Medicines Adverse Reactions Committee

Meeting date	**6 December 2018**	Agenda item	3.2.3
Title	**Dose reductions for Pradaxa (dabigatran etexilate): DVT/PE indications**		
Submitted by	Medsafe Clinical Risk Management Team	Paper type	For advice
Active constituent Pradaxa	**Medicines** Dabigatran etexilate	**Sponsors** Boehringer Ingelheim (NZ) Ltd	
International action	Following a positive CHMP opinion (25 April 2014), *Pradaxa* (dabigatran etexilate) was approved by the EMA for the treatment and prevention of DVT and/or PE with dose reduction recommendations for patients aged ≥80 years, and patients who receive concomitant verapamil. These dose reductions are similar to those approved by the EMA for the 'prevention of stroke and systemic embolism in patients with atrial fibrillation' indication. The TGA product information for *Pradaxa* (dabigatran etexilate) has also harmonised dose reduction recommendations across the 'treatment of DVT/PE' and 'prevention of stroke in patients with AF' indications. The NZ *Pradaxa* (dabigatran etexilate) datasheet has no dose reduction recommendations for the 'Treatment and prevention of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death' indications. This reflects the clinical data, as a reduced dose was not studied for this indication. In the US there are no such dose reductions.		
Previous MARC meetings	Nil		
Prescriber Update	Nil		
Schedule	Prescription medicine		
Usage data	DataPharm (beta) shows the following usage data for 2017 (the most recent year for which data is available)		

Medicine	Number of people who received a dispensing from a community pharmacy in 2017
Pradaxa cap 150mg	28506
Pradaxa cap 110mg	28254
Pradaxa cap 75mg	1286

Advice sought	**The Committee is asked to advise whether:** – The current New Zealand *Pradaxa* (dabigatran etexilate) datasheet dosage recommendations for the treatment and prevention of DVT/PE should be continued; or – The Pradaxa dose reductions for subgroups in the 'treatment and prevention of DVT and/or PE' indication should be harmonised with those for the 'prevention of stroke in patients with atrial fibrillation'.

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1.0 PURPOSE

Earlier this year, The New Zealand Formulary (NZF) asked Medsafe why the New Zealand dosing recommendations for elderly patients (75-79 years and 80+ years) taking dabigatran for the treatment or prevention of DVT/PE differ from those in Europe. After further investigation of the EU and NZ product information we found additional dosage reduction considerations/recommendations for certain sub-populations in the EU that are not currently considered/recommended in New Zealand for this indication. These sub-populations included patients with moderate renal impairment (CrCl 30-50mL/min), those taking concomitant verapamil, and those at an increased risk of bleeding. A summary table is provided in 3.1 which highlights these differences.

Medsafe is seeking MARC advice about the appropriateness of harmonising dose reductions for some special populations for the oral direct thrombin inhibitor *Pradaxa* (dabigatran) across two of its indications.

Dabigatran is approved for the following two indications where the dosage is generally 150 mg twice daily:

- prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (SPAF) – approved 1/7/2011
- treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death, as well as prevention of recurrent DVT and/or PE and related death– approved 17/7/2014.

For the SPAF indication, 110 mg twice daily is recommended in the NZ datasheet for patients aged 80 years or above, and may be considered for patients with:

- moderate renal impairment (CrCl: 30 to 50 mL/min), if the bleeding risk is high and the thromboembolic risk is low.
- patients aged 75-80 years if their thromboembolic risk is low and bleeding risk is high
- patients at risk of bleeding with one or more than one of the following risk factors: age ≥75 years, moderate renal impairment (CrCl: 30-50 mL/min), concomitant treatment with strong P-gp inhibitors, anti-platelets or previous gastro-intestinal bleed (see Annex 1: NZ datasheet).

These dose reductions are not currently recommended for the DVT/PE indication.

2.0 PREVENTION OF STROKE IN PATIENTS WITH AF

2.1 Dose reduction for sub-populations in EU, Australia, New Zealand and the US

In the EU, Australia and New Zealand, the reduced 110 mg twice daily dose can be considered for some sub-populations (for example, patients with moderate renal impairment [CrCl: 30 to 50 mL/min]).

In the US, dosage reductions for patients with moderate renal impairment (CrCl:30 to 50 mL/min) are recommended solely in patients who also have concomitant use of P-gp inhibitors; “reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole” (Annex 3: FDA approved label). During the FDA evaluation process the issue of making the 110 mg strength available was considered at some length. If the 110-mg strength was available, then loss of efficacy would be a concern in many patients who would inappropriately opt for the lower dose (Annex 2: CDER Summary Review).

2.2 SPAF indication RE-LY study

The support for the 110 mg twice daily dose for *Pradaxa* in the SPAF indication comes partly from the RE-LY study (1160.26). This was a randomised parallel-group study comparing two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily), to open-label warfarin in AF patients at moderate to high risk of stroke or systemic embolism.

3.0 TREATMENT AND PREVENTION OF DVT/PE

3.1 Summary table of the current dosage recommendations (NZ, EU, AU and US)

Table 1: Dabigatran sub-population dosing recommendations for the treatment of acute DVT/PE (aVTEt) and the prevention of recurrent DVT/PE (sVTEp) indication according to jurisdiction

Sub-population	**New Zealand**	**Europe**	**Australia**	**USA**
Normal dosing recommendations	Treatment: 150mg twice daily for up to 6 months, following treatment with a parenteral anticoagulant for at least 5 days. Prevention: 150mg twice daily. Therapy could be continued life-long depending on the individual patient risk.	Treatment and Prevention: 150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.	Treatment and Prevention: 150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.	Treatment: 150mg twice daily after 5-10 days of parenteral anticoagulation. Prevention: 150mg twice daily after previous treatment.
Renal Impairment (CrCl)				
<30mL/min (NZ, EU, AU)/ ≤30mL/min (US only) (severe renal impairment)	Contraindicated	Contraindicated	Contraindicated	Dosing recommendations cannot be provided
30-50mL/min (moderate renal impairment)	Treatment and Prevention: 150mg twice daily (i.e. no dosage reduction)	Treatment and Prevention: 110mg-150mg twice daily (i.e consideration of a lower dose)	Treatment and Prevention: 110mg-150mg twice daily (i.e consideration of a lower dose)	Treatment and Prevention 150mg twice daily (i.e. no dosage reduction)
Age (years)				
75-80	Treatment and Prevention: 150mg twice daily (i.e. no dosage	Treatment and Prevention: 110mg-150mg twice daily	Treatment and Prevention: 110mg twice daily	Treatment and Prevention 150mg twice daily (i.e. no dosage

	reduction)	(i.e consideration of a lower dose)	(i.e. lower dose)	reduction)
80+	Treatment and Prevention: 150mg twice daily (i.e. no dosage reduction)	Treatment and Prevention: 110mg twice daily (i.e. lower dose)	Treatment and Prevention: 110mg twice daily (i.e. lower dose)	Treatment and Prevention 150mg twice daily (i.e. no dosage reduction)
Use of concomitant P-gp inhibitors				
Strong P-gp inhibitors (:eg amiodarone, quinidine or verapamil)	Treatment and Prevention: 150mg twice daily (i.e. no dosage reduction)	Treatment and Prevention 110mg twice daily for patients taking concomitant verapamil.	Treatment and Prevention: 150mg twice daily (i.e. no dosage reduction)	Treatment and Prevention: For CrCl < 50mL/min with concomitant use of P-gp inhibitors – avoid co-administration.
Patients at risk of bleeding				
Single risk factors (NZ)/ increased risk (AU, EU)	Treatment and Prevention: No dosage adjustment necessary.	Treatment and prevention: 110-150mg twice daily (i.e consideration of a lower dose)	Treatment and prevention: 110-150mg twice daily (i.e consideration of a lower dose)	Label does not describe this population.
Multiple risk factors	Treatment and Prevention: Should only be given if the expected benefit outweighs bleeding risk. Limited clinical data are available.	No information provided in the product information about this sub-population.	Treatment and Prevention: Should only be given if the expected benefit outweighs bleeding risk. Limited clinical data are available.	Label does not describe this population.

3.2 DVT/PE indication RE-COVER study: PK data

The DVT/PE study programme did not include the 110 mg twice daily dosage. The study programme did, however, include the RE-COVER Study (1160.53) which had PK/PD related objectives. RE-COVER was a double-blind study in which patients with acute symptomatic DVT of the leg involving proximal veins, and/or acute symptomatic PE were randomised to receive six months of warfarin (dosed to maintain an INR of 2.0-3.0) or dabigatran 150 mg twice daily.

3.3 EMA assessment for DVT/PE indication

The EMA assessment of *Pradaxa* (dabigatran etexilate) for the DVT/PE indication resulted in dose adjustment recommendations for some sub-populations, even though such dosing had not been proposed by the Sponsor (Annex 4: EMA assessment report 2014).

The EMA assessment report, as well as the TGA's AusPAR, which followed the EMA approval of the DVT/PE indication (see section 3.4), explain the dose reductions. Both efficacy and risk of bleeding are related to dabigatran exposure. The elderly and patients with reduced renal function are at increased risk of bleeding. Extrapolating from the SPAF indication is supported by PK data showing similar dabigatran exposures for patients treated for the SPAF as well as the DVT/PE indication.

3.4 Sections from AusPAR

The following parts from the Australian Public Assessment Report (AusPAR) for dabigatran etexilate January 2016, gives TGA questions and the Sponsor's responses regarding the 110 mg twice daily dose for the DVT/PE indication. The full AusPAR is attached as Annex 6.

There are tables showing bleeding risk to be increased, especially for those older than 75 years of age, and those with creatinine clearance less than 50mL/min.

The Sponsor explains that for patients with moderate renal impairment and patients aged 75 years and over, the incidence of bleeding events was lower in DE treated patients compared with warfarin treated patients. In certain subgroups, the number of events was low.

There is a table showing the relatively similar trough dabigatran concentrations from patients in the two indications (stratified by age, renal function or verapamil co-medication at visit 4 and 9, respectively).

3.4.1 TGA questions and Sponsor comments regarding dose reduction to 110 mg twice daily for certain sub-populations

The sponsor is requested to provide a robust justification for each of the special populations (moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding) for why a dose reduction has not been proposed and why therefore the proposed dosing advice differs from that for the stroke prevention indication and differs from that in Europe for this new indication. In the response please include a discussion of the similarities or differences in dabigatran concentrations between stroke prevention in AF patients and the proposed DVT /PE patients for each of the special populations.

There has been a consistent relationship observed between DEs PK and PD in all populations studied, in human volunteers and in patients with different disease entities. Additionally, there has been a consistent relationship between dabigatran plasma levels (exposure and/or PK) and the occurrence of centrally adjudicated and investigator reported clinical safety (bleeding) and efficacy (strokes and systemic embolic events). The probability of bleeding events increases with increasing dabigatran plasma levels, while the occurrence of efficacy events decreases with increasing dabigatran plasma levels. Thus, as with all anticoagulants, improved efficacy can be obtained at the cost of increased bleeding risk. It is important to note that the consequences of bleeding and the occurrence and sequelae of PEs and/or VTEs differ among patients with different characteristics (age, renal function, concomitant illnesses, frailty, and so on). In general, patients with NVAF have more concomitant medical illnesses and take more drugs with an impact on bleeding (for example acetylsalicylic acid, anti-platelet agents, NSAIDs, verapamil, amiodarone, dronedarone, etcetera) than those treated for VTEs and/or their prevention. As such, NVAF patients have worse outcomes when bleeding occurs.

Given these known differences between NVAF and VTE patients, subgroup analyses of multiple factors known to impact clinical outcomes were conducted in the VTE populations studied in this development program. Factors analysed included renal impairment, age, previous gastrointestinal bleeds, and intake of aspirin, NSAIDs, P-gp inhibitors or SSRIs. Each factor was analysed as a single risk factor and selected combinations of key risk factors, specifically renal impairment and old age, where sample sizes were of potentially acceptable size were also analysed. Since there were relatively few MBEs on dabigatran, the safety profile assessment in the VTE indications primarily utilised the pool of all bleeding categories (MBEs, MBE/CRBEs, and any bleeds).

Overall, and in most subgroups, the incidence of centrally adjudicated MBEs, MBE/CRBEs, and any bleeding events was lower in DE treated patients compared with warfarin treated patients. In cases where bleeding was not lower on DE than warfarin, there were either very few patients in that subgroup, or the number of events differing between the groups was too small to make valid conclusions regarding potential differences.

The data from this VTE development program supports the recommendations made by the sponsor for the use of the 150 mg twice daily regimen for the overall population and for subgroups of patients with each of the individually analysed risk factors. Therefore, these data support a recommendation of no dose adjustment for any subgroup of patients with single risk factor receiving DE for acute VTE treatment or secondary prevention of recurrent VTE.

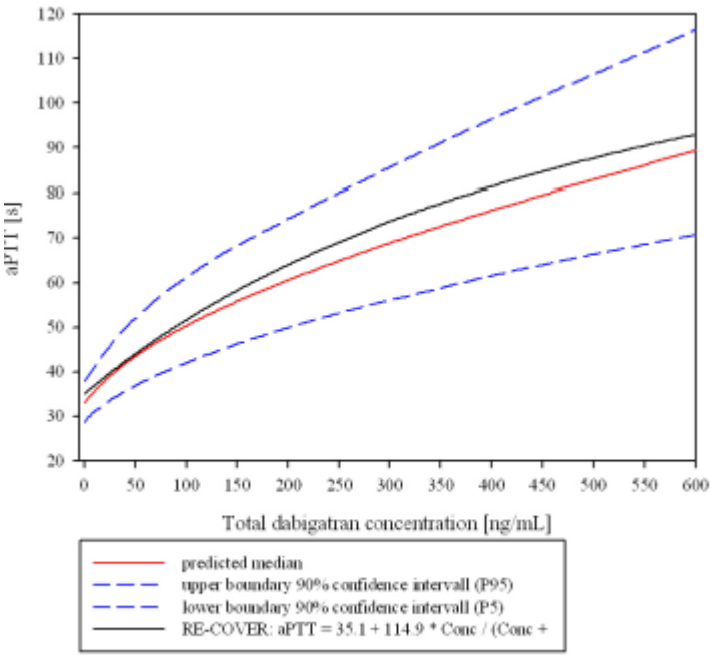
Data for patients with renal impairment, using various age categorisations and for the combination of varying degrees of renal impairment combined with age categorisations are provided below.

However, the sponsor acknowledges that in certain subgroups the number of events is small and a firm conclusion cannot be made. Therefore the sponsor agrees to harmonise the recommended dosage for the VTE indication and the SPAF indication. Please note, that the arguments and the data presented by the sponsor are identical to what has been submitted to EMA.

PK/PD data

As depicted in Figure 1, the relationship between total dabigatran concentration and the PD marker aPTT was highly comparable between data derived from Study 1160.53 (RE-COVER) with an analysis using pooled data from atrial fibrillation patients (Study 1160.20 PETRO), orthopaedic surgery patients (Study 1160.11, BISTRO I) and healthy volunteers (Study 1160.61).

Figure 1. PK/PD (aPTT) relationship comparing data from Study 1160.53 (RE-COVER) with pooled data from studies in patients with atrial fibrillation, orthopaedic surgery (Studies 1160.20 and 1160.11) and healthy volunteers (Study 1160.61).



Source data: BI Trial 1160.53 RE-COVER (U09-1400-01) Figure 11.5.4: 1
Dansirikul C et al., Thromb Haemost. 2012 Apr;107(4):775-85. Epub 2012 Mar 8.

The red and black lines show the predicted median dabigatran concentration - aPTT relationship for patients with atrial fibrillation (from PETRO, 1160.20) and VTE (from RECOVER, 1160.53), respectively. The blue hatched line shows the 95% confidence interval from the pooled analysis.

The dose of 150 mg twice daily was, therefore, consistently chosen for both clinical development programs, VTE and SPAF, as this dose was expected to provide the optimum risk/benefit profile.

With respect to subpopulations at a potentially higher risk of bleeding, the database in VTE patients is generally substantially smaller than the NVAF (RE-LY) database. This is especially true for PK datasets since, in the whole VTE program, trough plasma concentrations were only measured in Study 1160.53 (RE-COVER). However, the PK effects of age and renal impairment were very consistent across patient groups (see Table 10 above) especially when the absolute values in the age subgroups of ≥ 75 or 65 to < 75 and CrCl 30 to < 50 are compared across populations.

According to the recent exposure-response (MBE) analyses of Study 1160.53 (RE-COVER) data in VTE patients, the PK effect by age would theoretically result in a probability of MBE of 1.91% for age ≥ 80. This would still be below the overall average MBE frequency of 2.0% observed in Study 1160.53 (RE-COVER) for warfarin treated patients.

In the case of moderate renal impaired patients (CrCl 30 to < 50 mL/min), in the worst case (trough concentration = 185 ng/mL) the predicted probability of MBE would be 2.29%.

For patients ≥ 80 years or patients with moderate renal impairment, it is unclear how much of the beneficial clinical effect could be preserved with a dose of 110 mg as no clear exposure efficacy relationship could be established for VTE patients.

With respect to MBE, reduction of the dose from 150 to 110 mg twice daily assuming dose proportionality and applying the exposure MBE model would lead to a reduction in the probability of MBE from 2.29% to 1.73% and 1.91% to 1.45% for patients with CrCl 30 to < 50 mL/min and patients aged ≥ 80 years, respectively.

Clinical outcome data

Efficacy

The analyses of efficacy in subgroups were performed for the primary endpoint VTE and VTE related deaths and for the secondary endpoint of PE. Subgroups were analysed based on categories of age; gender; race; ethnicity; geographical region; BMI; smoking history; creatinine clearance; active cancer at any time; prior VTE (before the index event); thrombophilia; idiopathic VTE; history of bleeding; history of venous insufficiency; history of coronary artery disease; history of myocardial infarction; history of diabetes mellitus; use of concomitant ASA, P-gp inhibitors, NSAIDS, or anticoagulants; asymptomatic PE at baseline; symptomatic PE as index event; open label parenteral therapy for index event; and time since index event. No clinically important subgroup-by-treatment interactions were detected. Data on patients with renal impairment and age are included in the text.

Safety (bleeding)

Subgroup of patients with impaired renal function

Table 10 shows data from patients with normal and impaired renal function for both treatment groups from pooled aVTEt Studies 1160.53/1160.46 and Study 1160.47. Of note, patients with renal function less than 30 mL/min were to be excluded from participation in these VTE trials as for all other DE studies. Administration of DE to patients with CrCl < 30mL/min is contraindicated. In both the DE and warfarin treatment groups, the rates of MBE, MBE/CRBE and any bleeds increased with declining renal function. In almost all comparisons across bleeding categories (MBE, MBE/CRBE and any bleeds) and declining renal function of DE treated patient versus vitamin K antagonist (VKA) treated patients, there were less bleeds within the DE treatment group. The only exception is the MBE rate of DE patients with 30 to < 50mL/min being slightly higher (5.7%) compared with VKA patients (4.4%) but for MBE/CRBE or any bleeds the rates with DE were similar or less (11.3%/19.8%) compared with VKA (10.5%/25.4%), respectively.

Table 10. Summary of bleeding events (MBEs, MBEs/CRBEs, and any bleeding) by creatinine clearance category in the pivotal aVTEt and sVTEp studies; treated set.

Creatinine clearance categories, n/N (%)*	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	1/12 (8.3)	0/11 (0)	NC
30 to <50 mL/min	6/114 (5.3)	5/123 (4.1)	1.31 (0.40, 4.31)
50 to <80 mL/min	14/538 (2.6)	23/562 (4.1)	0.63 (0.33, 1.23)
≥80 mL/min	16/1861 (0.9)	23/1837 (1.3)	0.69 (0.36, 1.30)
Pooled aVTEt studies from start of double-dummy treatment			
<30 mL/min	0/8 (0)	0/10 (0)	NC
30 to <50 mL/min	6/106 (5.7)	5/114 (4.4)	1.32 (0.40, 4.31)
50 to <80 mL/min	9/504 (1.8)	16/536 (3.0)	0.58 (0.26, 1.31)
≥80 mL/min	9/1811 (0.5)	19/1783 (1.1)	0.47 (0.21, 1.03)
sVTEp Study 1160.47	**DE**	**W**	
<30 mL/min	0/0	0/4 (0)	--
30 to <50 mL/min	2/59 (3.4)	3/45 (6.7)	0.51 (0.09, 3.09)
50 to <80 mL/min	3/328 (0.9)	8/289 (2.8)	0.32 (0.09, 1.21)
≥80 mL/min	8/1031 (0.8)	14/1072 (1.3)	0.60 (0.25, 1.42)
MBEs/CRBEs			
Pooled aVTEt studies	DE	W	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	2/12 (16.7)	1/11 (9.1)	1.99 (0.17, 23.58)
30 to <50 mL/min	13/114 (11.4)	13/123(10.6)	1.11 (0.52, 2.40)
50 to <80 mL/min	49/538 (9.1)	79/562 (14.1)	0.63 (0.44, 0.90)
≥80 mL/min	71/1861 (3.8)	123/1837(6.7)	0.56 (0.42, 0.75)
Pooled aVTEt studies from start of double dummy treatment			
<30 mL/min	1/8 (12.5)	0/10 (0)	NC
30 to <50 mL/min	12/106 (11.3)	12/114 (10.5)	1.10 (0.49, 2.45)
50 to <80 mL/min	36/504 (7.1)	66/536 (12.3)	0.55 (0.36, 0.82)
≥80 mL/min	59/1811 (3.3)	110/1783 (6.2)	0.52 (0.38, 0.71)
sVTEp Study 1160.47	DE	W	
<30 mL/min	0/0 (0.0)	0/4 (0.0)	NC-
30 to <50 mL/min	3/59 (5.1)	5/45 (11.1)	0.46 (1.11, 1.91)
50 to <80 mL/min	23/328 (7.0)	33/289 (11.4)	0.60 (0.35, 1.02)
≥80 mL/min	54/1031 (5.2)	107/1072 (10.0)	0.52 (0.37, 0.72)
Any bleeding			
Pooled aVTEt studies	DE	W	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	3/12 (25.0)	3/11 (27.3)	1.07 (0.21, 5.50)
30 to <50 mL/min	25/114 (21.9)	34/123(27.6)	0.79 (0.47, 1.32)
50 to <80 mL/min	114/538 (21.2)	145/562 (25.8)	0.80 (0.62, 1.02)
≥80 mL/min	266/1861 (14.3)	380/1837 (20.7)	0.66 (0.57, 0.77)
Pooled aVTEt studies from start of double-dummy treatment			
<30 mL/min	2/8 (25.0)	2/10 (20.0)	1.47 (0.21, 10.47)
30 to <50 mL/min	21/106 (19.8)	29/114 (25.4)	0.79 (0.45, 1.38)
50 to <80 mL/min	97/504 (19.2)	125/536 (23.3)	0.78 (0.60, 1.02)
≥80 mL/min	231/1811 (12.8)	342/1783 (19.2)	0.64 (0.54, 0.75)
sVTEp Study 1160.47	DE	W	
<30 mL/min	0/0 (0)	1/4 (25.0)	--
30 to <50 mL/min	16/59 (27.1)	15/45 (33.3)	0.87 (0.43, 1.78)
50 to <80 mL/min	67/328 (20.4)	79/289 (27.3)	0.70 (0.51, 0.97)
≥80 mL/min	194/1031 (18.8)	275/1072 (25.7)	0.70 (0.58, 0.84)

* In the VTE studies, patients with CrCl < 30 mL/min were not enrolled.

The efficacy of DE 150 mg twice daily appeared favourable in this population, with no endpoint event in 114 patients, while in warfarin treated patients with moderate renal impairment, 5/123 (41%) had VTE or VTE related death. The incidence in DE patients with CrCl ≥ 80 mL/min was 58/1,860 (3.1%).

Subgroup of elderly patients

Table 11 shows data from patients stratified by age for both treatment groups from pooled aVTEt Studies 1160.53/1160.46 and Study 1160.47. For both treatment groups, the bleeding rates in all bleeding categories generally increased with increasing age. Bleeding rates in the DE group were consistently lower across age groups and bleeding categories compared to VKA patients. The only exceptions with the aVTEt studies with groups of patients > 75 years of age with similar MBE bleeding rates (DE: 3.5%/VKA :3.8%) and patients > 80 years with one major bleed in excess in the DE group (DE3.3% versus VKA 2.5%); and in study 1160.47 the patient group of 65 to 75 years with more MBEs or MBE/CRBE with DE (2.7%, 10%) compared with VKA (1.0%, 7,6%), respectively.

Table 11. Bleeding events (MBEs, MBEs/CRBEs and any bleeding) by age categories in the pivotal aVTEt and sVTEp studies; treated set.

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies, from start of any treatment			
<65 years	14/1771 (0.8)	24/1746 (1.4)	0.57 (0.30, 1.11)
65 to 75 years	12/529 (2.3)	15/532 (2.8)	0.76 (0.36, 1.64)
>75 years	11/253 (4.3)	12/276 (4.3)	1.03 (0.45, 2.33)
≥80 years	6/135 (4.4)	3/125 (2.4)	1.99 (0.50, 7.95)
Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	11/1722 (0.6)	19/1685 (1.1)	0.57 (0.27, 1.20)
65 to 75 years	5/503 (1.0)	11/515 (2.1)	0.43 (0.15, 1.24)
>75 years	8/231 (3.5)	10/262 (3.8)	0.90 (0.35, 2.28)
≥80 years	4/122 (3.3)	3/121 (2.5)	1.31 (0.29, 5.86)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	3/987 (0.3)	14/1019 (1.4)	0.22 (0.06, 0.78)
65 to 75 years	9/329 (2.7)	3/307 (1.0)	2.70 (0.73, 9.96)
>75 years	1/114 (0.9)	8/100 (8.0)	0.10 (0.01, 0.82)
≥80 years	0/52 (0)	4/47 (8.5)	--
MDEs/CRDEs			
Pooled aVTEt studies, from start of any treatment			
<65 years	65/1771 (3.7)	117/1746 (6.7)	0.54 (0.40, 0.73)
65 to 75 years	42/529 (7.9)	63/532 (11.8)	0.66 (0.44, 0.97
>75 years	29/253 (11.5)	37/276 (13.4)	0.88 (0.54, 1.43)
≥80 years	16/135 (11.9)	17/125 (13.6)	0.95 (0.48, 1.88)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	58/1722 (3.4)	102/1685 (6.1)	0.55 (0.40, 0.76)
65 to 75 years	29/503 (5.8)	54/515 (10.5)	0.52 (0.33, 0.82)
>75 years	22/231 (9.5)	33/262 (12.6)	0.74 (0.43, 1.26)
≥80 years	11/122 (9.0)	16/121 (13.2)	0.69 (0.32, 1.48)
sVTEp Study 1160.47	DE	W	
<65 years	40/987 (4.1)	101/1019 (9.9)	0.40 (0.28, 0.58)
65 to 75 years	33/329 (10.0)	23/307 (7.5)	1.35 (0.79, 2.30)
>75 years	7/114 (6.1)	21/100 (21.0)	0.28 (0.12, 0.65)
≥80 years	4/52 (7.7)	10/47 (21.3)	0.39 (0.12, 1.27)
Any bleeding			
Pooled aVTEt studies, from start of any treatment			
<65 years	256/1771 (14.5)	363/1746 (20.8)	0.66 (0.56, 0.78)
65 to 75 years	100/529 (18.9)	133/532 (25.0)	0.73 (0.56, 0.95)
>75 years	55/253 (21.7)	71/276 (25.7)	0.87 (0.61, 1.24)
≥80 years	33/135 (24.4)	33/125 (26.4)	0.99 (0.61, 1.60)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	229/1722 (13.3)	324/1685 (19.2)	0.66 (0.56, 0.78)
65 to 75 years	81/503 (16.1)	115/515 (22.3)	0.68 (0.51, 0.91)
>75 years	44/231 (19.0)	64/262 (24.4)	0.76 (0.52, 1.12)
≥80 years	25/122 (20.5)	31/121 (25.6)	0.79 (0.47, 1.34)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	176/987 (17.8)	261/1019 (25.6)	0.67 (0.55, 0.81)
65 to 75 years	70/329 (21.3)	75/307 (24.4)	0.84 (0.60, 1.16)
>75 years	32/114 (28.1)	37/100 (37.0)	0.74 (0.46, 1.19)
≥80 years	13/52 (25.0)	18/47 (38.3)	0.66 (0.32, 1.35)

In contrast, DE at a dose of 150 mg twice daily demonstrated favourable efficacy in this patient population. For the primary endpoint VTE and VTE related death the frequency was 0.7%, 4.0% and 2.8% in DE patients ≥ 80 years and DE patients < 80 years, respectively.

Combination of risk factors

The only meaningful subgroup of patients with more than one risk factor constitutes a group of patients ≥ 75 years of age combined with moderately reduced renal function (n = 76 patients on DE and n = 83 patients on warfarin). A new analysis for bleeding is shown in Table 12. Numerically more bleeds were recorded in DE treated patients for MBE and MBE/CRBE but less any bleeds compared to VKA treated patients. The results should be interpreted with caution as the sample size in this group is too small to form conclusions.

Table 12. Analysis of bleeding events in elderly patients with moderately reduced renal function.

Table 9.3.1.1 Frequency of centrally adjudicated MBE by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	MBE [n (%)]	20 (0.8)	37 (1.6)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	MBE [n (%)]	4 (5.3)	3 (3.6)

Table 9.3.3.1 Frequency of centrally adjudicated MBE or CRBE by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	MBE or CRBE [n (%)]	100 (4.2)	181 (7.6)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	MBE or CRBE [n (%)]	9 (11.8)	8 (9.6)

Table 9.3.2.1 Frequency of centrally adjudicated any bleeding by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	Any bleeding [n (%)]	339 (14.2)	482 (20.3)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	Any bleeding [n (%)]	15 (19.7)	21 (25.3)

Data have been presented evaluating the primary efficacy and multiple bleeding outcomes, including the primary bleeding outcome, for multiple subgroups of interest. Data demonstrating a consistent relationship for VTE patients between DE PK and PD was also presented. Data for age and renal impairment have been included in the text. In general, no risk factor identified a subgroup for which DE had neither any substantial increase in bleeding when compared to warfarin nor any loss of efficacy. For the subgroup combining older age and renal impairment the findings were similar. The risk of bleeding and its consequences was less severe in patients included in the VTE clinical development program compared to the NVAF development program, as there were very few bleeding events on DE and warfarin in the VTE development program. The totality of these data, support in general a recommendation to utilise only one dosing regimen, 150 mg twice daily for all patient subgroups for this treatment indication.

However as stated above, the sponsor acknowledges that in certain subgroups the number of events is small and a firm conclusion cannot be made. Therefore, the sponsor agrees to harmonise the recommended dosage for the VTE indication and the SPAF indication.

3.4.2 Further TGA questions and Sponsor comments regarding 110 mg twice daily dose reduction

The sponsor is requested to fully explain the rationale and predicted dabigatran concentrations in each of the patient subgroups who are proposed for the 110 mg twice daily dose compared with patients exposed to 150 mg twice daily for the VTE indications, given the lack of clinical data at the 110 mg twice daily dose from the submitted studies.

Sponsor's response

The sponsor considers the clinical data from the 4 pivotal trials with a total of 8,197 randomised patients sufficiently supportive for the recommendation that the 150 mg twice daily dosing is suitable for all patients in the VTE indication. However, the sponsor acknowledges that in certain subgroups, the number of events is small and a firm conclusion cannot be made, and therefore has agreed to harmonise the posology for the VTE indication and the SPAF indication based on the following argumentation.

The results of the 3 pivotal studies (DE versus. warfarin) demonstrate that DE given at a dose of 150 mg twice daily was non inferior to warfarin for the treatment of aVTEt and for the prevention of recurrent VTE events in a broad spectrum of low to high risk patients. In the fourth pivotal study, DE was superior to placebo in preventing recurrent VTEs in those thought to be at equipoise for the need for continuing anticoagulant therapy. There were no significant interactions between treatment and subgroup results, further supporting the use of 150 mg twice daily dose of DE in all patient subgroups.

The incidence of all categories of MBEs (MBEs, adjudicated MBEs with a fatal outcome, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, and intracranial MBEs) as well as life threatening bleeding events, any bleeding events (including MBEs, CRBEs, and nuisance/trivial bleeding), and discontinuation of study drug due to bleeding was consistently lower in DE 150 mg twice daily patients compared to warfarin for studies of short (6 months in the aVTEt studies) and longer duration (up to 36 months in sVTEp Study 1160.47). Fewer DE patients than warfarin patients discontinued study drug due to all severities of bleeding. In the overall results, and in most of the subgroups analyses including patients with moderate renal impairment and patients aged 75 years, the incidence of centrally adjudicated MBEs, MBE/CRBEs, and any bleeding events was lower in DE treated patients compared with warfarin treated patients.

From the PK/PD analyses of both RE-LY and RE-COVER studies, the pharmacodynamic response (anticoagulation), as well as therapeutic response (bleeding and antithrombotic efficiency), are closely related to dabigatran exposure. Furthermore, consistency could be demonstrated in the PK (Table 23), PK/PD and the relationship between exposure and clinical safety (major bleeding events) between the NVAF and VTE patient population, although no dedicated exposure to efficacy relationship could be demonstrated for the VTE patient population.

Table 23. Steady state total dabigatran trough concentrations (geometric Mean and geometric CV) in VTE (1160.53, RE-COVER) and AF patients (1160.26, RE-LY) treated with 150 mg twice daily by age, renal function (CrCl) and verapamil co-medication. For Study 1160.53, both measurements at visit 4 (1) and visit 9 (2) are presented. The age category in 1160.53/RECOVER was 50 to < 65 while in RE-LY, the equivalent category was < 65.

	RE-COVER		RE-LY	
	N	Dabigatran trough conc. (ng/mL)	N	Dabigatran trough conc. (ng/mL)
AGE (years)		gMean (gCV%)		gMean (gCV%)
≥75	84[1] 66[2]	121 (74.6) 139 (88.4)	1616	114 (76.9)
≥65-<75	186 159	70.6 (83.7) 77.0 (69.4)	1860	84.6 (73.9)
<65			746	67.1 (90.6)
50-<65	263 230	58.8 (76.8) 56.9 (81.2)		
CRCL (mL/min)	N	gMean (gCV%)	N	gMean (gCV%)
30-<50	32 23	170 (83.6) 185 (61.3)	761	144 (80.6)
50-<80	181 170	85.8 (65.2) 91.7 (84.8)	1969	95.2 (73.0)
≥80	627 544	50.5 (73.0) 49.4 (77.6)	1347	64.8 (71.6)
Verapamil Co-med	N	gMean (gCV%)	N	gMean (gCV%)
+Verapamil	14 11	82.4 (170) 97.3 (107)	322	110 (79.3)
-Verapamil	836 735	59.4 (80.1) 59.1 (89.3)	5940	90.6 (82.3)

[1] and [2] trough concentration at visit 4 and 9, respectively.

Therefore, in the subpopulations defined by the current NVAF label, exposure with 110 mg twice daily is expected to stay within or even above the average exposure in the majority of VTE patients receiving 150 mg twice daily. Hence, it can be assumed that most of the anticoagulation efficacy will be preserved with this VTE population with a higher risk of bleeding is treated with DE 110 mg twice daily.

In conclusion, the sponsor considers the existing data on the 110 mg twice daily dose from RE-LY together with the high consistency between the patient populations in terms of the PK, PK/PD and exposure-response results seen in the TR-LY and RE-COVER studies, as sufficient evidence to consider the 110 mg twice daily dose for the same sub-populations in VTE as in NVAF. However, the sponsor will continue to perform PK analysis in the ongoing and upcoming clinical trials where relevant, to check the consistency of the results between studies on the correlation of PK data to MBE events and ischaemic events and provide the results of these analyses within the upcoming PSURs.

For dosing in the elderly, if a reduced dose of 110 mg twice daily is proposed for the VTE indications, please explain the rationale supporting the age cut-off of ≥ 75 versus ≥ 80 years. Are there further analyses or simulations to support either age cut-off?

Sponsor's response

Please see also the response to question 6 above with detailed information about dabigatran plasma concentration across different patient population stratified by age, renal function and intake of P-gp inhibitors. The sponsor agrees to the proposal by TGA to align the dosages between the VTE indication and SPAF. This clearly has the advantage that a dosing error in the VTE indication and SPAF

can be prevented. An evaluation with an age cut-off ≥ 80 years has the limitation of a small sample size in this age group which does not allow for firm conclusions with n = 122 patients in the DE group and n = 121 patients in the warfarin group. Table 24 and 25 display the frequencies of MBE stratified by < or ≥ 75 years and < or ≥ 80 years. The MBE frequencies in the DE groups appear to be consistent if < 75 years (0.7%) is compared with < 80 years (0.9%) and ≥ 75 (3.0%) is compared with ≥ 80 years (3.3%). When the latter groups are compared with the warfarin groups a small numerical but not statistical difference in favour of warfarin can be seen.

Table 24. Frequency of centrally adjudicated MBE by age group (< 75, ≥ 75 years) for acute VTE treatment studies – treated set.

Age		DE	W
<75 years	Patients [N (%)]	2191 (100.0)	2165 (100.0)
	MBE [n (%)]	16 (0.7)	29 (1.3)
>=75 years	Patients [N (%)]	265 (100.0)	297 (100.0)
	MBE [n (%)]	8 (3.0)	11 (3.7)

Table 4.13.5.1.3.1.1 Frequency of centrally adjudicated MBE by age group (< 80, >=80 years) for acute VTE treatment studies - treated set

Table 25. Frequency of centrally adjudicated MBE by age group (<80, ≥80 years) for acute VTE treatment studies - treated set.

Age		DE	W
<80 years	Patients [N (%)]	2334 (100.0)	2341 (100.0)
	MBE [n (%)]	20 (0.9)	37 (1.6)
>=80 years	Patients [N (%)]	122 (100.0)	121 (100.0)
	MBE [n (%)]	4 (3.3)	3 (2.5)

4.0 DISCUSSION

The current New Zealand datasheet recommendation for dabigatran is 150 mg twice daily for the DVT/PE indication. This reflects dabigatran use in the studies supporting this indication.

Safety of dabigatran for the treatment and prevention of DVT/PE may be improved by dose reduction to 110 mg dabigatran twice daily in some sub-populations. However, efficacy of the reduced dose in the DVT/PE population is theoretical and has not been studied.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The current New Zealand Pradaxa (dabigatran etexilate) datasheet dosage recommendations for the treatment and prevention of DVT/PE should be continued; or
- The Pradaxa dose reductions for subgroups in the 'treatment and prevention of DVT and/or PE' indication should be harmonised with those for the 'prevention of stroke in patients with atrial fibrillation'.

6.0 GLOSSARY

aVTEt	acute venous thromboembolic event treatment
CRBE	clinically relevant (non-major) bleeding event
DE	dabigatran etexilate
DVT	deep vein thrombosis (of the leg)
ECT	ecarin clotting time
gCV	geometric coefficient of variation
gMean	geometric mean
MBE	major bleeding event
NVAF	non-valvular atrial fibrillation
PE	pulmonary embolism
SEE	systemic Embolic Event
SPAF	stoke prevention in atrial fibrillation
VKA	vitamin K antagonist
VTE	venous thromboembolism (DVT/PE)
W	warfarin

7.0 ANNEXES

1. New Zealand Pradaxa datasheet
2. CDER Summary Review
3. FDA approved label
4. EMA assessment report Pradaxa 25 April 2014 EMA/CHMP/230414/2014
5. EMA approved SPC downloaded 20 July 2018
6. AusPAR (Australian Public Assessment Report) for dabigatran etexilate January 2016.
7. TGA approved PI downloaded 18 July 2018