTE or pre-existing condition requiring anticoagulant therapy;

clinically relevant bleeding within the last 6 months; gastric or duodenal ulcer within the last 6 months; liver disease which was expected to have a potential impact on survival; elevated AST or ALT >2 X ULN; severe renal insufficiency (CrCl <30 mL/min); elevated creatinine which contraindicated venography; treatment within 7 days with anticoagulants – clopidogrel, ticlopidine, abciximab, aspirin >160 mg/day or NSAID with $t_{1/2}$ >12 hours or requiring these medicines during the study treatment period; intermittent pneumatic compression and electric stimulation of lower limb; pregnant or nursing women and pre-menopausal women without acceptable birth control; allergy to radio-opaque contrast media or iodine; thrombocytopenia or platelet count <100,000 cells/µL; allergy to heparins or dabigatran and dabigatran etexilate; active malignant disease or currently receiving cytostatic treatment; participated in a clinical trial in the last 30 days; leg amputee; alcohol or drug abuse and contraindications to enoxaparin.

For the knee study (RE-MODEL), the median age was 68 years for all treatment groups. The majority of patients were female in all treatment groups (64.2–68.9%). The mean BMI was also similar in all 3 treatment groups with 29.9 (dabigatran etexilate 220 mg), 30.1 (dabigatran etexilate 150 mg), and 29.8 kg/m^2 (enoxaparin), respectively.

For the hip study (RE-NOVATE), the median age was 65 years for all treatment groups. The majority of patients were female in all treatment groups (55.5–57.4%) and almost all patients were of white ethnic origin. The median BMI was 27.3 kg/m^2 in both dabigatran etexilate groups and 27.1 kg/m^2 in the enoxaparin group.

The most widely used type of anaesthesia was spinal anaesthesia. The second most frequent type of anaesthesia was general anaesthesia.

Both the knee (RE-MODEL) and the hip (RE-NOVATE) studies were non-inferiority studies. For determination of the minimal important difference against enoxaparin, the placebo-controlled studies with enoxaparin 40 mg QD were pooled and the incidences of deep vein thrombosis (DVT), total VTE and all-cause mortality for enoxaparin against placebo for each indication analysed. For the knee study (RE-MODEL), one third of the lower boundary of the 95% CI, i.e. 9.2%, was chosen to represent a rather strict and conservative estimate of the non-inferiority margin. For the hip study (RE-NOVATE), one third of the lower boundary of the 95% CI, 7.7% was chosen as the non-inferiority margin.

The results of the knee study (RE-MODEL) with respect to the primary end-point, total venous thromboembolism (VTE) including asymptomatic VTE plus all-cause mortality showed that the antithrombotic effect of both doses of dabigatran etexilate were statistically non-inferior to that of enoxaparin.

Similarly, total VTE including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again dabigatran etexilate at both once daily doses was statistically non-inferior to enoxaparin 40 mg daily.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 3 below. VTE was defined as the composite incidence of deep vein thrombosis and pulmonary embolism.

A third trial involving patients undergoing total knee replacement surgery received dabigatran etexilate 75 mg or 110 mg within 6–12 hours of surgery followed by 150 mg and 220 mg once daily thereafter for 12–15 days (RE-MOBILIZE). The comparator dosage of enoxaparin was 30 mg twice daily according to the US label. In the RE-MOBILIZE trial, non-inferiority was not established. There were no statistical differences in bleeding between the comparators.

In addition, a randomised, parallel group, double-blind, placebo-controlled phase II study, in Japanese patients where dabigatran etexilate 110 mg, 150 mg and 220 mg was administered once daily beginning the next day after elective total knee replacement surgery, was evaluated. The Japanese study showed an inverse relationship between dabigatran etexilate dose and the incidence of the primary endpoint (total VTE and all-cause mortality). The highest dabigatran etexilate dose resulted in the lowest incidence of total VTE and all-cause mortality.

In RE-MODEL and RE-NOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and Japanese placebo-controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. In Table 3, three of the trials have been grouped in to pre- and post surgery randomised trials.

Table 3: Analysis of major VTE and VTE-related mortality during the treatment period in the orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
Pre-operative randomisation studies			
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95% CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
95% CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	
Post-operative randomisation studies			
Japanese knee study			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	−5.8	−4.0	
95% CI	(−10.3, −1.3)	(−9.1, 1.1)	

Table 4 presents the combined incidences of major VTE and VTE related mortality for RE-MODEL and RE-NOVATE trials. The most frequent component of the composite endpoint was proximal DVT in all three treatment groups. Non-fatal pulmonary embolism (PE) during the treatment period in the two trials were observed in 1 patient in the dabigatran etexilate 150 mg group, 3 patients receiving enoxaparin and 5 patients receiving dabigatran etexilate 220 mg. VTE related mortality was observed for 1 patient in each of the dabigatran etexilate 220 mg and enoxaparin groups and for 4 patients in the dabigatran etexilate 150 mg group.

Table 4: Summary of primary endpoint components (N [%]) in the RE-NOVATE and RE-MODEL trials

Study	Worst event	Dabigatran 220 mg N (%)	Dabigatran 150 mg N (%)	Enoxaparin 40 mg N (%)
RE-MODEL and RE-NOVATE Knee/Hip Pivotal	FAS-major*	1415 (100.0)	1415 (100.0)	1428 (100.0)
	VTE-death	1 (0.1)	4 (0.3)	1 (0.1)
	PE	5 (0.4)	1 (0.1)	3 (0.2)
	Proximal DVT	35 (2.5)	53 (3.7)	50 (3.5)
	Major VTE/VTE mortality	41 (2.9)	58 (4.1)	54 (3.8)

* Full analysis set – major

Table 5: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

Major bleeding events (MBE) followed the International Society on Thrombosis and Haemostasis (ISTH) criteria and the EMEA guideline (including surgical wound site bleedings)

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multinational, randomised parallel group study of two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) compared to open-label warfarin in patients with non-valvular atrial fibrillation (AF) at moderate to high risk of stroke or systemic embolism. This trial used the Prospective Randomised Open label trial with Blinded Evaluation of outcomes (PROBE) design. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomised, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The population had approximately equal proportions of patients with $CHADS_2$ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular AF e.g. persistent, paroxysmal or permanent AF, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction ≤40%
- Symptomatic heart failure, ≥NYHA Class 2
- Age ≥75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension.

Patients were excluded if they had prosthetic heart valves requiring anticoagulation or with haemodynamically relevant valve disease that was expected to require surgical intervention during the course of the study; severe disabling stroke within the previous 6 months or any stroke within the previous 14 days; conditions associated with an increased risk of bleeding – major surgery in the previous month, planned surgery or intervention in the next 3 months, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery); gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated (e.g. surgery); symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder or bleeding diathesis; need for anticoagulant treatment for disorders other than atrial fibrillation; fibrinolytic agents within 48 hours of study entry; uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg); recent malignancy or radiation therapy (≤6 months) and not expected to survive 3 years; contraindication to warfarin treatment; reversible causes of atrial fibrillation (e.g. cardiac surgery, pulmonary embolism, untreated hyperthyroidism); plan to perform a pulmonary vein ablation or surgery for cure of the AF; severe renal impairment (estimated creatinine clearance ≤30 mL/min); active infective endocarditis; active liver disease, including but not limited to persistent ALT, AST, alkaline phosphatase ≥2 X ULN, known active hepatitis C, active hepatitis B, active hepatitis A; women who were pregnant, lactating or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study; anaemia (haemoglobin <100 g/L) or thrombocytopenia (platelet count <100 X 10^9/L); patients who had developed transaminase elevations upon exposure to ximelagatran; patients who had received an investigational drug in the past 30 days or were participating in another drug study; patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration.

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was vitamin K antagonist (VKA) naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomised to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50%

of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycaemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%) and proton pump inhibitors (17.8%).

For the primary endpoint, stroke and systemic embolism, no subgroups (i.e. age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin.

Based on the intent to treat population analysis, this study demonstrated that dabigatran etexilate, at a dose of 150 mg twice daily, is superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. The lower dose of 110 mg twice daily is non-inferior to warfarin (see Table 6).

Dabigatran etexilate 150 mg twice daily reduces other clinically relevant endpoints: ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage and total bleeding compared to warfarin, with similar rates of major bleeding (see Tables 7 and 16). Dabigatran etexilate 110 mg twice daily reduces the risk of intracranial haemorrhage, major bleeding and total bleeding (see Table 16). The yearly event rate for vascular death for dabigatran etexilate 150 mg twice daily was 2.28%, 110 mg twice daily was 2.43% and warfarin was 2.69%.

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects, which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.83%, warfarin 0.64%). Patients had similar baseline characteristics across the treatment groups, with respect to cardiovascular risk factors: hypertension, diabetes, prior coronary artery disease, prior MI, prior stroke, and active smoking. The baseline use of anti-platelet and antithrombotic therapies was similar across the three treatment groups. The reason for this finding is unknown.

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin. The underlying mechanism of the increased rate of GI bleeding has not been established.

Figure 1: Kaplan-Meier curve estimate of time to first stroke or systemic embolism in RE-LY

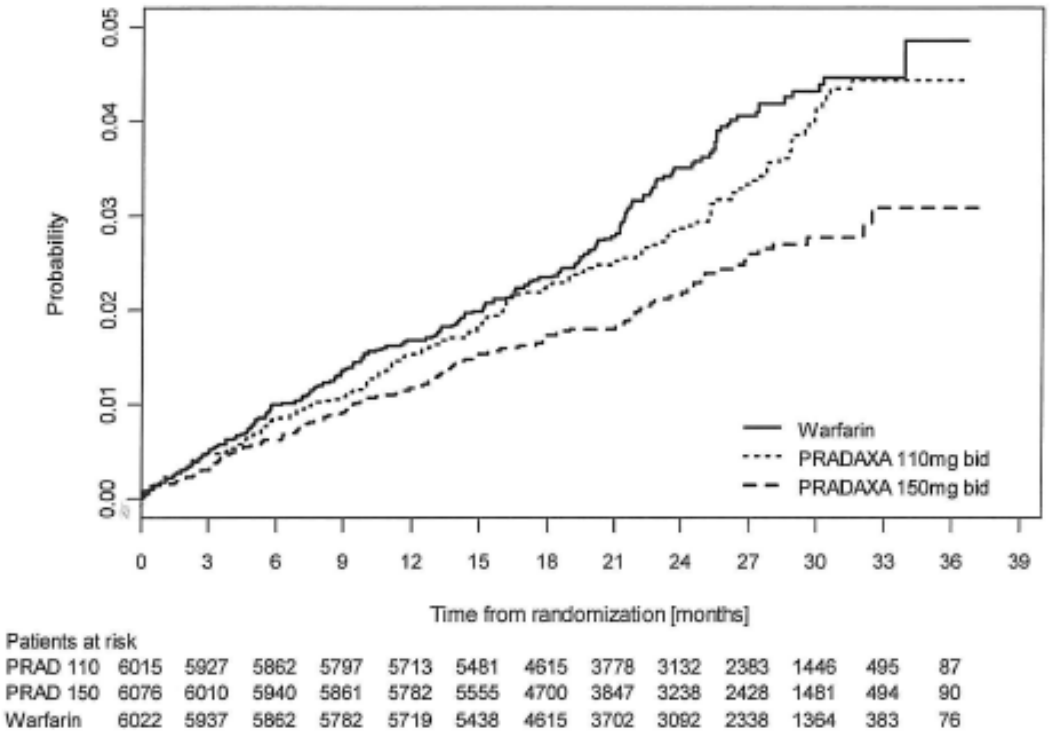


Table 6: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke and/or SEE			
Yearly event rate (%)	134 (1.11)	183 (1.54)	202 (1.71)
Hazard ratio over warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	
p-value superiority	0.0001	0.2943	
p-value noninferiority	<0.0001	<0.0001	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 7: Analysis of first occurrence of stroke, systemic embolism, ischaemic or haemorrhagic strokes during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke			
Yearly event rate (%)	122 (1.01)	171 (1.44)	186 (1.58)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
SEE			
Yearly event rate (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
Ischaemic stroke			
Yearly event rate (%)	103 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.75 (0.58, 0.97)	1.13 (0.89, 1.42)	
Haemorrhagic stroke			
Yearly event rate (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 8: Analysis of pulmonary embolism and myocardial infarction during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Pulmonary embolism			
Yearly event rate (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. warfarin (95% CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
Myocardial infarction			
Yearly event rate (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. warfarin (95% CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 9: Major bleeding events by age group during the study period in RE-LY

Age (years)	# of subjects	Dabigatran etexilate 110 mg twice daily Yearly event rate (%/ year)	Dabigatran etexilate 150 mg twice daily Yearly event rate (%/ year)	Warfarin Yearly event rate (%/ year)
<65	2981	0.81	0.88	2.43
>65 - <75	7894	2.29	2.60	3.24
≥ 75	7238	4.44	5.12	4.39

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

INDICATIONS

Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). (see Dosage and Administration section for details of treatment duration).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

CONTRAINDICATIONS

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product.
- Severe renal impairment (CrCl <30 mL/min).
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis.
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months, active peptic ulcer disease with recent bleeding.
- Indwelling spinal or epidural catheter and during the first two hours after removal (see Precautions).
- Hepatic impairment or liver disease expected to have any impact on survival.
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding.
- Gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated, e.g. by surgery.
- Conditions associated with increased risk of bleeding (see Precautions, Haemorrhagic risk, Table 10 Diseases / procedures with special haemorrhagic risks).
- Concomitant treatment with systemic ketoconazole (see Precautions).

- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.

PRECAUTIONS

Haemorrhagic risk

Dabigatran etexilate increases the risk of bleeding and can cause significant and sometimes fatal bleeding. As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL <30 mL/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Factors, such as decreased renal function (30–50 mL/min CrCL), age≥75 y ears or strong P-glycoprotein (P-gp) inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more of these factors may increase the risk of bleeding (see Dosage and Administration).

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors dronedarone, itraconazole, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Interactions with other medicines, Anticoagulants and platelet aggregation agents).

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors (as summarised in Table 10) are combined.

Table 10: Factors known to increase the haemorrhagic risk as identified in clinical studies

Factors increasing dabigatran plasma levels	• Moderate renal impairment (30-50 mL/min CrCL) • Selected P-glycoprotein-inhibitor comedication
Pharmacodynamic interactions	• Acetylsalicylic acid (ASA) • Non Steroidal Antiinflammatory Drugs (NSAID) • Clopidogrel
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastro-intestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis
Others	• Age ≥ 75 years

NSAIDs (half-lives <12 hours) given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. For the 220 mg dose of dabigatran etexilate, the bleeding incidence associated with NSAIDs is 1.5% compared to 1.4% for all patients. Concomitant use of NSAIDs with half-lives greater than 12 hours should be undertaken with caution.

The increase in yearly event rates of major bleeds by concomitant medications in the RE-LY study are shown in Table 11.

Table 11: Analysis of increase in major bleeding events by concomitant medications in RE-LY

Concomitant Medication	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
	Fold Increase in Yearly Event Rates of Major Bleeding		
Acetylsalicylic Acid (ASA)	1.91	1.95	1.93
Clopidogrel	2.06	1.92	2.02
COX-2 Inhibitors	1.63	1.60	1.81
Non Steriodal Antiinflammatory Drugs (NSAIDs)	1.53	1.36	1.49
Proton Pump Inhibitors	2.57	3.45	2.72
Verapamil	1.10	1.33	1.06
H2 blockers	2.59	2.30	2.35

Patients taking dabigatran etexilate with PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

Gastrointestinal bleeds

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin (see Adverse Effects, Table 17). The underlying mechanism of the increased rate of GI bleeding has not been established. Patients with an increased risk of bleeding (e.g. recent gastrointestinal bleeding), should be closely monitored clinically (looking for signs of bleeding or anaemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see Precautions, Effect on laboratory tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

Achlorhydria

See Interactions with other medicines, Co-medication with gastric pH-elevating agents, Pantoprazole for effect of elevated gastric pH on dabigatran bioavailability.

Myocardial Infarction

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects, which was not statistically significant (see Clinical Trials and Adverse Effects).

Interaction with P-glycoprotein inducers

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should generally be avoided (see Precautions, Interactions with other medicines).

Interaction with P-glycoprotein inhibitors

Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical surveillance (looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Precautions, Interactions with other medicines). The concomitant use of dabigatran etexilate with cyclosporin, tacrolismus or itraconazole is not recommended.

Hepatic impairment

Patients with liver disease expected to have any impact on survival or with elevated liver enzymes >2 Upper Limit Normal (ULN) were excluded in clinical trials. Therefore the use of dabigatran etexilate is contraindicated in this population. A liver function test is recommended prior to initiating treatment.

Renal Insufficiency

Pharmacokinetic studies demonstrated up to a 3 fold increase in drug exposure in patients with reduced renal function including age-related decline of renal function (see Pharmacokinetics). In patients with moderate renal impairment in RE-LY, the observed major bleeding rate was comparable between dabigatran 110 mg and 150 mg (dabigatran 110 mg 5.65%/year versus dabigatran 150 mg 5.27%/year versus warfarin 5.68%/year). Based on theoretical considerations of drug exposure a reduced dose may be considered in these patients (see Dosage and Administration). The presence of one or more factors known to increase haemorrhagic risk (see Table 10) may increase the risk of bleeding. Caution should be exercised. Close clinical surveillance is recommended.

Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL < 30 mL/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Surgery and Interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate.

<u>Preoperative Phase</u>

In advance of invasive or surgical procedures dabigatran etexilate should be stopped temporarily due to an increased risk of bleeding. If possible, dabigatran etexilate should be discontinued 1 to 2 days (Cr/CL ≥50 mL/min) or 3 to 5 days (Cr/CL <50 mL/min) before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required, consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Dabigatran etexilate is contraindicated in patients with severe renal dysfunction (CrCL <30 mL/min) but should this occur then dabigatran etexilate should be stopped at least 5 days before major surgery.

If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery/ intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in

the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture

Procedures such as spinal anaesthesia may require complete haemostatic function. In patients treated with dabigatran etexilate and who undergo spinal or epidural anaesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural haematomas that may result in long-term or permanent paralysis cannot be excluded.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged postoperative use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

Hip fracture surgery

There is no data on the use of dabigatran etexilate in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Effects on fertility

Rat fertility was unaffected by treatment with dabigatran etexilate at oral doses of up to 200 mg/kg/day (approximately 4-5 times clinical exposure, based on AUC). There was a significant decrease in the number of implantations at 70 and 200 mg/kg/day (3 and 4 times clinical exposure, respectively based on AUC), which was associated with an increase in pre-implantation loss. The effect on human fertility is unknown.

Use in pregnancy (Category C)

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. There are no adequate and well-controlled studies in pregnant women. It is not known whether dabigatran etexilate can cause foetal harm when administered to pregnant women. Dabigatran etexilate should not be used during pregnancy.

Studies in rats have shown that small amounts of dabigatran and/or its metabolites cross the placenta.

Embryofoetal development studies with oral dabigatran etexilate showed delayed ossification and general disturbances in foetal development of rats at 15 and 70 mg/kg/day (1 to 4 fold anticipated human exposure based on AUC). The delayed ossification, however, was transient, since offspring of rats treated with 15, 30 and 70 mg/kg/day during gestation and lactation showed normal body weights, normal body weight development, normal survival after birth and normal physical postnatal

development. Morphogenic effects such as cleft thoracal vertebral body (rats) and dilated cerebral ventricles (rabbits) were seen at a maternotoxic dose of 200 mg/kg/day (relative exposure of 8 and 13, respectively). Maternal toxicity in rats at >70 mg/kg/day was associated with an increased rate of resorptions, and a significant decrease in viable foetuses was seen at 200 mg/kg/day. In rats allowed to deliver, mortality due to excessive vaginal bleeding was seen at 70 mg/kg/day and in one dam at 15 mg/kg/day. An increase in post-implantation loss was seen at 70 mg/kg/day in these animals.

Use in lactation

Dabigatran and/or its metabolites were present in the milk of lactating rats given oral doses of dabigatran etexilate. The ratio of the dabigatran concentration in rat milk to that in the plasma of the mothers was 0.4. No clinical data are available. As a precaution, use of dabigatran etexilate is not recommended in women who are breast-feeding.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Paediatric use

There is no experience in children. Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Use in the elderly

The clinical studies have been conducted in a patient population with a mean age >65 years. Patients should be treated with the dose of dabigatran etexilate as recommended in the Dosage and Administration section. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Precautions, Renal Insufficiency). The risk of stroke is higher in the elderly, however the risk of bleeding increases with increasing age (see Table 9). Careful clinical observation is advised and a dosage adjustment may be necessary in elderly patients (≥75 years) due in part to age-related impairment of renal function (see Table 10). These patients should be treated with caution (see Dosage and Administration), particularly if they are also taking a drug which is a P-glycoprotein inhibitor (see Precautions, Interaction with P-glycoprotein inhibitors).

Trauma

Patients who are at increased risk of trauma accidents or surgery may have a higher risk of traumatic bleeding.

Body Weight

Limited data in patients <50 kg are available (see Pharmacokinetics, Special populations, Body weight).

Carcinogenicity

Carcinogenicity studies were performed with dabigatran etexilate in mice and rats for up to 2 years. An increased incidence of granulosa cell tumours without increased incidence of preneoplastic precursor lesions as seen in the ovaries of rats treated at 100 and 200 mg/kg/day (3 and 8 times clinical exposure, respectively based on AUC). 10 adverse event reports referring to ovarian masses or adnexal masses were observed during the RE-LY trial. The mechanism for the ovarian effects in animals is unclear and the long term effects for humans are unknown, although dabigatran etexilate is not expected to pose a carcinogenic risk to humans. No tumours were seen in rats at 30 mg/kg/day (similar to clinical exposure at the maximum recommended dose) or in studies in mice.

Genotoxicity

Dabigatran etexilate and its active moiety, dabigatran, were not mutagenic in a bacterial reverse mutation assay (Ames test) and did not induce mutations or chromosome damage in mouse lymphoma cells. Dabigatran etexilate was negative at doses of up to 2000 mg/kg in rats in the mammalian erythrocyte micronucleus test.

Excipients

The product contains the excipient sunset yellow FCF CI15985, which may cause allergic reactions.

Interactions with other medicines

Interaction studies have only been performed in adults.

<u>Anticoagulants and platelet aggregation agents</u>

The following treatments are not recommended concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see Dosage and Administration and Precautions, Haemorrhagic risk).

Enoxaparin: The switch from enoxaparin to dabigatran has been clinically tested in a phase I study. After 3 days treatment of once daily 40 mg enoxaparin s.c., dabigatran exposure was slightly lower 24 hours following the last dose of enoxaparin than after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran administration with enoxaparin pre-treatment compared to that after treatment with dabigatran

alone, which was considered to be due to the carry-over effect of enoxaparin treatment. The other dabigatran-related anti-coagulation tests, i.e., aPTT, ECT and TT, were mainly not affected after a 24 hour washout of enoxaparin.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and had no *in vitro* effects on human cytochrome P450 enzymes. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following drugs: atorvastatin (CYP3A4) and diclofenac (CYP2C9). Therefore, related medicinal product interactions are not expected with dabigatran.

Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

Diclofenac: When dabigatran etexilate was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended (see Precautions, Haemorrhagic risk section).

P-glycoprotein inhibitors/inducers

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore, co-administration of dabigatran etexilate and a P-gp inhibitor or inducer may alter the plasma dabigatran concentration. Co-medications with P-gp transporter inhibitors and inducers have been investigated.

Co-medication with P-glycoprotein inhibitors

Amiodarone: When dabigatran etexilate was coadministered with a single dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and Cmax were increased by about 60% and 50%, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180% and AUC by about 150%). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 90% and AUC by about 70%) or administration of multiple doses of verapamil (increase of C_{max} by about 60% and

AUC by about 50%). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours.

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

In the RE-LY study, patients treated concomitantly with verapamil had on average a 16% higher trough dabigatran plasma concentration and a 20% higher 2 hours post-dose dabigatran plasma concentration only, compared to patients who were not on concomitant verapamil. Accordingly, the annualised bleeding rates in patients who had used verapamil at least once together with warfarin, dabigatran etexilate 110 mg twice daily or 150 mg twice daily were 3.33%, 3.09% and 3.92%, respectively.

Clarithromycin: When clarithromycin 500 mg bid was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increase of C_{max} by about 19% and AUC by about 15%).

Ketoconazole: Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and C_{max},ss were increased on average by 53% and 56%, respectively with concomitant quinidine.

Co-medication with P-glycoprotein inducers

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by 65.5% and 67%, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

The concomitant use of PRADAXA with P-gp inducers reduces exposure to dabigatran and should generally be avoided.

Co-medication with P-glycoprotein substrates

Digoxin: When dabigatran etexilate was coadministered with digoxin, no changes on digoxin plasma levels and no clinically relevant changes on dabigatran exposure have been observed.

Co-medication with platelet inhibitors

Acetylsalicylic acid (ASA): The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation

in a phase II study in which randomised ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12% to 18% and 24% with 81 mg and 325 mg ASA, respectively.

From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin (see Precautions, Haemorrhagic risk, Table 11).

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective monotreatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 30% to 40%.

Co-medication with gastric pH-elevating agents

Pantoprazole: When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration – time curve of approximately 30% was observed. Pantoprazole and other proton-pump inhibitors (PPIs) were co-administered with dabigatran etexilate in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with dabigatran etexilate had no meaningful effect on the extent of absorption of dabigatran.

The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect was minor (fractional decrease in bioavailability not significant for antacids and 14.6% for PPIs).

In the phase III study RE-LY PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (-11%). Accordingly, PPI comedication seemed to not be associated with a higher incidence of stroke or systemic embolism, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance. An increased risk of bleeding with PPIs and H2 antagonists was observed for both the dabigatran and warfarin treatment groups (see Precautions, Haemorrhagic risk, Table 11). Patients taking PPIs or H2-blockers may be at

increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

Effect on laboratory tests

The aPTT test may be useful in determining an excess of anticoagulant activity. Dabigatran concentration exceeding 450 – 500 ng/mL would result in an aPTT of greater than 2.5 times control. An aPTT greater than 2.5 times control is suggestive of excess anticoagulation (see Pharmacology).

ADVERSE EFFECTS

The safety of dabigatran etexilate has been evaluated overall in 22,687 patients.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,596 patients were treated in 5 controlled studies with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg once daily of dabigatran etexilate, while 522 received doses less than 150 mg once daily and 1,168 received doses in excess of 220 mg once daily.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,091 patients were enrolled. Of these 6,076 were treated with 150 mg twice daily of dabigatran etexilate, while 6,015 received doses of 110 mg twice daily.

In total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding

Bleeding is the most relevant side effect of dabigatran etexilate. Depending on the indication treated, bleeding of any type or severity occurred in approximately 14% of patients treated short-term for elective hip or knee replacement surgery and in 16.5% yearly of AF patients treated long-term for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery

A total of 10,596 patients were treated in 5 controlled VTE prevention trials with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg daily of dabigatran etexilate, while 522 received doses less than 150 mg daily and 1,168 received doses in excess of 220 mg daily.

The adverse reactions that can with reasonable certainty be attributed to dabigatran, and occurred with a similar frequency with enoxaparin, are those of bleeding or signs of bleeding e.g. anaemia and wound discharge. The definition of major bleeding events (MBE) followed the International Society on Thrombosis and Haemostasis (ISTH) criteria and the EMEA guideline. According to the MedDRA coding system, bleeding events are distributed over several System Organ Classes (SOC); therefore, a summary description of major and any bleeding is given in Table 12 below.

Table 12 shows the number (%) of patients experiencing major and total bleeding event rates during the treatment period in the VTE prevention randomised clinical trials, according to dose.

Table 12: Bleeding broken down to randomisation procedure, severity and dosage of dabigatran etexilate and enoxaparin

Pre-operative randomisation trials			
	150 mg N (%)	220 mg N (%)	Enoxaparin 40 mg N (%)
Pooled data BISTRO II, RE-MODEL, RE-NOVATE trials (1160.19, 1160.25, and 1160.48)			
Treated	1866 (100.0)	1825 (100.0)	2240 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	35 (1.6)
Any bleeding	258 (13.8)	251 (13.8)	290 (12.9)
Pooled data from hip and knee studies, RE-MODEL and RE-NOVATE trials (1160.25, 1160.48)			
Treated	1866 (100.0)	1825 (100.0)	1848 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258 (13.8)	251 (13.8)	247 (13.4)
Post-operative randomised trials			
RE-MOBILIZE trial (1160.24)			
Treated	871 (100.0)	857 (100.0)	868 (100.0)
Major Bleeding	5 (0.6)	5 (0.6)	12 (1.4)
Any bleeding	72 (8.3)	74 (8.6)	84 (9.7)
Japanese knee study (1160.50)			
	150 mg N (%)	220 mg N (%)	Placebo N (%)
Treated	126 (100.0)	129 (100.0)	124 (100.0)
Major Bleeding	0 (0.0)	3 (2.3)	1 (0.8)
Any bleeding	13 (10.3)	14 (10.9)	10 (8.1)
Pooled data RE-MOBILIZE and Japanese knee study (1160.24, and 1160.50)			
	150 mg N (%)	220 mg N (%)	Enoxaparin 60 mg* N (%)
Treated	997 (100.0)	986 (100.0)	868 (100.0)
Major Bleeding	5 (0.5)	8 (0.8)	12 (1.4)
Any bleeding	85 (8.5)	88 (8.9)	84 (9.7)

*Bleeding data for Enoxaparin 60 mg is from RE-MOBILIZE study (1160.24)

Overall bleeding rates were similar between treatment groups and not significantly different.

Adverse reactions classified by System Organ Class (SOC) and preferred terms reported from any treatment group of all controlled VTE prevention studies are shown in the tables below.

Table 13: Adverse Reactions ≥1:100

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3181 (100)
Blood and lymphatic system			
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
Vascular disorders			
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Wound haemorrhage	35 (1.3)	28 (1.0)	31 (1.0)
Investigations			
Haemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)
Injury, poisoning and procedural complications			
Wound secretion	130 (4.7)	130 (4.8)	93 (3.0)
Post-procedural haematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post-procedural haemorrhage	28 (1.5)	43 (2.4)	32 (1.7)
Anaemia post-operative	37 (1.4)	54 (2.0)	56 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Post-procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Renal and urinary			
Haematuria	34 (1.2)	31 (1.2)	25 (0.8)

Table 14: Adverse Reactions >1:1000 <1:100

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3108 (100)
Vascular disorders			
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Musculoskeletal and cumulative tissue disorders			
Haemarthrosis	9 (0.3)	7 (0.3)	17 (0.5)
Blood and lymphatic system			
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Respiratory and thoracic system			
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastro-intestinal disorders			
Gastro-intestinal haemorrhage	1 (0.0)	1 (0.0)	3 (0.1)
Haemorrhoidal haemorrhage	4 (0.1)	8 (0.3)	2 (0.1)
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Skin and sub-cutaneous tissue disorders			
Ecchymosis	16 (0.6)	16 (0.6)	21 (0.7)
General disorders and administration site conditions			
Bloody discharge	2 (0.1)	6 (0.2)	6 (0.2)
Catheter site haemorrhage	2 (0.1)	1 (0.0)	6 (0.2)
Investigations			
Occult blood positive	6 (0.2)	3 (0.1)	1 (0.0)
Blood urine present	4 (0.1)	2 (0.1)	0 (0.0)
Haematocrit decrease	0 (0.0)	6 (0.2)	4 (0.1)
Injury, poisoning and procedural complications			
Incision site haemorrhage	12 (0.4)	8 (0.3)	10 (0.3)
Surgical and medical procedures			
Post-procedural drainage	11 (0.4)	13 (0.5)	16 (0.5)
Wound drainage	1 (0.0)	4 (0.1)	2 (0.1)
Hepatobiliary disorders / Investigations *			
Alaninine aminotransferase increased	18 (0.7)	7 (0.3)	28 (0.9)
Aspartate aminotransferase increased	9 (0.3)	5 (0.2)	15 (0.5)
Hepatic enzyme increased	4 (0.1)	5 (0.2)	11 (0.4)
Hepatic function abnormal / Liver function test abnormal*	6 (0.2)	10 (0.4)	7 (0.2)
Transaminases increased	0 (0.0)	2 (0.1)	1 (0.1)

* SOC pooled because of equivalence of some preferred terms

Table 15: Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase III controlled VTE prevention studies.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3108 (100)
Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Two doses (110 mg and 150 mg twice daily) of dabigatran etexilate were compared to warfarin in the RE-LY study (Randomised Evaluation of Long - term anticoagulant therapy), the Phase III trial in the prevention of thromboembolic stroke and systemic embolism for safety in more than 18,000 atrial fibrillation patients with a median duration of 20 months.

Drug Discontinuation

Over the course of the trial, the total number of patients with adverse events leading to treatment discontinuation was 19% for dabigatran etexilate 110 mg, 20.5% for dabigatran etexilate 150 mg and 15.6% for warfarin. The most frequent adverse events leading to discontinuation were gastrointestinal events.

Bleeding Definitions

In the RE-LY study, bleeding was classified as major using the following guidelines.

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in haemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:

- Fatal bleed; symptomatic intracranial bleed; reduction in haemoglobin of at least 50 grams per litre; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Bleeding

Table 16 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RE-LY study, with the yearly bleeding rate in (%). Both dabigatran etexilate doses were associated with a lower yearly event rate for life-threatening bleeds, intracranial haemorrhage and any bleeds as compared with warfarin treatment. Subjects randomised to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.80 [p=0.0026]).

In Table 16, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Within life-threatening, intracranial bleeds are a subcategory of life-threatening bleeds. Intracranial bleeds include intracerebral (haemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 16: Frequency and yearly event rate (%) of major and other bleeding events in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds*	342 (2.87)	399 (3.32)	421 (3.57)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Hazard ratio vs. warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
ICH+	27 (0.23)	38 (0.32)	90 (0.76)
Hazard ratio vs. warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	<0.0001	<0.0001	
Any bleeds#	1754 (14.74)	1993 (16.56)	2166 (18.37)
Hazard ratio vs. warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	<0.0001	0.0016	

*****Adjudicated Bleeds
+ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
Investigator-reported bleeding events

Table 17: Frequency and yearly event rate (%) of major, life-threatening and any gastrointestinal bleeding in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Major GI bleeds	134 (1.14)	186 (1.57)	125 (1.07)
Hazard ratio vs. warfarin (95% CI)	1.07 (0.84, 1.36)	1.47 (1.17, 1.85)	
GI life-threatening bleeds	67 (0.57)	94 (0.79)	57 (0.49)
Hazard ratio vs. warfarin (95% CI)	1.17 (0.82, 1.67)	1.62 (1.17, 2.26)	
Any GI bleeds	600 (5.41)	681 (6.13)	452 (4.02)
Hazard ratio vs. warfarin (95% CI)	1.35 (1.19, 1.53)	1.52 (1.35, 1.72)	

The risk of major bleeding with dabigatran etexilate 110 mg and 150 mg was consistent across all major subgroups of baseline characteristics with the exception of age. There was a higher risk of bleeding with dabigatran etexilate 150 mg in patients ≥75 years of age (hazard ratio vs. warfarin (95% CI) 1.18 (0.98, 1.43)).

GI/dyspepsia

Dabigatran etexilate subjects had the highest incidence of GI AEs (34.6%, 34.5%, and 24.0% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively). Additional GI events that were reported more frequently with dabigatran etexilate treatment included upper abdominal pain, gastritis, abdominal discomfort, gastroesophageal reflux disease, dysphagia, and flatulence (Table 18). There was no consistent dose-response relationship with respect to GI AEs.

Table 18: Number (%) of subjects with dyspepsia and gastritis-like symptoms (safety set) in RE-LY.

Preferred term/investigator term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983	6059	5998
Total with dyspepsia/gastritis	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia*	761 (12.7)	738 (12.2)	354 (5.9)
Gastritis-like symptoms#**	297 (5.0)	257 (4.2)	142 (2.4)

Percentages were calculated using total number of subjects per treatment as the denominator.
*Dyspepsia includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort
**Gastritis-like symptoms includes gastritis, GERD, oesophagitis, gastritis erosive, gastric haemorrhage, gastritis haemorrhagic, haemorrhagic erosive gastritis
Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reporting the same subject.

Liver Function Tests

In the RE-LY study, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in dabigatran etexilate vs. warfarin treated patients (Table 19).

Table 19: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Total treated	5983	6059	5998
ALT or AST > 3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST > 5xULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.

Myocardial Infarction

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.83%, warfarin 0.64%) (see Clinical Trials).

Overview of adverse events from RE-LY

The incidence of AEs was similar between subjects treated with dabigatran etexilate 110 mg twice daily and dabigatran etexilate 150 mg twice daily (78.6% and 78.3%, respectively) versus 75.9% of subjects treated with warfarin. The incidence of SAEs was similar across treatment groups. However, dabigatran etexilate subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalisation as compared to warfarin subjects.

Adverse events classified by SOC and preferred terms reported ≥ 2% from any treatment group of the RE-LY study are shown in Table 20 below. Diarrhoea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with dabigatran etexilate 110 mg and dabigatran etexilate 150 mg treatment, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively).

Table 20: AEs reported in at least 2.0% of subjects in dabigatran etexilate arms (safety set).

System organ class/ Preferred term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Infections and infestations			
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)
Urinary tract infection	242 (4.0)	252 (4.2)	316 (5.3)
Upper respiratory tract infection	266 (4.4)	262 (4.3)	297 (5.0)
Bronchitis	262 (4.4)	277 (4.6)	285 (4.8)
Pneumonia	226 (3.8)	219 (3.6)	236 (3.9)
Influenza	138 (2.3)	144 (2.4)	132 (2.2)
Sinusitis	80 (1.3)	98 (1.6)	120 (2.0)
Blood and lymphatic system disorders			
Anaemia	181 (3.0)	207 (3.4)	165 (2.8)
Metabolism and nutrition disorders			
Gout	125 (2.1)	116 (1.9)	162 (2.7)
Nervous system disorders			
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Headache	253 (4.2)	236 (3.9)	242 (4.0)
Syncope	155 (2.6)	150 (2.5)	155 (2.6)
Cardiac disorders			
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Cardiac failure congestive	196 (3.3)	187 (3.1)	210 (3.5)
Cardiac failure	169 (2.8)	171 (2.8)	201 (3.4)
Palpitations	141 (2.4)	138 (2.3)	162 (2.7)
Angina pectoris	124 (2.1)	113 (1.9)	125 (2.1)
Vascular disorders			
Hypertension	253 (4.2)	234 (3.9)	266 (4.4)
Hypotension	120 (2.0)	127 (2.1)	130 (2.2)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	498 (8.3)	526 (8.7)	551 (9.2)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Epistaxis	109 (1.8)	127 (2.1)	178 (3.0)
Dyspnoea exertional	110 (1.8)	120 (2.0)	116 (1.9)
Gastrointestinal disorders			
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Diarrhoea	355 (5.9)	367 (6.1)	328 (5.5)
Nausea	245 (4.1)	259 (4.3)	208 (3.5)
Constipation	188 (3.1)	177 (2.9)	167 (2.8)
Abdominal pain upper	177 (3.0)	170 (2.8)	80 (1.3)
Gastritis	147 (2.5)	127 (2.1)	87 (1.5)
Abdominal pain	130 (2.2)	137 (2.3)	141 (2.4)
Vomiting	132 (2.2)	124 (2.0)	117 (2.0)
Abdominal discomfort	119 (2.0)	112 (1.8)	64 (1.1)
Gastrooesophageal reflux disease	117 (2.0)	99 (1.6)	46 (0.8)
Skin and subcutaneous tissue disorders			
Rash	114 (1.9)	142 (2.3)	159 (2.7)

Musculoskeletal and connective tissue disorders			
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Pain in extremity	227 (3.8)	228 (3.8)	212 (3.5)
Osteoarthritis	129 (2.2)	140 (2.3)	142 (2.4)
Musculoskeletal pain	120 (2.0)	121 (2.0)	116 (1.9)
General disorders and administration site conditions			
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Asthenia	165 (2.8)	157 (2.6)	161 (2.7)
Chest discomfort	129 (2.2)	110 (1.8)	88 (1.5)
Injury, poisoning and procedural complications			
Fall	183 (3.1)	178 (2.9)	234 (3.9)
Contusion	149 (2.5)	152 (2.5)	197 (3.3)

Percentages were calculated using total number of subjects per treatment as the denominator.

Adverse reactions (<2%) observed with exposure to dabigatran 110 mg twice daily and 150 mg twice daily during the RELY trial are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Nervous system disorders

Uncommon: intracranial haemorrhage

Vascular disorders

Uncommon: haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders

Uncommon: haemoptysis

Gastrointestinal disorders

Uncommon: dysphagia, gastrointestinal ulcer, gastrooesophagitis

Hepatobiliary disorders

Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders

Uncommon: skin haemorrhage

Musculoskeletal and connective tissue disorders

Rare: haemarthrosis

Renal and urinary disorders

Common: urogenital haemorrhage

Uncommon: haematuria

General disorders and administration site conditions

Rare: catheter site haemorrhage, injection site haemorrhage

Injury, poisoning and procedural complications

Rare: traumatic haematoma, incision site haemorrhage

DOSAGE AND ADMINISTRATION

PRADAXA should be swallowed whole with a full glass of water, with or without food.

The capsule should not be chewed, broken, or opened as this may increase the risk of bleeding (see Pharmacokinetics, Absorption).

Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement)

The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment (30–50 mL CrCL/min) have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg once daily, taken as 2 capsules of 75 mg.

Treatment of PRADAXA should be initiated orally within 1–4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following knee replacement surgery: Treatment for a total of 10 days.

VTE prevention following hip replacement surgery: Treatment for a total of 28–35 days.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The recommended daily dose of PRADAXA is 300 mg taken orally as a 150 mg capsule twice daily.

In patients with moderate renal impairment (30–50 mL CrCL/min) a reduced dose of 220 mg given as a 110 mg capsule twice daily may be considered.

Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as a 110 mg capsule twice daily.

For patients with a potentially higher risk of major bleeding (see Precautions, Haemorrhagic risk, Table 10) a reduced dose of 220 mg given as 110 mg twice daily may be considered.

Treatment should be continued life-long.

Special patient populations

Hepatic impairment

Patients with liver disease expected to have any impact on survival or with elevated liver enzymes >2 ULN were excluded in clinical trials. Therefore the use of PRADAXA is not recommended in this population.

Renal impairment

Treatment in patients with severe renal impairment (creatinine clearance <30 mL/min) with PRADAXA is not recommended. There are no data to support use in this population.

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* After i.v. application 85% of dabigatran in plasma is cleared through the kidneys. Patients with moderate renal impairment (30–50 mL/min creatinine clearance) appear to be at higher risk of bleeding. Dosing should be reduced to 150 mg PRADAXA taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* In patients with moderate renal impairment (30–50 mL/min creatinine clearance) a reduced dose of 220 mg given as a 110 mg capsule twice daily may be considered.

Weight

No dose adjustment is necessary.

Post-surgical patients with an increased risk for bleeding

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30–50 mL/min), should be treated with caution (see Precautions and Pharmacology).

Children and adolescents

There is no experience in children and adolescents. PRADAXA is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or oral verapamil

Simultaneous initiation of treatment with PRADAXA and oral verapamil should be avoided (see Contraindications).

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who receive concomitant PRADAXA and amiodarone or quinidine (see Precautions, Interaction with other medicines).

  Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg and maintained on that dose when patients are commenced on PRADAXA whilst receiving existing oral verapamil treatment (see Contraindications, Precautions, Interaction with other medicines).

  Treatment initiation with oral verapamil should be avoided in patients following major orthopaedic surgery who are already treated with PRADAXA.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* P-gp inhibitors verapamil, amiodarone and quinidine do not require dose adjustments (see Precautions, Interactions with other medicines). Patients should be treated with a daily dose of 300 mg taken orally as a 150 mg capsule twice daily.

  The effect of individual P-gp inhibitors vary and results should not be extrapolated to other P-gp inhibitors.

  When verapamil needs to be initiated on stable dabigatran etexilate therapy or dabigatran etexilate and verapamil need to be initiated concurrently, dabigatran etexilate should be given at least 2 hours before verapamil for the first three days.

<u>Switching from Pradaxa treatment to parenteral anticoagulant</u>

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* Wait 24 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* Wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

<u>Switching from parenteral anticoagulants treatment to Pradaxa</u>

PRADAXA should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous unfractionated heparins).

<u>Switching from Vitamin K antagonists to Pradaxa</u>

The vitamin K antagonist should be stopped. PRADAXA can be given as soon as the INR is <2.0.

Switching from Pradaxa to Warfarin

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCL >50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCL 31-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCL 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCL <15 mL/min, no recommendations can be made.

Because PRADAXA can contribute to an elevated INR, the INR will better reflect warfarin's effect after PRADAXA has been stopped for at least 2 days.

Cardioversion

Patients can stay on PRADAXA while being cardioverted.

Missed dose

- *Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery:* The patient should continue with their remaining daily doses of PRADAXA at the same time the next day. Do not take a double dose to make up for missed individual doses.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* A missed PRADAXA dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Do not take a double dose to make up for missed individual doses.

OVERDOSAGE

In case of poisoning or overdose, advice should be sought from a Poisons Information Centre.

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of dabigatran etexilate is not available.

Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma.

As protein binding is low dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X may be considered. There is some experimental evidence to support the role of activated prothrombin complex concentrate and factor VIIa in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

PRESENTATION AND STORAGE CONDITIONS

Capsules 75 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75. Blister packs: 10, 30, 60 capsules. Bottle: 60 capsules.
Capsules 110mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110. Blister packs: 10, 30, 60 capsules. Bottle: 60 capsules.
Capsules 150 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R150. Blister packs: 10, 60 capsules. Bottle: 60 capsules.
Capsules (blister packs):	Store below 30°C. Protect from moisture.
Capsules (bottle):	Store below 30°C. Protect from moisture. Once opened, the bottle must be used within 30 days. Keep the bottle tightly closed.

Not all pack sizes and presentations are being distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF APPROVAL

TGA approval date: 29 April 2011

Therapeutic Goods Administration

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