23 August 2012

EMA/556143/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pradaxa

dabigatran etexilate

Procedure No.: EMEA/H/C/000829/II/0031

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 29 March 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Pradaxa	dabigatran etexilate	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.2, 4.3, 4.4, 4.5, 4.9 (all 3 strengths) and 5.1 (110 and 150 mg strengths) of the SmPC in order to minimise the risk related to bleeding events in patients treated with Pradaxa following the AR for FUM 029. The Package Leaflet was proposed to be updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Jens Heisterberg

2. Scientific discussion

2.1. Introduction

Pradaxa 75 and 110 mg hard capsules were authorised in the EU on 18 March 2008 for primary prevention of venous thromboembolic events (primary VTE prevention) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. On 1 August 2011 the extension of the indication to: prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) was approved. In the context of this variation a new strength of 150 mg hard capsule was registered as a line extension to the marketing authorisation.

In October 2011 the CHMP finalised the variation II/22 for Pradaxa following the assessment of fatal bleeding events related to the use of Pradaxa. The database lock point (DBL) used for this variation was 23 August 2011. It was concluded that a specific statement should be included in section 4.2 of the Pradaxa SmPC that an estimation of kidney function is mandatory in all patients, prior to initiation of Pradaxa treatment, also under certain circumstances during treatment.

In December 2011 the CHMP requested the MAH to provide the tabulated description of all fatal bleeding cases associated with Pradaxa use, in light of the significant increase in the number of fatal bleeding events associated with the use of Pradaxa since the completion of variation Pradaxa EMEA/H/C/000829/II/0022. The MAH was asked to provide an in-depth analysis and discussion of whether the occurrence of fatal bleedings events in the real-world setting observed so far is higher than expected from the RE-LY study results. In addition, a recent meta-analysis by Ken Uchino and Adrian V Hernandez was published (Circulation. 2011; 124: A15500) where it was suggested that Pradaxa is associated with an increased risk of myocardial infarction/acute coronary syndrome. The MAH was requested to provide its view on the meta-analysis. The assessment of these responses was done within the ARs for FUM 029 and for FU2 029.1. The cut-off date for the data submitted within FUM 029 was 31 October 2011. The cut off date for the data submitted within the MAH's responses to the AR for FUM 029 and assessed in the AR for FU2 029.1 was 31 December 2011. The CHMP finalized the assessment of the FU2 029.1 in March 2012. In addition an Ad Hoc Experts Group meeting on Pradaxa was convened on 6th March 2012 to advise the CHMP in particular on the possible improvement in the prevention and medical management of bleedings related to the use of Pradaxa (Minutes from the Ad Hoc Experts Group meeting included in Attachement 8). The current variation was submitted to update the SmPC with regards to the contraindications and warnings related to haemorrhagic risk factors and to respond to additional questions as requested in the ARs for FUM 029 and FU2 029.1 (Attachement 7). The Rapporteur's AR for current variation included mainly the discussion on the possible SmPC modifications. To present a fuller picture of the information assessed the CHMP ARs for FUM 029, FU2 029.1 are included as attachments.

2.2. Clinical Safety aspects

2.2.1. Methods – analysis of data submitted

Analysis of all fatal bleeding cases

In light of the significant increase in the number of fatal bleeding events associated with the use of Pradaxa (in terms of post-marketing reports/spontaneous reporting), the MAH was requested to provide tabulated description of all fatal bleeding cases associated with Pradaxa use. The following information was asked to be included, wherever feasible: case ID, country, nature of bleeding event

leading to death, age, sex, weight, Pradaxa dose at time of event, indication for Pradaxa treatment, time from start of Pradaxa treatment to start of bleeding event, renal function, concomitant medication and risk factors for bleeding.

In December 2011 the MAH was asked to perform a worldwide search for spontaneous and health authority individual case safety reports (ICSRs) that concern A) fatal bleeding events or B) serious bleeding cases where another cause of death was reported or the cause of death was unknown in patients treated with dabigatran etexilate. The date of data cut-off was 31 October 2011. This has resulted in the identification of 340 ICSRs. These included 260 cases of fatal bleedings (A) and 80 serious bleeding cases with another or unknown cause of death reported (B). In total, the 340 cases had reported 449 bleeding events as some subjects experienced more than one event, corresponding to about 1.3 events/case. The MAH has also provided an extensive spreadsheet encompassing all the aforementioned 340 cases and including information as requested in the question with the exception of renal function which has been addressed separately in the narrative response above. In addition to being included in the spreadsheet, also country, region, gender, age, time to onset, dose, site of bleeding, concomitant medication, medical history and concomitant diseases have been addressed separately in the narrative response.

Table 1 Country distribution of all cases broken down by number of cases, where the outcome of the bleeding was reported as fatal bleeding (N=260) plus serious bleeding cases where a other cause of death was reported or the cause of death was unknown (fatal other cause of death; N=80) (period 18 Mar 2008 to 31 Oct 2011)

Table 2

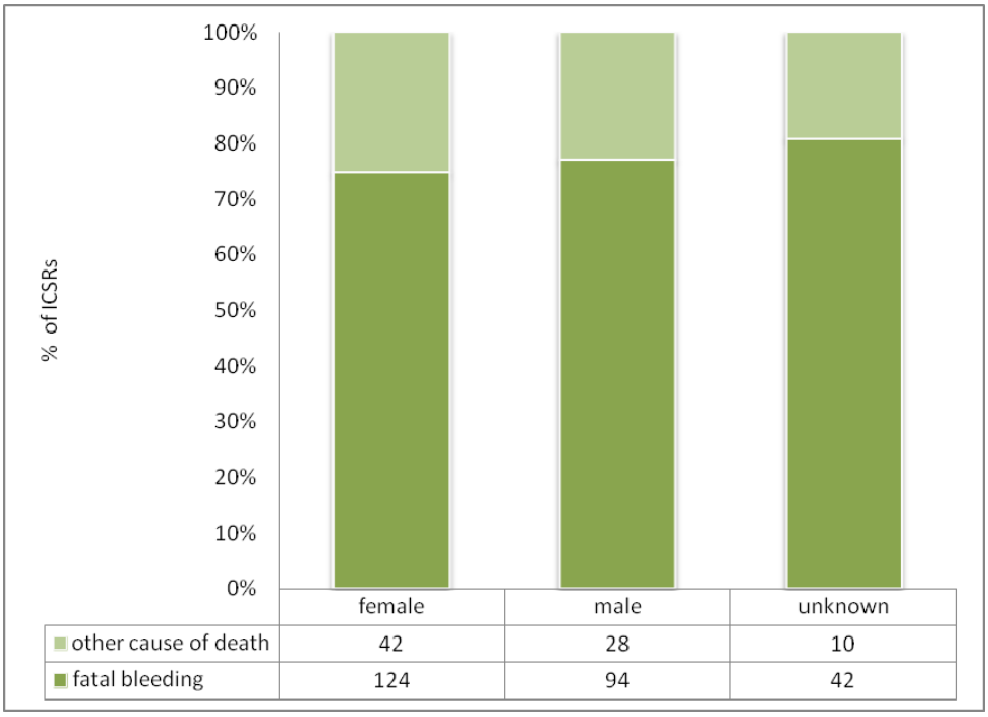
	No. of cases (*for each country listed*)	
	Cases with a fatal bleeding event	**Cases with serious bleeding events where another cause of death was reported or the cause of death was unknown**
Country	**N = 260**	**N = 80**
EU/ EEA		
Czech Republic		1
Finland	1	
France	7	
Germany	2	3
Greece	1	
Ireland	3	
Latvia	1	
Netherlands	1	
Norway	1	
Portugal	1	
Slovakia (Slovak Republic)	1	
United Kingdom	4	2
Subtotal	**23**	**6**
North America		
Canada	22	3
United States	169	44
Subtotal	**191**	**47**
South/ Middle America, Caribbean		
Argentina	4	1
Brazil		1
Colombia	1	1
Ecuador		1
Mexico		2
Peru	1	
Venezuela	2	1
Subtotal	**8**	**7**
Africa/ Middle East		
Bahrain	1	
Lebanon		1
South Africa	1	
Subtotal	**2**	**1**
Asia/ Australia		
Australia	6	3
Indonesia	1	1
Malaysia	1	
New Zealand	4	10
Philippines	3	
Subtotal	**15**	**14**
Japan		
Japan	21	5
Subtotal	**21**	**5**
Total	**260**	**80**

In Table 1 the MAH has presented the country distribution of the reported 340 cases by 31 October 2011. According to this table there were 23 cases with a fatal bleeding event plus 6 cases with serious bleeding events with another or unknown cause of death reported in the EU/EEA. As expected, the majority of cases derive from the United States (169 fatal bleedings + 44 cases with serious bleeding events with another or unknown cause of death reported - in total 213 events). Compared to Europe, a larger quantity of dabigatran etexilate has been used in the United States where dabigatran etexilate was approved on 19 October 2010 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The therapeutic indications are different in the EU (primary prevention of VTE in orthopaedic surgery plus prevention of stroke in AF) and the US (prevention of stroke in AF). While the AF indication involves long-term treatment, the duration of treatment is short in the orthopaedic surgery indications. From this perspective, the MAH was asked to calculate reporting rates for EU and US separately. Furthermore, the MAH was requested to present the main characteristics (in terms of gender distribution, mean age, dose, mean time to onset, rate of severe renal impairment) for the EU and US cases separately in a tabular format.

The MAH based its response (assessed within the AR for FU2 029.1) on the 457 ISRs of serious bleedings with fatal outcome for any reason, including bleeding as well as other and unknown causes of death (fatal bleeding B) that were reported worldwide as of 31 December 2011. Hereof were the "subgroup" of 368 ISRs of serious bleedings with fatal outcome (fatal bleeding A). The majority of all cases (fatal bleeding B) were from the US (263 cases (58%)), and sixty-two cases (14%) refer to a patient from any country in the European Economic Area (EEA). The reporting rate was higher in the US compared to the EEA. The MAH has displayed the main characteristics as far as available. The interpretation of this information was, however, hampered by the limited availability of many of the requested parameters. While sex was available for most of the cases, age was available for 46 cases in the EEU and 139 cases in the US. The mean age was slightly higher in the US compared to the EU (80 vs. 76 years) but this may reflect the different indications authorised in the US and Europe. (pVTE not authorised in the US). The same applied for the doses, which were higher in the US compared to Europe, consistent with the higher doses authorised for the SPAF indication compared to the pVTEp indication. The quantification of renal impairment was only possible in few of those patients, hence no conclusions could be drawn from the comparison of the data in the EU and US presented by main characteristic of patients (in terms of gender distribution, mean age, dose, mean time to onset, rate of severe renal impairment). Overall, CHMP agreed with the MAH that a comparison was hampered by the difference in approved indications in the US and the EU.

At data cut-off 31 October 2011, 21 cases of fatal bleedings plus 5 cases with serious bleeding events with another or unknown cause of death reported had accumulated in Japan. A follow up measure FUM 0028 followed by variation II/22 completed in October 2011 was triggered by six cases of fatal bleeding reported on 12 August 2011 by the Japanese Authorities. Dabigatran etexilate was first marketed in Japan in January 2011. Variation II/22 led to changes in the product information stressing the importance of assessing renal function.

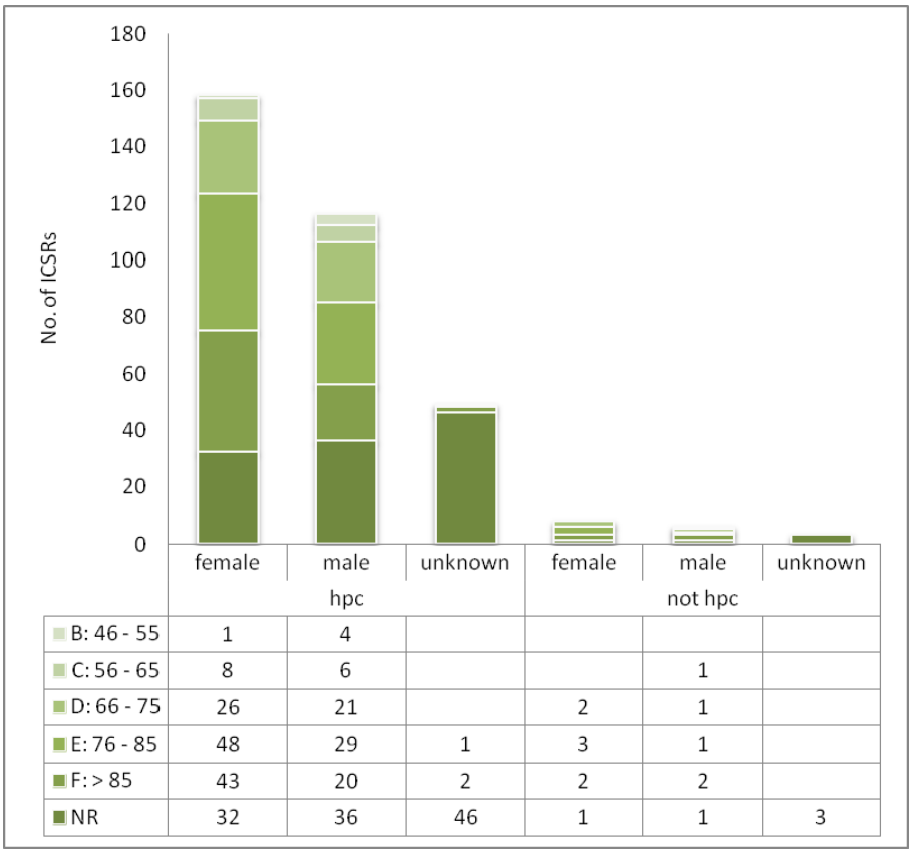
When breaking the 340 reported cases with the data cut-off 31 Oct 2011 down by outcome (fatal bleeding vs. bleeding events with other or unknown cause of death) and gender, no unexpected differences were observed. It has been shown that 166 cases were reported in female patients and 122 cases by male patients. Gender information was not available in 52 (15.3%) of cases. In both sexes, fatal bleedings represented the majority of events (Figure 1).



	female	male	unknown
other cause of death	42	28	10
fatal bleeding	124	94	42

Figure 1 Case outcome and gender (data cut-off 31 October 2011)

A total of 323 cases (95%) have been confirmed by health professionals (Figure 2).



	female	male	unknown	female	male	unknown
	hpc			not hpc		
B: 46 - 55	1	4				
C: 56 - 65	8	6			1	
D: 66 - 75	26	21		2	1	
E: 76 - 85	48	29	1	3	1	
F: > 85	43	20	2	2	2	
NR	32	36	46	1	1	3

Figure 2 Cases by patient age in years (vertical) and patient gender and health care professional confirmation (horizontal) (data cut-off 31 October 2011)

Age was not known in 119 (35%) of the spontaneous reports. When focusing on confirmed cases where age was known (n= 209), the MAH stated 274 but this could not be replicated from the numbers in Figure 2), 143 cases were reported in patients > 75 years of age (68%). This confirms that high age is a major risk factor for bleeding events.

When analyzing the 449 reported bleeding events by site of bleeding (Figure 3), it has been shown that the majority of events were gastrointestinal bleedings as expected.

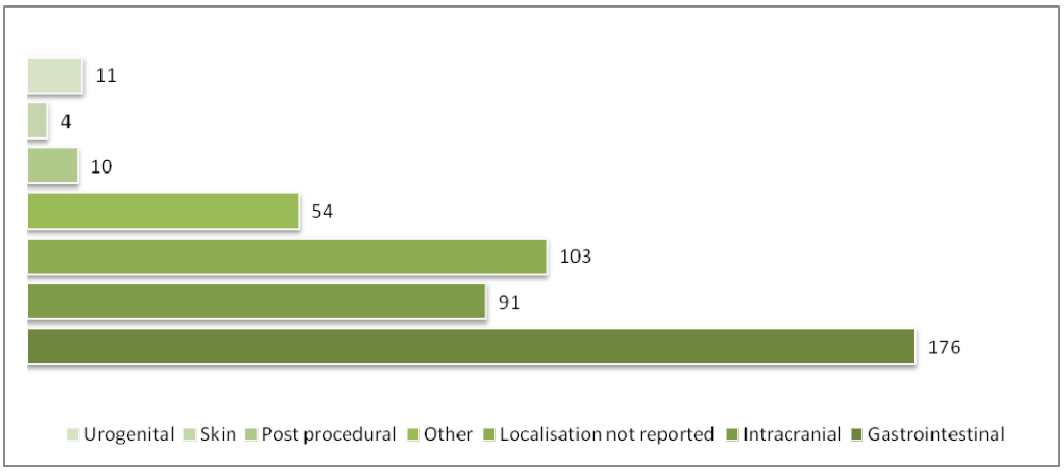
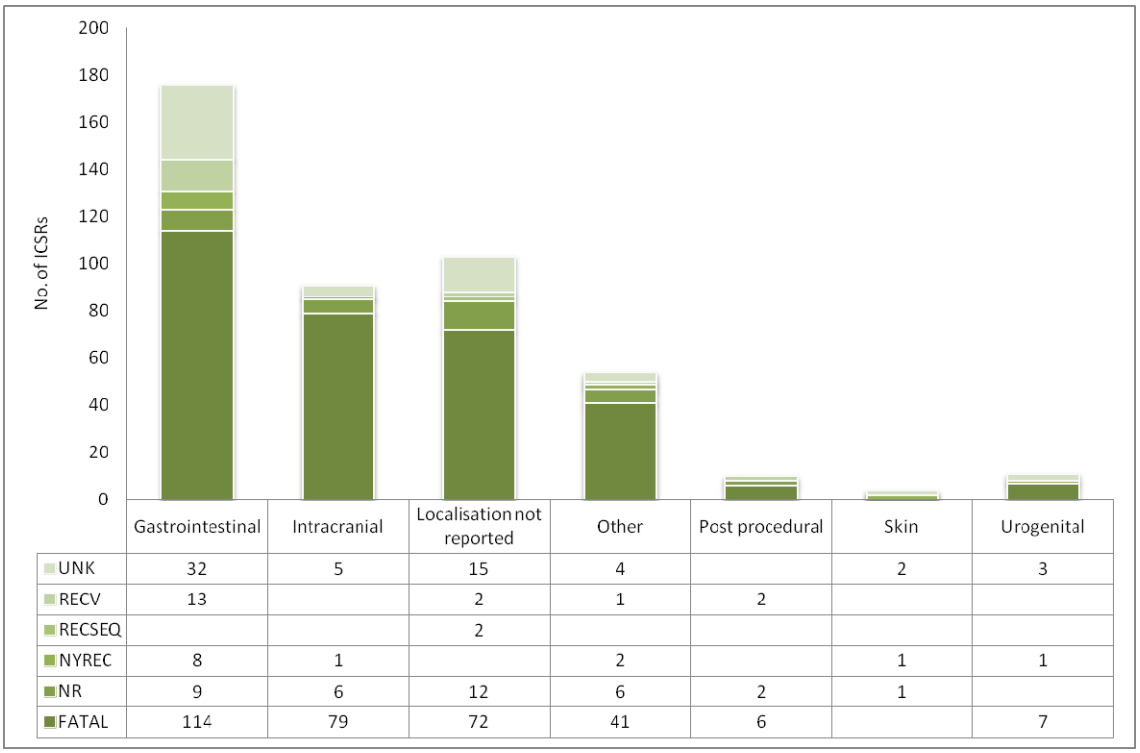


Figure 3 Events by site of bleeding (data cut-off 31 October 2011)

The bleeding site was known for 346 events. 176 of these events occured in the GI tract. 91 events represented intracranial bleedings. Figure 4 illustrates the outcome of the bleeding events in relation to the site of bleeding.



	Gastrointestinal	Intracranial	Localisation not reported	Other	Post procedural	Skin	Urogenital
UNK	32	5	15	4		2	3
RECV	13		2	1	2		
RECSEQ			2				
NYREC	8	1		2		1	1
NR	9	6	12	6	2	1	
FATAL	114	79	72	41	6		7

Figure 4 Events by outcome of serious bleeding event (vertical) and bleeding site (horizontal) (data cut-off 31 October 2011)

The outcome was unreported or unknown for 21.6% of events. For the remainder, a complete recovery was only reported for 5.3% and a recovery with sequelae in 0.6% of events. In the large majority of events (319 (71%)), the events were fatal confirming the seriousness of these events. The analysis of time to onset of the first bleeding event demonstrates that most bleeding events occurred relatively early during treatment with dabigatran (26.1% in the first 10 days and 67.8% within the first month of therapy (Figure 5)).

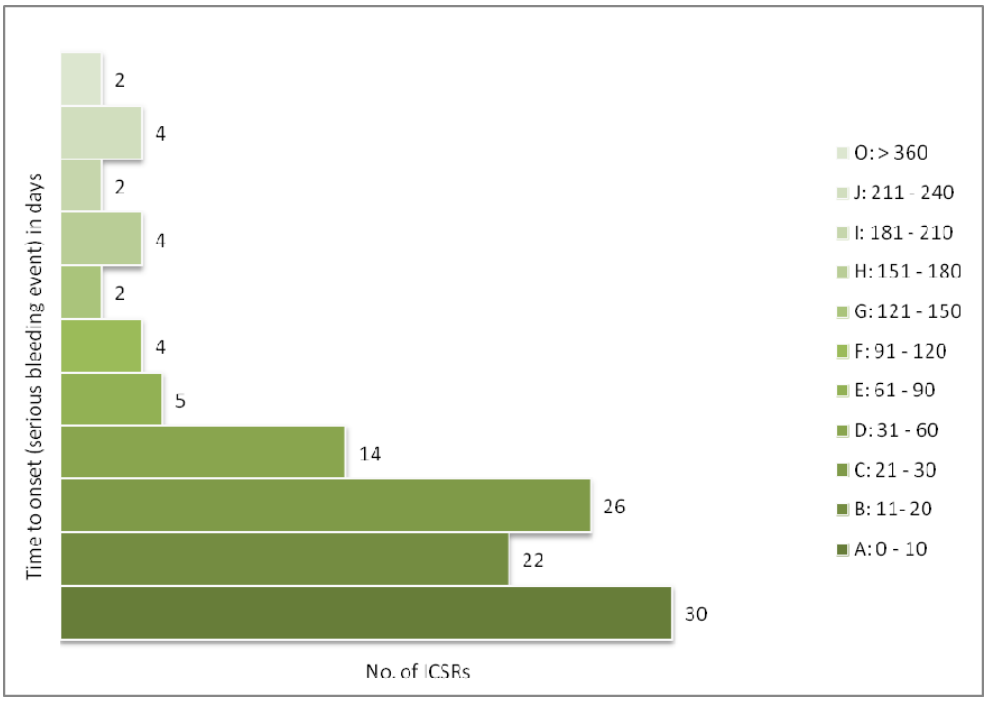


Figure 5 Cases by time to onset (in days) of first bleeding event (data cut-off 31 October 2011)

Of note, time to onset was overall reported in only 33.8% of cases. No unexpected pattern was observed when the number of cases were broken down by age and time to onset, but this analysis is limited by the fact that both variables were only known in a limited number of cases (Figure 7).

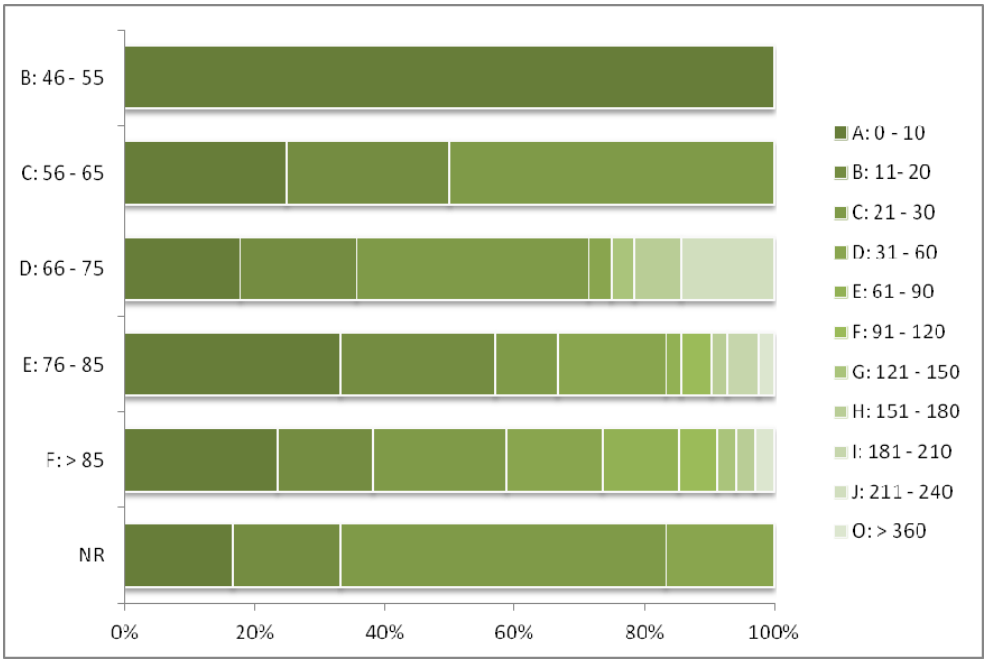
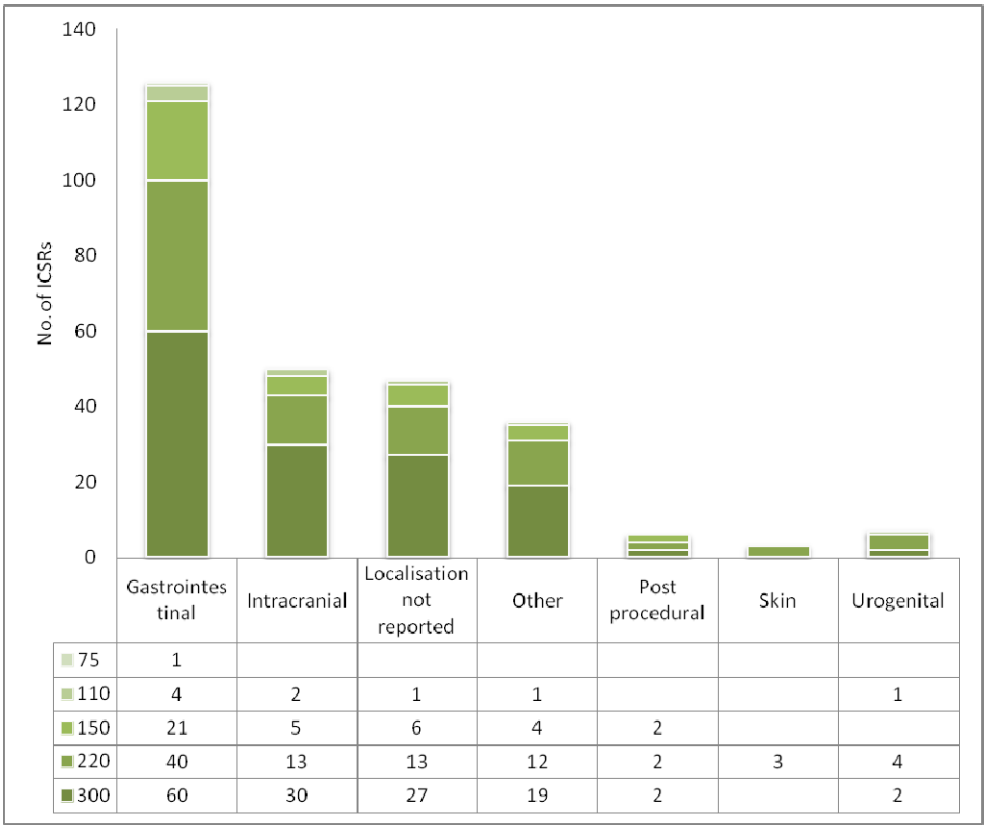


Figure 7 Cases by patient age (vertical) and time to onset (in days) of first bleeding event (horizontal). (data cut-off 31 October 2011)

The MAH has also analyzed the relationship between daily dose of dabigatran etexilate at the time of the event and the site of bleeding (Figure 8).

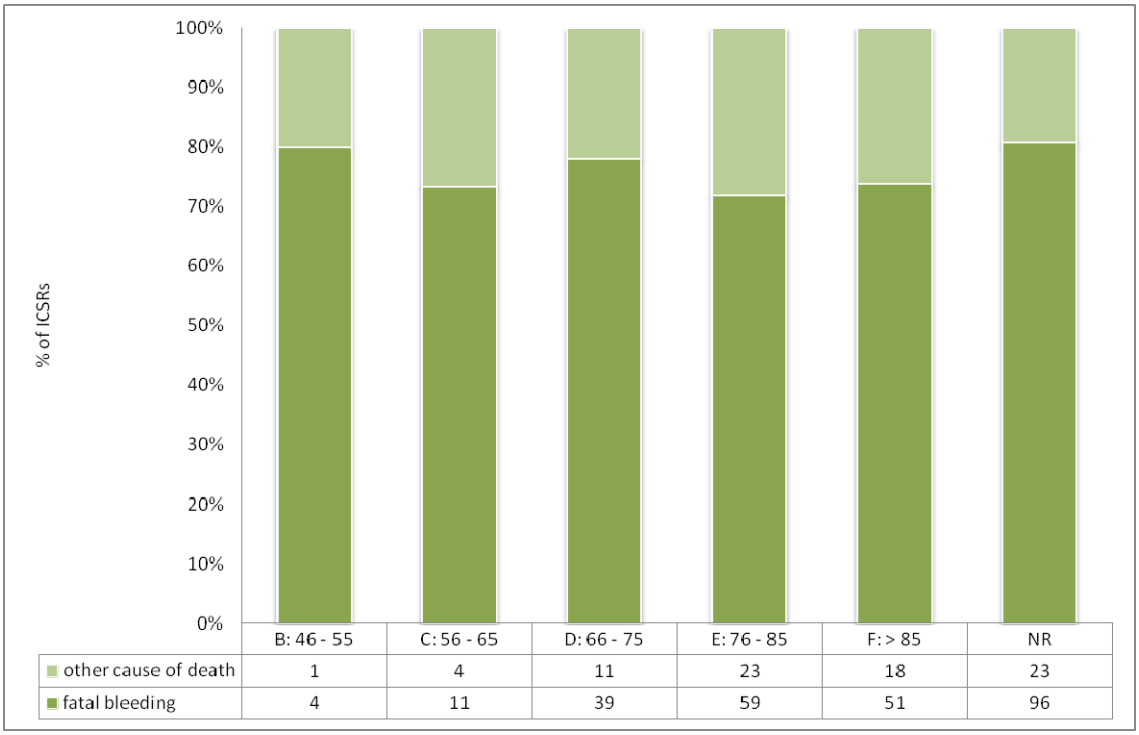


	Gastrointestinal	Intracranial	Localisation not reported	Other	Post procedural	Skin	Urogenital
75	1						
110	4	2	1	1			1
150	21	5	6	4	2		
220	40	13	13	12	2	3	4
300	60	30	27	19	2		2

Figure 8 Events by daily dose at the time of event (vertical) and bleeding site (horizontal); data cut-off 31 October 2011

The dose was only reported in 183/340 cases (data cut off 31 Oct 2011). 2 events were excluded from the analysis because of ”implausible or isolatedly reported dose”. The figure 8 illustrates that the majority of events occurred with the 220 and 300 mg daily doses as expected. From the provided spreadsheet, it was clear that at least 40 patients receiving the 300 mg daily dose (mainly US patients more than 80 years old) would have received 220 mg daily because of their age alone had they been treated according to the EU SmPC. The true number of elderly on a high dose is likely to be considerably higher considering that information about age or dose was missing in a large number of the cases. The MAH was requested to provide an analysis of the cases in terms of: a. How many patients of the 340 cases received a higher dose of Pradaxa than recommended as per the EU SmPC? b. How many patients received Pradaxa despite one or more contraindications as per the EU SmPC? In response the MAH has re-evaluated the 340 cases with respect to dose and contraindications. The assumptions made for this evaluation were based on the recommended doses as per European SmPC for the SPAF indication (i.e. a lower dose of 110 mg BID for patients ≥ 80 years, for patients with high risk of bleeding, e.g. patients with moderate renal impairment, and for patients with verapamil as concomitant treatment) and the primary VTE prevention indication (i.e. 150 mg OD for patients ≥ 75 years, for patients with moderate renal impairment, and for patients concomitantly treated with verapamil, amiodarone or quinidine, as well as 75 mg OD for patients with moderate renal failure and concomitant treatment with verapamil). The contraindications comprised severe renal failure, concomitant treatment with ketoconazole, cyclosporine, itraconozole, tacrolimus, and furthermore reported concomitant diseases were reviewed for information concerning active clinically significant bleeding, organic lesions at risk of bleeding, spontaneous or pharmacological impairment of haemostasis, hepatic impairment or liver diseases. It was possible to get information on dosage in approximately half of the reports, that is to say in 173 of the 340 patients. Based on this figure, in 40 (23.1%) of the 173 patients a higher dose than recommended in the EU SmPC was administered (38 of these from the USA where different dose recommendations are in place) and 27 patients (15.6%) had contraindications, predominantly severe renal failure (mostly in Japan). In summary, as per the EU approved label 23.1% of those patients where the posology used was known, were treated with a dose that was too high and 15.6% of patients appeared to have contraindications. Although the MAH has not explicitly commented on the overlap between those patients with too high doses as per EU posology and patients with contraindications as per EU SmPC, it can be deducted from the data (higher dose than as per EU recommendation is mostly related to US cases, most reports on contraindications related to severe renal impairment came mostly from Japan) that the majority were separate reports. No futher actions were deemed necessary by the CHMP based on the provided information. The necessity of assessment of renal function (severe renal impairment being the most frequent contraindication that was neglected) has been stressed in the SmPC.

When breaking the cases down by outcome and age (Figure 9), the distribution among the groups of fatal bleedings vs. bleedings with other causes of death reported was overall similar across age groups. As noted before, the majority of events occurred in patients older than 75 years.



	B: 46 - 55	C: 56 - 65	D: 66 - 75	E: 76 - 85	F: > 85	NR
other cause of death	1	4	11	23	18	23
fatal bleeding	4	11	39	59	51	96

Figure 9 Case outcome (vertical) and age group (horizontal); data cut-off 31 October 2011

The breakdown of events by patient age and bleeding site (Figure 10) did not reveal a consistent pattern.

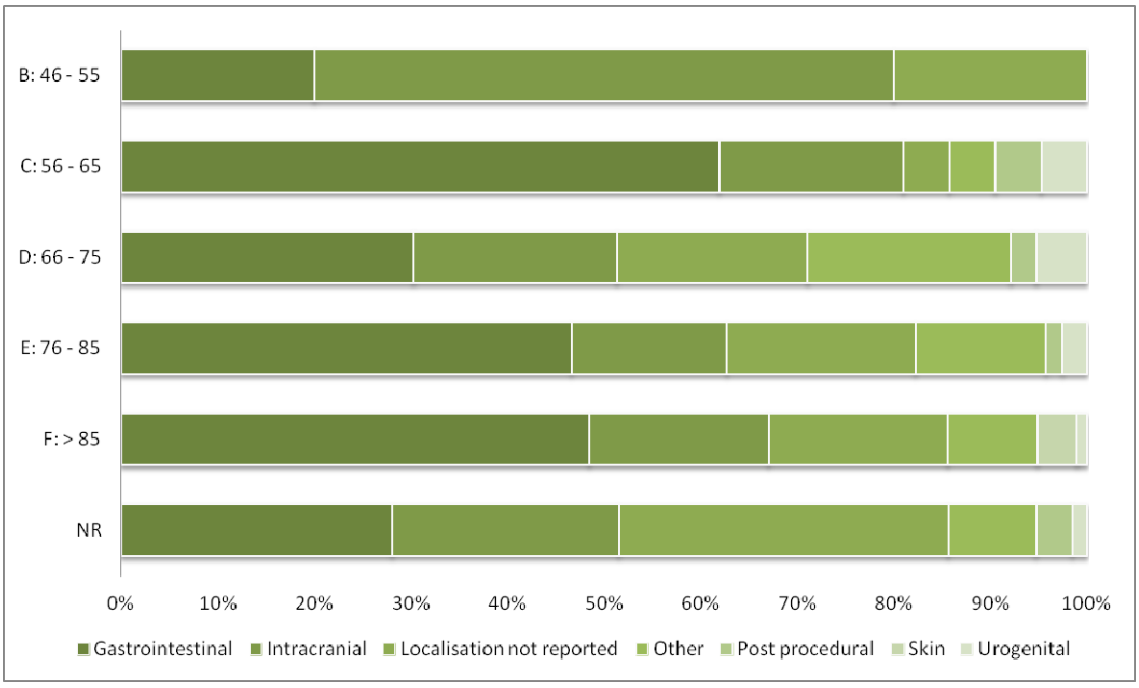


Figure 10 Events by patient age (vertical) and bleeding site (horizontal); data cut-off 31 October 2011

The analysis of potentially confounding risk factors for bleeding events was hampered by the relatively large amount of missing data. Only 34.4% of reports contained information on concomitant medication. Table 2 presents co-suspected medications as assessed by the reporter.

Table 2 Co-suspected medications as assessed by the reporter

Generic Name (Suspect/Query)	Case Count	% of Case Count
Dabigatran	340	100.00%
Acetylsalicylic Acid	9	2.65%
Warfarin	5	1.47%
Clopidogrel Bisulfate	3	0.88%
Enoxaparin Sodium	2	0.59%
Ticlopidine Hydrochloride	2	0.59%
Amiodarone	1	0.29%
Clindamycin Hydrochloride	1	0.29%
Diltiazem	1	0.29%
Dronedarone Hydrochloride	1	0.29%
Edaravone	1	0.29%
Furosemide	1	0.29%
Heparin	1	0.29%
NSAID's	1	0.29%
Omeprazole	1	0.29%
Telmisartan	1	0.29%
Tramadol	1	0.29%
Verapamil Hydrochloride	1	0.29%
Vincents	1	0.29%

According to the reporters relatively few patients received concomitant medication that may also have increased the risk of bleeding (acetylsalicylic acid (9), warfarin (5), clopidogrel (3), enoxaparin (2), heparin (1)). The table presenting concomitant medications reported in a percentage higher than 3% actually reveal that 25 patients received concomitant acetylsalicylic acid, and 6 clopidogrel (Table 3). Four patients have received citalopram, an SSRI that might also interact with dabigatran.

Table 3 Summary of concomitant medications reported in a frequency higher than 3%

Generic Name (Co-Med)	Case Count	% of case count
Patients with data available	117	100.00%
Furosemide	36	30.77%
Acetylsalicylic Acid	25	21.37%
Digoxin	22	18.80%
Carvedilol	16	13.68%
Lisinopril	14	11.97%
Omeprazole	13	11.11%
Metoprolol	12	10.26%
Simvastatin	12	10.26%
Allopurinol	11	9.40%

Generic Name (Co-Med)	Case Count	% of case count
Amiodarone	9	7.69%
Atorvastatin Calcium	9	7.69%
Spironolactone	9	7.69%
Isosorbide Mononitrate	8	6.84%
Paracetamol	8	6.84%
Diltiazem	7	5.98%
Levothyroxine Sodium	7	5.98%
Potassium Chloride	7	5.98%
Rosuvastatin Calcium	7	5.98%
Clopidogrel	6	5.13%
Diltiazem Hydrochloride	6	5.13%
Potassium	6	5.13%
Esomeprazole Magnesium	5	4.27%
Ferrous Sulfate	5	4.27%
Metformin	5	4.27%
Amlodipine Besilate	4	3.42%
Atenolol	4	3.42%
Azosemide	4	3.42%
Citalopram Hydrobromide	4	3.42%
Ergocalciferol	4	3.42%
Famotidine	4	3.42%
Glyceryl Trinitrate	4	3.42%
Insulin Glargine	4	3.42%
Losartan	4	3.42%
Metoclopramide	4	3.42%
Nicorandil	4	3.42%
Rabeprazole Sodium	4	3.42%
Ramipril	4	3.42%
Telmisartan	4	3.42%

Information on past medical history was provided in 20% of cases. As expected from the target population, a number of patients have a past history of cardiovascular/CNS events (central nervous system vascular disorders (14), coronary artery disorders (7)). Furthermore, some patients have also reported previous gastrointestinal haemorrhages (5) and gastrointestinal ulceration/perforation (3) which may indicate a higher risk of gastrointestinal bleeding (Table 4).

Table 4 Summary of all diseases reported as medical history

Past Disease (MedDRA HLGT level)	Case Count	% of case count
Patients with data available	68	100.0
Central nervous system vascular disorders	14	20.6
Vascular therapeutic procedures	9	13.2
Cardiac therapeutic procedures	8	11.8
Coronary artery disorders	7	10.3
Bone and joint injuries	5	7.4

Past Disease (MedDRA HLGT level)	Case Count	% of case count
Bone and joint therapeutic procedures	5	7.4
Cardiac arrhythmias	5	7.4
Gastrointestinal haemorrhages NEC	5	7.4
Infections - pathogen unspecified	4	5.9
Gastrointestinal therapeutic procedures	3	4.4
Gastrointestinal ulceration and perforation	3	4.4
Therapeutic procedures and supportive care NEC	3	4.4

Similarly, information about concomitant diseases (available in 43.5% of cases) reveal that a number of patients had concomitant diseases that are known to be associated with a higher risk of vascular events including hemorrhages (vascular hypertensive disorders (67), glucose metabolism disorders (27), gastrointestinal bleeding events (gastrointestinal neoplasms (7)) and lifestyle issues (alcohol?) (7). These are confounding factors (Table 5).

Table 5 Summary of concomitant diseases reported in more than 3% of the 148 patients with information available.

Concomitant Diseases (HLGT)	**Case Count**	**% of case count**
Patients with data available	148	100.00%
Vascular hypertensive disorders	67	45.27%
Heart failures	36	24.32%
Coronary artery disorders	32	21.62%
Glucose metabolism disorders (incl diabetes mellitus)	27	18.24%
Renal disorders (excl nephropathies)	25	16.89%
Bronchial disorders (excl neoplasms)	23	15.54%
Lipid metabolism disorders	18	12.16%
Cardiac arrhythmias	16	10.81%
Joint disorders	15	10.14%
Arteriosclerosis, stenosis, vascular insufficiency and	12	8.11%
Central nervous system vascular disorders	12	8.11%
Allergic conditions	10	6.76%
Mental impairment disorders	10	6.76%
Anaemias nonhaemolytic and marrow depression	9	6.08%
Gastrointestinal motility and defaecation conditions	9	6.08%
Thyroid gland disorders	9	6.08%
Cardiac therapeutic procedures	8	5.41%
Depressed mood disorders and disturbances	7	4.73%
Gastrointestinal neoplasms malignant and unspecified	7	4.73%
Hepatic and hepatobiliary disorders	7	4.73%
Lifestyle issues	7	4.73%
Vascular therapeutic procedures	7	4.73%
Cardiac valve disorders	6	4.05%
General system disorders NEC	6	4.05%
Infections - pathogen unspecified	6	4.05%
Lipid analyses	6	4.05%
Cardiac disorder signs and symptoms	5	3.38%
Myocardial disorders	5	3.38%
Purine and pyrimidine metabolism disorders	5	3.38%
Respiratory disorders NEC	5	3.38%
Vascular disorders NEC	5	3.38%

Finally, the MAH has analyzed the 340 cases according to renal function. Again, information is unfortunately very limited (only available in 12.9% of cases) and potentially unrepresentative as this background information might be more prone to be reported in patients with renal insufficiency. Nevertheless, Table 7 demonstrates that in 44 patients with available data on renal dysfunction, 23 patients had a CrCl or a GFR indicating severe renal impairment.

Table 7 Number of cases with data on renal dysfunction broken down by severity assessed by creatinine clearance and glomerular filtration rates

Severity of renal failure	**CrCl**	**GFR**	**Total**	
	n	**n**	**N**	**%**
Number of ICSRs with data available	39	5	44	100.0
Mild	5	1	6	13.6
Moderate	9	4	13	29.5
Severe	23	0	23	52.3
Decreased CrCl	1	0	1	2.3
Low CrCl	1	0	1	2.3

Despite the abovementioned limitations, these data in view of the CHMP confirm that severe renal insufficiency is indeed a major risk factor for bleeding events. However, in the cases it was unclear whether the reported severe renal impairment was present at the time of bleeding or whether it followed the bleeding event (as a complication). The MAH was requested to clarify for each case, if possible. This information was hoped to give some idea of whether higher proportions of patients with severe renal impairment have fatal bleeding events as opposed to more minor adverse effects. The total number of reports referring to patients with severe renal impairment would also provide some level of information regarding whether an unacceptably high number of such patients have been exposed to dabigatran etexilate.

Clarification on the cases with severe renal failure has been provided by the MAH. In 26 of the 457 patients (cut off date: 31 December 2011) with serious bleeding events reported with any (including unknown) cause of death, information on severe renal impairment was provided. Each single patient was checked for concomitant and past diseases, date of occurrence of the bleeding event, dates of relevant laboratory parameters used for estimation of renal function and Pradaxa treatment dates. In 13 of the 26 severely renally impaired patients the severe renal impairment was existing before the bleeding event. In 6 patients the severe renal impairment was a consequence of the blood loss (prerenal failure) and in 7 cases an assessment was not possible. In addition, the MAH was asked to provide the proportions of patients with normal renal function and mild, moderate and severe renal impairment in their overall safety database of all ADRs. From the provided data it appears that a higher percentage of patients where a serious bleeding with death was reported had severe renal insufficiency (47%) compared to all post-marketing ISRs where severe renal insufficiency was reported in 30%. However, these data must be interpreted extremely carefully. In only 673 ISRs out of 24,312 ISRs (2.8%) quantifiable information on renal function was available. However, such information was available in 66 out of those 457 ISR with serious bleedings entailing death (12%). Due to the limitations of the spontaneous reportings in the opinion of the CHMP no firm conclusions could be drawn on this issue.

The DHPC recently circulated in the EU (following the CHMP conclusion on variation Pradaxa II/22) provided a reminder to prescribers that dabigatran etexilate treatment is contraindicated in patients with severe renal impairment and stressed the importance of assessing renal function. The MAH was asked to comment on how they intend to determine whether the DHPC has reduced prescribing in patients with severe renal impairment. Overall, it seems too early to determine whether the DHPC, which was distributed between end October and mid November 2011 (except in France where this was planned in parallel to the launch of the SPAF indication in April 2012), has reduced prescribing in patients with severe renal impairment. While the monthly number of cases of serious bleedings with fatal outcome and severe renal impairment was approximately 1-2 in the EEA from August to September, it increased to 8 cases both in November and December 2011. This corresponds to a considerable increase of the monthly reporting rate, especially in the two last months of 2011, when expressed by 100,000 patient years. The rates were 14.5 in August, 19.2 in September, 25.5 in

October, 78.9 in November and 93.7 in December 2012. It was agreed with the MAH that this may be due to a reporting bias and due to increased awareness following the DHPC, however, this remains speculation. Following the request of a drug utilization study, protocols were already submitted for the assessment to the CHMP. These are handled within FUM25 (study 1160.136 GLORIA-AF) and FUM26 (study 1160.144 Study to assess potential off-label use outside AF), and both procedures are still on-going. It was considered that the already requested measures are sufficient to address the drug utilization program.

Summary

In summary, the MAH had provided tables of information summarizing various characteristics of the group of patients with fatal bleeding reactions within FUM 029. This approach was accepted by the CHMP. However, no attempt to discuss/analyse the cases, or to relate risk factors/characteristics together has been initially made. The MAH provided within responses to the FUM 029 a discussion of the cases with multiple risk factors for bleeding and made an attempt to identify those that are likely to be the most important. The discussion was linked to renal function status which was not discusse previously and in relation to other risk factors and outcomes. The discussion concentrated on possible PK and PD drug interactions and considered whether current SmPC warnings are adequate. In the response the MAH stated that by 31 October there were 340 ISR reported and by 31 December 2011 457 ISR of serious bleeding events reported as fatal plus bleeding events with other or unknown cause of death. Of these 457 cases, age and gender were available for 283 case reports. The MAH's analyses provided in response to the RA for FU 029 were built on these latter cases. In these cases, any of the risk factors: antiplatelet use, P-gp-inhibitor use or severe renal impairment were reported in 83 cases (29%). There was an increase of fatal bleeding cases with age in the presence of severe renal impairment. For the other risk factors and the combination of risk factors, an association with age was not seen. However, overall the number of fatalities in patients with combined risk factors was low. As the risk factors are already mentioned appropriately in the EU SmPC, as severe renal impairment is a contraindication and as the SmPC was recently strengthened with respect to the need for assessment of renal function, the current SmPC and the conducted measures were regarded by the CHMP as sufficient. The CHMP agreed that the analysis did not provide a basis for determining further risk minimization activities. However, the number of cases with multiple risk factors was relatively low, and it was felt that it would be difficult to disentangle the relative contribution of each risk factor from an analysis of post-marketing events.

Fatal bleeding cases in the real world setting as compared to the RE-LY study

The MAH was asked to analyze and discuss of whether the occurrence of fatal bleedings events in the real-world setting observed so far is higher than expected from the RE-LY study results. The MAH has compared the occurrence of fatal bleeding events post-marketing with the rate observed in the RE-LY study. Reference was made to Table 8.

Table 8 Cumulative numbers and reporting rates for bleeding events from post marketing reporting and from the RE-LY trial

Event category	**No. of PM ICSRs**	**Reporting rates per 10 000 patient years RE-LY (safety dataset)**			
		PM	**DE 110 mg bid**	**DE 150 mg bid**	**Warfarin**
Fatal A[1]	260	6.3	16.6	19.5	31.0
Fatal B[2]	340	8.3			
Serious[3]	2,433	59.4	288.0	341.1	354.6
DE = Dabigatran Etexilate; ICSR = Individual Case Safety Report; MBE = Major Bleeding Event; NA = Not Applicable; PM = Post Marketing					

[1]	Post marketing: Fatal bleeding events; RE-LY: Adjudicated MBE where the investigator has indicated 'death' as MBE criterion per protocol definition
[2]	Post marketing: Serious bleeding events (fatal or non-fatal) in a case with a fatal outcome; RE-LY: Not applicable
[3]	Post marketing: Regulatory serious events; RE-LY: MBE per protocol definition

Fatal A events corresponded to the cases, where the outcome of the bleeding was reported as fatal bleeding. Fatal B events correspond to the cases, where the outcome of the bleeding was reported as fatal bleeding plus serious bleeding cases where another cause of death was reported or the cause of death was unknown. A cumulative reporting rate has been calculated based on the number of individual case safety reports (ICSRs) (= numerator) and global bulk sales (= denominator). The resulting post-marketing fatal bleeding rate was estimated to be 6.3 (Fatal A events) and 8.3 (Fatal B events) per 10,000 patient years. In comparison, it was 16.6 for the 110 mg BID dose and 19.5 for the 150 mg BID dose in the RE-LY study. It was also noted that the rate was 31.0 for warfarin in the RE-LY study. The MAH concluded and the CHMP agreed that the post-marketing bleeding rates for dabigatran etexilate are substantially less than the respective rates seen in the RE-LY groups for both doses of dabigatran etexilate. If the reporting rate in the post-marketing phase had been higher than in the RE-LY study, there would clearly have been a safety concern. The fact that reporting rate in the post-marketing phase is lower gives some reassurance as to the safety profile of the product. However, there are several limitations to the performed calculations as the reporting rate of serious bleeding events is likely to be underestimated for two reasons. Firstly, underreporting in spontaneous reporting systems is a well known phenomenon and in particular this is likely to be the case when the event is expected. However, this tendency could to some extent be counteracted by the seriousness of the event in question and the fact that Pradaxa represents a new treatment modality in the prevention of stroke in atrial fibrillation patients and the consequent increased attention about Pradaxa among physicians. Secondly, the denominator is likely to be overestimated since it is based on bulk sales and not the amount of drug actually consumed. Put in other words, the estimate does not take into account stocks of drug at wholesalers, pharmacies or patients. Finally, the evaluation of the observed versus expected rates of bleeding is further complicated by lack of information on relevant covariates for the patients using the drug post-marketing, i.e. whether patients at low or high risk of bleeding are treated. Therefore, post-marketing bleeding-rates must be interpreted with caution. In conclusion, one would have liked the difference in fatal bleeding rates based on post-marketing reports and the RE-LY study, respectively, to be larger than actually seen. However, at present there is no solid evidence to suggest that the fatal bleeding rate in patients treated with Pradaxa in the clinical setting is larger than in the RE-LY study. In the AR for FUM 029 the MAH was requested to provide an estimate of the actual drug consumption post-marketing and to repeat the calculation of the cumulative post-marketing bleeding rate on this basis (drug in stock should be excluded from the denominator) and comment on the result. The MAH was also asked to comment on the likely level of under-reporting of fatal bleedings.

The MAH has presented 3 different estimates of patient exposure to marketed Pradaxa:

1. Global data from the IMS Health MIDAS database which covers product sales volume by wholesalers into pharmacies and/or hospitals and excludes drug in stock at the wholesaler level, as well as product samples.

2. Commercial product sold ex-factory since the first Pradaxa launch, excluding product samples (distributed by company representatives) or free goods. (Boehringer Ingelheim's standard method for estimating patient exposure to Pradaxa).

3. Commercial product sold ex-factory, including product samples and free goods.

Overall, the methodologies applied for estimating post-marketing exposure were endorsed. The most conservative method is method a. Also according to this method, the fatal bleeding rate was still below the rates observed in the RE-LY study for both the 110 mg BID and the 150 mg BID doses (1.7-2 fold difference) and for warfarin (3-fold difference). It is agreed that a bleeding event is more likely to stimulate adverse event reporting than most other events, especially if it has a serious or fatal outcome and in view of the attention of healthcare professionals due to the novelty of the therapeutic principle of Pradaxa and its recent launch. In conclusion, the requested more conservative re-calculations of the fatal bleeding rate based on post-marketing reports have been provided. Based on the provided data, the rates are still lower than the rates observed in the RE-LY study.

Development of an antidote for Pradaxa and medical management of major bleeding events

Within the FUM 029 the MAH was asked to provide an update on how far the development of an antidote to Pradaxa has progressed. A reversal agent/antidote for dabigatran is under early development (preclinical stage). The MAH was requested to comment on whether any new advice on management of bleeding in dabigatran etexilate treated patients is available, and whether the information in section 4.9 of the SmPC is still complete/up-to-date. Also, it was noted that the information provided in the Canadian product monograph was more extensive than that of the EU SmPC. The MAH proposed an addition to section 4.9 suggesting treatment options that may be considered in case of overdose: activated prothrombin complex concentrates, recombinant Factor VIIa, concentrates of coagulation factors II, IX or X, and platelet concentrates (where thrombocytopenia is present or long acting antiplatelet drugs have been used). The evidence for these treatments is at this stage theoretical, and clinical data supporting them in the treatment of Pradaxa overdose are lacking. But this limitation has been appropriately stated in the proposed text. Hence, the proposal was supported by the CHMP. It should be noted that an Ad hoc expert meeting was convened on 6 March 2012 to address this issue. Experts supported the new proposal for the management of the major bleeding, in particular the recommendation to consider the use of activated PCC, recombinant factor VIIa or concentrates of coagulation factors. Also, the administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used were found justified. The experts didn't see the preference for any of the suggested treatment options given only experimental evidence to support the role of these agents in counteracting the anticoagulant effect of dabigatran and the fact that their usefulness in clinical settings has not been established. Instead, they suggested leaving it at the discretion of the treating physician. Some experts stated however that the increased risk of rebound thromboembolism could be observed with the use of some of these agents (PCC).

The topic of (the lack of) an antidote has recently been highlighted in the New England Journal of Medicine in a letter to the editor: http://www.nejm.org/doi/full/10.1056/NEJMc1111095. It was suggested in the letter that patients treated with dabigatran who experience injury/trauma are at increased risk of serious bleedings, including fatal bleedings. Further, the EMA has recently conducted an analysis in EudraVigilance to compare the reported risk associated with the use of dabigatran etexilate in acutely injured patients to the reported risk associated with older (warfarin, acenocoumarol) and another new oral anticoagulant (rivaroxaban). The primary endpoint in the analysis were case count numbers, a measure of disproportionality of reporting (PRR) and percentage of reported fatal cases on selected MedDRA terms reflecting acute neurological haemorrhagic events and injuries. The study confirmed that a high number of reports involving dabigatran etexilate suggesting a haemorrhagic neurological complication or an acute injury have been transmitted to EudraVigilance. The number of reports is very close to the number of reports involving warfarin. The number of reports involving rivaroxaban is generally lower compared to dabigatran etexilate and warfarin. It was particularly highlighted that there was a high number of reports of falls involving

dabigatran etexilate. The MAH was asked to comment on the NEJM letter and the EMA analysis. Further, the MAH was requested to provide an analysis of cases of serious bleedings observed in Pradaxa-treated patients experiencing acute injury/trauma, both from clinical trials and from post-marketing reports. The analysis should include a comparison to other oral anticoagulants. Finally, in light of the lack of an antidote the MAH was asked in the AR for FUM 029 to discuss possible implications for the product information and the RMP for Pradaxa. In response the company provided the assessment of the following:

- Comments to the recent article in NEJM regarding the management of Pradaxa-treated patients experiencing trauma
- Comments to the EMA analysis on serious bleedings in patients experiencing acute injury/trauma
- Analysis of trauma-associated bleedings from clinical trials (the RE-LY study)
- Analysis of trauma-associated bleedings from post-marketing events

Comments to the recent article in NEJM regarding the management of Pradaxa-treated patients experiencing trauma:

Regarding the availability of means for assessing the degree of anticoagulation: The MAH pointed out that there are indeed readily available tests for the degree of dabigatran-related anticoagulation: aPTT which is widely available, ECT and TT. However, here it should be noted that aPTT can only be regarded as a qualitative/semi-quantitative test and that the other, more precise methods are not widely accessible and results are not reported rapidly.

Regarding the availability of a reversal strategy: The MAH acknowledges that there is currently no available antidote and that prothrombin complex concentrates (PCC) and other clotting cofactors as a reversal strategy are currently unproven. This was supported, and this caveat has been mentioned in the new recommendations for treatment of overdose in section 4.9 of the SmPC.

Regarding the fact that life-threatening bleeding complications can occur after an injury in patients taking dabigatran etexilate: The MAH acknowledged this fact, but also referred to the RE-LY where the number of major bleedings was less in patients treated with dabigatran etexilate than in patients treated with warfarin. The comments provided by the MAH to the article in NEJM were considered by the CHMP to be acceptable.

Comments to the EMA analysis on serious bleedings in patients experiencing acute injury/trauma:
The MAH refered to the RE-LY study, where haemorrhagic neurological complications were less frequent in patients on dabigatran etexilate than in patients treated warfarin, and that there are no other controlled data to indicate the opposite. Further, post-hoc analyses of the RE-LY study showed that the incidence of trauma-related bleedings were less than in warfarin-treated patients. In addition, the MAH listed the well-known methodological weaknesses associated with analyses of post-marketing reports on which the EMA analysis is based. The MAH's comments to the EMA analysis were considered by the CHMP to be acceptable.

Analysis of trauma-associated bleedings from clinical trials (the RE-LY study):
The presence of trauma was not routinely recorded in major bleeding cases in the RE-LY study. However, the MAH has conducted a post-hoc analysis of trauma in relation to intracranial haemmorrhage (ICH). Two experts independently re-evaluated each ICH case to additionally identify the primary site of intracranial bleeding by review of imaging reports, presence of associated head trauma, and neurologic outcomes. The frequency of traumatic intracerebral, subdural and subarachnoid haemorrhages was generally numerically lower for both doses (110 and 150 mg BID) of dabigatran etixilate compared to warfarin. For fatal ICH related to trauma, the numbers of events were

too low to allow a meaningful analysis. Bearing in mind the limitations of the provided analysis (post hoc analysis, no routine recording of presence of trauma), there is no indication in the RE-LY study of any excess of ICH related to trauma with dabigatran etixilate compared to warfarin. The provided analysis and the interpretation by the MAH were considered by the CHMP acceptable.

Analysis of trauma-associated bleedings from post-marketing events:
The MAH has analyzed post-marketing reports in patients treated with Pradaxa who experienced a serious bleeding event as well as trauma (a serious accident or injury). Cut-off was 31 December 2011, and 144 patients were identified. In the cases with fatal outcome, more often fall and head injury was reported, the proportion of patients of older age was higher, and generally patients received a higher Pradaxa dose. None of these findings can be said to be unexpected. The provided analyses by the MAH were acceptable.

Possible implications for the product information and the RMP for Pradaxa:
The MAH stated that in the EU SmPC recommendations for dose adaptation in elderly patients have been provided, and it is reflected in the RMP. However, the MAH didn't initially provide an overall discussion of possible implications of the issues related to trauma for the product information and the RMP. The provided analyses were considered by the CHMP satisfactory. However, the MAH was asked to discuss whether the issue of management of Pradaxa-treated patients experiencing trauma/acute injury is adequately addressed in the SmPC and RMP or if amendments are needed. It should be noted that an Ad hoc Expert meeting on 6 March 2012 was consulted on this topic. The importance of the education of patients and prescribers was expressed during the meeting, in particular the need for easy access to the educational materials. The good example of the educational strategy used in Japan was presented by the MAH (that according to the MAH is planned to be copied in the EU) and was felt reassuring by the experts. The experts reviewed the recommendations for management of major bleeding included in the RELY study protocol that were provided by the MAH and found them to follow standard practice and to be in line with the latest proposal of the SmPC. It was proposed that the consultation of a coagulation expert in case of major bleeding could be recommended in the SmPC as it was in the protocol of the RELY study. The information about the danger of dehydration was included into the PIL as it may lead to changes in renal function in susceptible patients.

In addition the CHMP found the contraindication "Organic lesion at risk of bleeding" ambiguous since it was not entirely clear which diseases and conditions are encompassed by the term. Based on the available evidence, the MAH was requested to propose a revised wording for the contraindication, specifically with regard to the nature of the lesions that will constitute a contraindication. Such a revised wording should include common examples of lesions or conditions which would contraindicate Pradaxa treatment. The MAH agreed to remove the current contraindication "Organic leasion at risk of bleeding" and proposed to replace it with "Lesion or condition which significantly increases the risk of major bleeding, such as major arteriovenous malformations or vascular aneurysms; major intraspinal or intracerebral vascular abnormalities". The dilemma was that on one hand one would like to provide firm, specific guidance to prescribers about what constitutes a contraindication with regard to increased bleeding risk, and on the other hand it is important to allow for an individual assessment by the prescribing physician of the benefits and risks in each individual case where there are haemmorhagic risk factors.The arguments made by the MAH that is important to balance risk and benefit on an individual basis and allow for the physician to make benefit-risk assessment for as many patients as possible were in many respects supported by the CHMP. The problem with the proposed wording was however that it leaved the impression that only the mentioned conditions (major arteriovenous malformations or vascular aneurysms; major intraspinal or intracerebral vascular abnormalities) are contraindications. Certainly, other conditions such as active ulcerative

gastrointestinal disease would in severe cases be reasons not to use Pradaxa. Consequently, after considering the various options CHMP is of the opinion this to be the most appropriate solution that the contraindication "Organic lesion at risk of bleeding" is replaced by: "Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities".

It has been also noted that the contraindication "Spontaneous or pharmacological impairment of haemostasis" was not fully consistent with other sections of the SmPC. The contraindication may imply that any medication that impairs or has the potential to impair haemostasis is contraindicated. This would include any anticoagulant/antiplatelet agent, including acetylsalicylic acid, NSAIDs and SSRIs. However, in other sections of the SmPC (4.4 and 4.5), warnings and further details about the interactions were provided, but the use of the agents are not specified as contraindicated. For all anticoagulants and antiplatelet agents as well as other medicines or classes of medicines known to (potentially) impair haemostatis, the MAH was asked to - based on all available evidence - discuss the appropriate level of caution (contraindication, warning/precaution or neither) that should be applied when used concomitantly with Pradaxa and to propose changes to the SmPC accordingly. Further, the MAH was asked to discuss whether recommendations about the use of these concomitant medicines in patients undergoing hip/knee replacement should be provided, including advice as to if/when these medicines should be discontinued prior to surgery and when they can be safely restarted afterwards. In response the MAH proposed to remove "pharmacological impairment of haemostasis" as a contraindication arguing that combination of any medicine that impairs hemostasis with Pradaxa will increase the risk of bleeding but may be justified based on the physician's judgement of the benefit-risk balance in each individual treatment. As for the previously discussed contraindication the dilemma was also here the balance between providing firm, specific guidance to prescribers about what constitutes a contraindication with regard to increased bleeding risk and allowing for an individual assessment by the prescribing physician of the benefits and risks in each individual case where there are hemorrhagic risk factors. Overall, the removal of the contraindication was supported by the CHMP. Instead the following contraindication was agreed by the CHMP: "Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2)". With regard to the other part of the original contraindication, it was considered that "Spontaneous impairment of haemostasis" is too unspecific and may be interpreted as including conditions that should not be regarded as absolute contraindications. Hence, the mention of "Congenital or acquired coagulation disorders" and "Thrombocytopenia or functional platelet defects" in section 4.4 as conditions that require a careful benefit-risk assessment was considered more appropriate. A more precise definition of severe conditions relating to these disorders that would constitute a contraindication was considered, but it was concluded that the now proposed text in section 4.4 is sufficient to make prescribers aware that they should only use Pradaxa in patients with these conditions after a thorough benefit-risk assessment and only when the benefit outweighs the bleeding risk.

Ad Hoc Experts Group Meeting for Pradaxa 6 March 2012

Following the CHMP request, an ad hoc expert group meeting was convened on 6 March 2012 to provide advice on the list of questions adopted by the CHMP at its February 2012 meeting (please, see the Minutes from the Ad Hoc Experts Group meeting enclosed in Attachement 8). The questions posed to experts were regarding: (1) the need for the routing monitoring of Pradaxa, (2) the monitoring/treatment/ follow up which could improve management of Pradaxa treated patients

experiencing trauma/acute injury and major bleeding, (3) the recommendations regarding management of bleeding events in patients taking Pardaxa and (4) the need for dose modification or SmPC clarifications to diminish the risk of bleeding events.

The majority of experts agreed that no routine monitoring of the anticoagulant activity of Pradaxa is recommended (which is the recommendation in the current Product Information (PI)) because the desired plasma drug level and the therapeutic window are not known and there is significant variability of more widely available tests such as the aPTT making interpretation difficult. It was recognised that the RELY study (that included about 18 000 patients) was not a plasma-level-driven trial; on the contrary the results were based on the specific dosing regimen that is reflected in the current PI.

The experts reviewed the recommendations for management of major bleeding included in the RELY study protocol that were provided by the MAH and found them to follow standard practice and to be in line with the latest proposal of the PI. It was proposed that the consultation of a coagulation expert in case of major bleeding could be recommended in the PI as it was in the protocol of the RELY study. The information about the danger of dehydration was suggested to be included into the PIL as it may lead to changes in renal function in susceptible patients.

The new proposal for the management of the major bleeding, in particular the recommendation to consider the use of activated PCC, recombinant factor VIIa or concentrates of coagulation factors (section 4.9 of the SmPC proposed within FUM 029) was supported by the Group. Some experts admitted however that the increased risk of rebound thromboembolism could be observed with the use of some of these agents (PCC).

The experts confirmed that the standard dose currently proposed for majority of patients (150 mg BID) should left in the PI because the results of the RELY trial are based on this dosing regimen. The Group felt that the wording of Section 4.2 is relatively clear given the complexity of the information included in this section. Nevertheless, the proposal to further clarify this section was supported by the experts.

The CHMP agreed with the advice received from the experts.

Risk of myocardial infarction/acute coronary syndrome

A recent meta-analysis by Ken Uchino and Adrian V Hernandez (Circulation. 2011; 124: A15500) suggested that Pradaxa was associated with an increased risk of myocardial infarction/acute coronary syndrome. Within the FUM 029 the MAH was requested to provide the MAH's view on the meta-analysis.

In the RE-LY study supporting the new indication in atrial fibrillation patients, a slightly higher rate of myocardial infarction (MI) was noted in patients treated with either of the Pradaxa doses than in patients treated with warfarin. This lead to the following wording in the SmPC:*"In the phase III study RE-LY (see section 5.1.) the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone."* This finding from the RE-LY study formed a background for conducting the meta-analysis by Ken Uchino and Adrian V Hernandez (Circulation. 2011; 124: A15500) presented at the American Heart Association Congress in 2011. The objective of the meta-analysis was

to systematically evaluate the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran etexilate for several indications, and the authors conducted a search in PubMed of non-inferiority randomized controlled studies of dabigatran etexilate that reported MI or ACS as secondary outcomes. Seven trials encompassing 31,097 patients were selected and are summarized below: two studies in prophylaxis of stroke in atrial fibrillation (AF) (RE-LY and PETRO), one study in acute venous thromboembolism (RE-COVER), one study in acute coronary syndrome (ACS) (RE-DEEM), three studies in prophylaxis of deep venous thrombosis in hip or knee replacement surgery (RE-NOVATE, RE-MODEL and RE-MOBILIZE). Control arms included warfarin, enoxaparin or placebo. The result of the meta-analysis was that dabigatran etexilate was significantly associated with a higher risk for MI or ACS than the control group (dabigatran etexilate 255/20718=1.23% vs. control 91/10379=0.88%; OR 1.31, 95% CI 1.03-1.67). Similar results were seen when using the revised RE-LY dataset or when excluding the short-term orthopedic surgery trials. The authors conclude that dabigatran etexilate is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls, and that clinicians should consider the potential of these serious harmful cardiovascular effects in the use of dabigatran etexilate.

The MAH highlighted a number of methodological weaknesses and limitations of the meta-analysis. They can be summarized as follows: (1) pooling of data across trials with different comparators, patient populations, indications and doses, (2) Inclusion of low subtherapeutic doses from phase II trials, (3) Using an outdated dataset from the RE-LY study for the primary analysis, (4) Non-inclusion of other published data (from the RE-MEDY and RE-SONATE studies) and data available to the MAH. Instead, the MAH draws the attention to its own Acute Coronary Syndrome Overview (U11-3561-01). This overview was completed just prior to the start of the current procedure and is an extensive analysis of acute coronary syndrome events associated with the use of dabigatran etexilate, and the main topics are: epidemiology, non-clinical aspects of atherothrombosis, the atrial fibrillation study (RE-LY), the ACS study (RE-DEEM), the venous thromboembolism (VTE) studies, meta-analyses. The section in the company review on the RE-LY study in AF patients is mainly a repetition of the already known and assessed results of the study. However, the MAH emphasized that an excess of first MI occurrence in the dabigatran etexilate treatment arms, compared to warfarin was still present, more than three months after their RE-LY study drug was discontinued. The MAH suggested that the difference in MI incidence rates could have been due to underlying imbalances between the treatment groups rather than the treatments themselves as nearly 20% of the MIs in the dabigatran etexilate treatment groups occurred off treatment. Further subgroup analyses were presented, and one particular finding was noted, namely that in the subgroup of patients with valvular heart disease (VHD) at baseline, the difference in MI rate favouring warfarin was much higher than in the overall population. The company suggested that the low rate in the warfarin-treated group could be a chance finding. The hazard ratios (HR) for MI and death compared to warfarin in this subgroup were close to 1 and similar to the HRs seen for the overall population. The MAH reiterated the favourable results for dabigatran etexilate compared to warfarin on major endpoints and concluded that overall for AF patients receiving dabigatran etexilate for stroke prevention, the small numeric imbalance in MI occurrence for patients receiving dabigatran etexilate compared to warfarin was outweighed by lower rates of stroke, vascular death, CV death, and all cause death. This conclusion was generally endorsed by the CHMP, but the MAH was asked to discuss whether the findings in the subgroup of patients with valvular heart disease (VHD) warrant strengthening of the product information. Following further explanation the CHMP agreed with the MAH that the results from the RE-LY study on the frequency of MI in warfarin-treated patients with or without VHD lacked biological/clinical plausibility and were not readily explainable other than as a spurious finding. Further, even if it was a true finding, the current wording of the atrial fibrillation indication to a large extent excludes patients with VHD.

The section on the phase II dose-finding RE-DEEM study in ACS patients summarized the rates of MI (fatal and non-fatal) which were 1.6% for placebo and 3.0, 2.7, 1.7, and 2.3% for dabigatran etexilate doses 50, 75, 110, and 150 mg bid, respectively. The MAH noted that fatal MIs only occurred in the placebo and two lowest dabigatran etexilate doses, 50 and 75 mg bid. In the high dose dabigatran etexilate 110 mg bid and dabigatran etexilate 150 mg bid treatment groups there were no fatal MIs, and similar total MI rates, and lower all cause death rates, compared to those receiving placebo.

In the section on the VTE studies, both the orthopaedic surgery (hip and knee replacement) primary prevention VTE studies and the acute VTE/secondary prevention of VTE studies were discussed. In the initial three orthopaedic surgery studies (RE-MOBILIZE, RE-MODEL and RE-NOVATE), the incidence rates of ACS and MI were low and comparable between the dabigatran etexilate and the comparator used in all these studies, enoxaparin (0.39 and 0.41%, respectively). Studies in acute VTE (RE-COVER and RE-COVER II) and a secondary VTE prevention study (RE-MEDY) included warfarin as an active comparator and showed low incidence rates of MI, but there were numerically more MIs reported in the dabigatran etexilate treatment groups than in the warfarin groups, especially in RE-COVER II and REMEDY. In another secondary VTE prevention study (RE-SONATE) comparing dabigatran etexilate to placebo (RE-SONATE), there was only one MI in each treatment group.

The CHMP assessed the meta-analysis conducted by the company itself. The meta-analysis was performed to assess the frequency of MI and CV outcome events individually and in several composite endpoints. In a subanalysis that included only clinical trials comparing dabigatran etexilate to warfarin (six studies in AF and acute VTE/secondary prevention of VTE), there were more MI events in the dabigatran etexilate treatment groups than those receiving warfarin. From randomization to study termination, the odds ratios (OR) for MI (95% CI) were 1.30 (0.96, 1.76) and 1.42 (1.07, 1.88), for dabigatran etexilate 110 mg bid or 150 mg bid, compared to warfarin, respectively. The assessment of events for studies comparing dabigatran etexilate to enoxaparin (five studies, all in primary prevention of VTE in orthopaedic surgery) or placebo (three studies in primary prevention of VTE in orthopaedic surgery, secondary prevention of VTE and treatment of ACS) was limited due to smaller treatment groups and infrequent outcome events, and consequently the confidence intervals were wide. The odds ratio (OR) for MI (95% CI) was 0.5 (0.22, 1.10) for dabigatran etexilate 220 mg qd compared to enoxaparin. The odds ratios (OR) for MI (95% CI) were 1.07 (0.36, 3.20) and 1.37 (0.50, 3.70), for dabigatran etexilate 110 mg bid or 150 mg bid, compared to placebo, respectively.

The pitfalls in meta-analyses on adverse events reported from clinical trials were recently highlighted in a Commentary by Huang et al. (Pharmacoepidemiology and Drug safety 2011: 20: 1014-1020). The metaanalysis by Uchino & Hernandez did not provide sufficient information to assess whether the standards recommended by Huang et al. were met. The main criticism by the MAH was that the meta-analysis pooled a set of heterogeneous trials, and this was a valid point according to Huang et al. who suggested that meta-analyses should be conducted with subpopulations that share a similar benefit-risk profile. The MAH has provided its own comprehensive overview of MI/ACS associated with the use of dabigatran etexilate. The overview includes a meta-analysis that to some extent addresses the weaknesses of the meta-analysis by Uchino and Hernandez. When looking at the studies with warfarin as a comparator individually and from the meta-analysis, it appeared to be a consistent and relatively robust finding that the incidence of MI in patients treated with dabigatran etixilate was higher than in patients treated with warfarin. The absolute differences were small, and it was agreed by the CHMP that the difference is counterbalanced by dabigatran etexilate's beneficial effects in terms of stroke reduction and lower observed rates of CV mortality and overall mortality by a solid margin. It was not finally established whether the difference in MI rates between dabigatran etixilate and warfarin represent a true adverse effect of dabigatran or is caused by a protective effect of warfarin (or both). To some extent the question is academic and of limited practical interest given the differences favouring dabigatran etixilate over warfarin on a number of other important endpoints. Since no

increased rate of MI was convincingly shown in studies where dabigatran etexilate was compared to placebo or enoxaparin, it seems plausible that the imbalance in the RE-LY trial could be explained by a protective effect of warfarin. The dose-response relationship with regard to the incidence of MI was not clear-cut; some analyses suggested a dose-response relation, but in the study in ACS (RE-DEEM) the incidence of MI was highest in patients treated with the lowest doses of dabigatran etixilate. In conclusion, the MAH response regarding this issue was considered by the CHMP as satisfactory.

The CHMP requested in addition an analysis of post-marketing reports of myocardial infarction/acute coronary syndrome in the perspective of what was observed in the clinical trials with Pradaxa, in particular the RE-LY study. The approach taken by the MAH for answering this question was very similar to the approach taken when addressing the fatal bleedings topic. The MAH has performed a worldwide search for spontaneous and health authority individual case safety reports (ICSRs) that concern the MedDRA terms "myocardial infarction", "angina unstable", "ECG signs of myocardial ischaemia" and "myocardial ischaemia". The cut-off date for the data was 31 October 2011. This has resulted in the identification of 133 ICSRs. For myocardial infarction alone, 126 cases were identified. In 44 patients, a fatal outcome was reported. The majority of the cases were reported from North America. No indication was reported in 52 cases, atrial fibrillation was the indication in 62 cases, primary VTE prevention in 17 cases, and off-label use in 2 cases. As seen with the reports on fatal bleedings, information about demographics, other baseline characteristics and concomitant medication was lacking in a large proportion of the reports. Looking at the information that was available, there were no major unexpected findings with regard to gender and age distribution for the post-marketing reported events compared to the events observed in the RE-LY study. However, the proportion of very old patients was higher in the post-marketing reported cases. The MAH has compared the occurrence of MI/ACS reports post-marketing with the rate of MI observed in the RE-LY study. A cumulative reporting rate has been calculated based on the number of individual case safety reports (ICSRs) (= numerator) and global bulk sales (= denominator). The resulting post-marketing MI/ACS rate was estimated to be 3.2 per 10,000 patient years. In comparison, the rate was about 80 per 10,000 patient years in the RE-LY study. Further, the MAH compared the occurrence of fatal MI/ACS reports post-marketing with the rate of fatal MI (calculated from the adjudication categories of vascular death as sudden and non-sudden cardiac death occurring after a recent MI) in the RE-LY study. The resulting post-marketing fatal MI/ACS rate is estimated to be 1.1 per 10,000 patient years. In comparison, the rate was 6.8 per 10,000 patient years in the RE-LY study (the two does combined). The MAH concluded that the post-marketing MI/ACS and fatal MI/ACS rates for dabigatran etexilate were substantially less than the respective rates seen in the RE-LY groups for both doses of dabigatran etexilate. The CHMP agreed that the reported rates of MI in the post-marketing setting were many-fold lower than observed in the RE-LY study. There was no suggestion that the MI rate in patients treated with Pradaxa in the clinical setting was larger than in the RE-LY study. Similarly to what was requested for fatal bleedings, the MAH was asked to provide an estimate of the actual drug consumption post-marketing and to repeat the calculation of the cumulative post-marketing MI/ACS rate on this basis (drug in stock should be excluded from the denominator). The MAH was also requested to comment on the likely level of under-reporting of MI/ACS. The point made by the MAH in response document that coronary ischemia and associated events would typically not raise strong suspicion of a causal association with anticoagulant therapy and consequently may be subject to more pronounced underreporting than bleeding events was supported. Even with most conservative (i.e. highest) rate of MI/ACS reports post-marketing (40.0 per 100,000 patient years), it was still many-fold lower than the rate of MI observed in the RE-LY study (about 800 per 100,000 patient years). Please note that in the last round of company responses, the rates were given as cases per 10,000 patient years. Overall, post-marketing MI/ACS and fatal MI/ACS rates for dabigatran etexilate are substantially less than the respective rates seen in the RE-LY groups for both doses of dabigatran etexilate and there was no suggestion that the MI rate in patients treated with Pradaxa in the clinical setting is larger than in the

RE-LY study. It is the position of the MAH that no changes are needed in the SmPC following the results of the meta-analysis and the analysis mentioned above. The CHMP agreed that the current wording in section 4.4 and 4.8 of the SmPC on MI is balanced.

The MAH has provided the RE-LY coagulation biomarker substudy findings, which described the levels of D-dimer, prothrombin fragment 1+2 (PF1,2), factor VIIa (FVIIa) and soluble tissue factor (sTF) at baseline and their relation to outcome events, in order to justify that there is no pathophysiological mechanism associated with dabigatran resulting in an increased risk of MI. However, it was widely accepted that the pathophysiological mechanism for MI mainly involves platelet activation and, consistently, antiplatelet therapy is the main pharmacological treatment after an ACS. Despite the fact that the PETRO dose-finding study with dabigatran showed an increase in urinary 11-dehydrothromboxane B2 (DTB2), which could be a marker of platelet activation (Ezekowitz et al. Am J Cardiol. 2007), the RE-LY coagulation biomarker substudy did not address this issue. The MAH was requested to discuss any clinical/preclinical data suggesting an increase in platelet aggregation/activation with dabigatran either during treatment or early after stopping dabigatran. In particular, the increase in urinary 11-dehydrothromboxane B2 (DTB2) in the PETRO study, which "needs resolution", according to the authors' conclusions, was asked to be addressed by the MAH, since it may be a consequence of a potential platelet activation by dabigatran. The MAH has provided a brief overview of the non-clinical evidence relating to thrombosis, atherothrombosis and platelet aggregation. With regard to the latter, there appear to be conflicting results in that the PETRO study showed an increase in urinary 11-dehydrothromboxane B2 (DTB2) whereas this was not the case in the RE-LY study. Additional non-clinical information will be available soon and will be assessed within the upcoming studies (included already previously in the RMP). The non-clinical data will obviously have to be seen in the context of the clinical data. The response by the MAH was considered satisfactory.

General issues

The MAH was requested to explain their follow-up procedures for serious ADRs and how they intend to improve the quality of spontaneous reports. The MAH has in its response outlined the company's standard procedures to obtain follow-up information on spontaneously reported adverse events. These procedures are in line with what is typically seen in the pharmaceutical industry. It is noted that the MAH uses event specific questionnaires in order to obtain more specific information about certain events/event categories and that the MAH in last quarter of 2011 introduced a bleeding event questionnaire. The latter is obviously relevant for the recording of bleeding events associated with Pradaxa. Further, the MAH stated that it has intensified the follow-up on reported adverse events in the second half of 2011 and that improvements have been observed from Q1 2011 to Q4 2011 on a number of parameters. While the quality of post-marketing reports to a high degree is dependent on the procedures implemented by the MAH, it should also be acknowledged that poor quality and lack of information in post-marketing reports is inevitable in a substantial proportion of the cases - even with the best intentions and efforts by the pharmaceutical company. The MAH's response was considered acceptable by the CHMP.

2.2.2. Discussion

Fatal bleeding events

In December 2011 the MAH was asked to perform a worldwide search for spontaneous and health authority individual case safety reports (ICSRs) that concern A) fatal bleeding events or B) serious bleeding cases where another cause of death was reported or the cause of death was unknown in patients treated with dabigatran etexilate. This has resulted in the identification of 340 ICSRs. These

included 260 cases of fatal bleedings (A) and 80 serious bleeding cases with another or unknown cause of death reported (B). In total, the 340 cases had reported 449 bleeding events as some subjects experienced more than one event. The MAH has provided an extensive spreadsheet encompassing all the aforementioned 340 cases and including information as requested in the question with the exception of renal function which has been addressed separately. Overall, this approach taken by the MAH was supported by the CHMP, although an elaborate discussion of the presented data was additionally requested. The analysis was hampered by the missing or incomplete data typically associated with post-marketing reports. According to the CHMP it did not reveal risk factors or findings that have not already been adequately addressed in the revised SmPC for Pradaxa (such as high age and impaired renal function). It was evident that a substantial number of very old patients were treated with doses higher than recommended in the EU SmPC.

From a calculation based on the search results described above as numerator and the bulk sales figures as denominator, the resulting post-marketing fatal bleeding rate was estimated to be 6.3 (Fatal A events) and 8.3 (Fatal B events) per 10,000 patient years (please see definition of Fatal A and B events under question 1b). In comparison, it was 16.6 for the 110 mg BID dose and 19.5 for the 150 mg BID dose in the RE-LY study. The rate was 31.0 for warfarin in the RE-LY study. There was no solid evidence to suggest that the fatal bleeding rate in patients treated with Pradaxa in the clinical setting was larger than in the RE-LY study. However, the denominator for the calculation may have been overestimated due to sold drug not actually having been taken by patients. Consequently, the MAH provided an estimate of the actual drug consumption post-marketing and repeat the calculation of the cumulative post-marketing bleeding rate and also discussed the likely level of underreporting. The information provided was considered reassuring by the CHMP.

Finally, an update on the development of a reversal agent/antidote for dabigatran has been provided by the MAH. The MAH commented on two recent publications on serious bleedings related to acute injury/trauma and provided an analysis of the topic with data both from clinical trials and from post-marketing reports. In light of the lack of an antidote the detailed information on recommended medical management of bleeding events associated with the use of Pradaxa was included into the product information and the RMP for Pradaxa. In addition an advice from the Ad Hoc experts Group was requested in this regard by the CHMP and the modifications to the SmPC were supported by the experts.

In conclusion, several sections of the SmPC were modified to provide further more specific guidance to the prescribers to diminish the risk related to bleeding events in patients taking Pradaxa. Furthermore educational materials were updated and should further diminish this risk.

Myocardial infarction/acute coronary syndrome

The objective of the meta-analysis by Ken Uchino and Adrian V Hernandez (Circulation. 2011; 124: A15500) was to systematically evaluate the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran etexilate for several indications. Seven trials encompassing 31,097 patients were selected. Control arms included warfarin, enoxaparin or placebo. The analysis indicated that dabigatran etexilate was significantly associated with a higher risk for MI or ACS than the control group (dabigatran etexilate 255/20718=1.23% vs. control 91/10379=0.88%; OR 1.31, 95% CI 1.03-1.67). The CHMP was of the opinion that the poster by Uchino and Hernandez does not provide sufficient information to assess whether the standards recommended for meta-analyses were met. The main criticism by the MAH was that the meta-analysis pooled a set of heterogeneous trials, and this was considered to be a valid point by the CHMP. The MAH has provided its own comprehensive overview of MI/ACS associated with the use of dabigatran etexilate. The overview included a meta-analysis that to some extent addresses the weaknesses of the meta-analysis by Uchino and Hernandez. When looking

at the studies with warfarin as a comparator individually and from the meta-analysis, it appeared to be a consistent and relatively robust finding that the incidence of MI in patients treated with dabigatran etixilate was higher than in patients treated with warfarin. The absolute differences were small, and it was agreed by the CHMP that the difference was counterbalanced by dabigatran etexilate's beneficial effects in terms of stroke reduction and lower observed rates of CV mortality and overall mortality by a solid margin.

Based on the current level of evidence it could not be finally established whether the difference in MI rates between dabigatran etixilate and warfarin represented a true adverse effect of dabigatran or was caused by a protective effect of warfarin (or both). To some extent the question was considered academic and of limited practical interest given the differences favouring dabigatran etixilate over warfarin on a number of other important endpoints. Since no increased rate of MI was convincingly shown in studies where dabigatran etexilate was compared to placebo or enoxaparin, it seemed plausible that the imbalance in the RE-LY trial could be explained by a protective effect of warfarin. The dose-response relationship with regard to the incidence of MI was not clear-cut; some analyses suggest a dose-response relation, but in the study in ACS (RE-DEEM) the incidence of MI was highest in patients treated with the lowest doses of dabigatran etixilate. Overall, the CHMP concluded that the MAH responded to the Uchino and Hernandez analysis satisfactory.

The MAH has compared the occurrence of MI/ACS reports post-marketing with the rate of MI observed in the RE-LY study. A cumulative reporting rate has been calculated based on the number of individual case safety reports (ICSRs) (= numerator) and global bulk sales (= denominator). The resulting post-marketing MI/ACS rate was estimated to be 3.2 per 10,000 patient years. In comparison, the rate was about 80 per 10,000 patient years in the RE-LY study. It was agreed that the reported rates of MI in the post-marketing setting are many-fold lower than observed in the RE-LY study. There was no suggestion that the MI rate in patients treated with Pradaxa in the clinical setting is larger than in the RE-LY study. It was the position of the MAH supported by the CHMP that no changes were needed in the SmPC. It was agreed that the current wording in section 4.4 and 4.8 on MI is balanced.

The conclusion of the CHMP is that the apparent excess risk of MI in atrial fibrillation patients treated with Pradaxa compared to patients treated with warfarin continues to be outweighed by lower rates of stroke, vascular death, CV death, and all cause death in the opinion of the CHMP.

Conclusions pertaining to both fatal bleedings and MI/ACS

The poor quality of the spontaneous reports and the level of missing information for several parameters was a concern. For example, only 12.9% of bleeding cases included information regarding renal status. Similarly only a small number of cases provided details of past medical history, concomitant medications, time to onset etc. The MAH explained their follow-up procedures for serious ADRs and how they intend to improve the quality of spontaneous reports. This response was considered satisfactory by the CHMP and the Committee agreed that the benefit-risk of Pradaxa remains positive.

2.3. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan. In the updated RMP the educational materials were brought in line with the SmPC modifications. The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product. No new additional risk minimisation activities were required.

2.4. Changes to the Product Information

Main modifications agreed by the CHMP to be included in the SmPC for Pradaxa were following:

- Section 4.2 of the SmPC was reorganised to improve the readability of the SmPC and to add the information about the recommended method to assess the renal function;

- In Section 4.3 previous contraindication: "Organic lesions at risk of bleeding" was modified into "Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities";

- In Section 4.3 previous contraindication: "Spontaneous or pharmacological impairement of hemostasis" was modified into: "Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2);

- In section 4.4 Table 1 (Summarises factors which may increase the haemorrhagic risk) was revised and aligned with the modified contraindications;

- In section 4.5 the information about concomitant use of Pradaxa and anticoagulant and antiplatelet aggregation agents was modified;

- In section 4.9 the information was included to improve the medical management of major bleedings in patients taking Pradaxa;

- In section 5.1 the information about the major bledding events related to the concomitant use of antiplatelets, ASA or clopidogrel and both dabigatran etexilate and warfarin, was included.

The below listed changes were agreed by the CHMP to the Product Information (PI):

Pradaxa 75 mg

4.2 Posology and method of administration

"For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg:

- Patients with moderate renal impairment (creatinine clearance, CrCL 30-50 ml/min) [see Renal impairment (prevention of VTE)]
- Patients who receive concomitant verapamil, amiodarone, quinidine [see Concomitant use of Pradaxa with strong P-glycoprotein (P-gp) inhibitors, i.e. amidarone, quinidine or verapamil (prevention of VTE)]
- Patients aged 75 or above [see Elderly (prevention of VTE)]"

"..Assessment of renal function (prevention of VTE):

In all patients:

- Renal function should be assessed by calculating the creatine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \; (\times 0.85 \text{ if female})}{\text{serum creatinine [μmol/l]}}$$

- For creatinine in mg/dl:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \; (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dl]}}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment."

"Renal impairment (prevention of VTE)

Treatment with Pradaxa in patients with severe renal impairment (CrCL < 30 ml/min) is contraindicated (see section 4.3).

In patients with moderate renal impairment (CrCL 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections 4.4 and 5.1).

~~Renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2).~~

~~While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).~~."

Elderly(prevention of VTE)

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections 4.4 and 5.1).

"As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min). While on treatment the renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc) (see sections 4.3, 4.4 and 5.2)."

4.3 Contraindications

"

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances

of switching therapy to or from Pradaxa (see section 4.2) or when UHF is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)

- ~~Organic lesion at risk of bleeding~~
- ~~Spontaneous or pharmacological impairment of haemostasis~~
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)"

4.4 Special warnings and precautions for use

Haemorrhagic risk

"As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of drugs affecting haemostasis by inhibition of platelet aggregation. 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."

"Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux ~~requiring proton pump inhibitors (PPI) or histamine 2 (H_2) blocker treatment~~ increase the risk of GI bleeding. The administration of a PPI can be considered to prevent GI bleeding. «

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"Table 1 summarises factors which may increase the haemorrhagic risk. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) ~~(strong P-gp inhibitors are contraindicated, see section 4.3 and 4.5)~~ Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis • ~~Other anticoagulants should not be used unless in switch situations are contraindicated except in switch situations (see section 4.3)~~
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • ~~Active ulcerative GI disease~~ • ~~Recent GI bleeding~~ • Recent biopsy, major trauma~~ or head injury~~ • ~~Recent ICH~~ • ~~Brain, spinal or ophthalmic surgery~~ • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal

	reflux

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Pradaxa should only be given if the benefit outweighs bleeding risks.

4.5 Interaction with other medicinal products and other forms of interaction

"There is no or only limited experience with the following treatments ~~have not been studied and~~ which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic agents, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and platelet aggregation agents such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone~~, rivaroxaban, and vitamin K antagonists~~ (see section 4.4).

"UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section~~s~~ 4.3~~4.2 and 4.4~~)."

4.9 Overdose

"Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. 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 should be given according to the physician's judgement.
Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings"

Pradaxa 110 mg

4.2 Posology and method of administration

"For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg:

- Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 ml/min) [see Renal impairment (prevention of VTE)]
- Patients who receive concomitant verapamil, amiodarone, quinidine [see Concomitant use of Pradaxa with strong P-glycoprotein (P-gp) inhibitors, i.e. amidarone, quinidine or verapamil (prevention of VTE)]
- Patients aged 75 or above [see Elderly (prevention of VTE)]"

"Assessment of renal function (prevention of VTE):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method.The formula is as follows:

- For creatinine in μmol/l:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [}\mu\text{mol/l]}}$$

- For creatinine in mg/dl:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dl]}}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment."

"*Renal impairment (prevention of VTE)*

Treatment with Pradaxa in patients with severe renal impairment (CrCL < 30 ml/min) is contraindicated (see section 4.3).

In patients with moderate renal impairment (CrCL 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections 4.4 and 5.1).

~~Renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2).~~

~~While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).~~"

"Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors (SPAF)

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.

For the following two groups the recommended daily dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily:
- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups, the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:
- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

See further down and sections 4.4, 4.5, 5.1 and 5.2."

"Assessment of renal function (SPAF):

In all patients:
- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

Additional requirements in patients with mild to moderate renal impairment and in patients aged over 75 years:

- Renal function should be assessed during treatment with Pradaxa at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [μmol/l]}}$$

- For creatinine in mg/dl:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dl]}}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment."

"*Renal impairment (SPAF)*

Treatment with Pradaxa in patients with severe renal impairment (CrCL < 30 ml/min) is contraindicated (see section 4.3).

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of Pradaxa is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of Pradaxa to 220 mg taken as one 110 mg capsule twice daily should be considered (see sections 4.4 and 5.2). Close clinical surveillance is recommended in patients with renal impairment.

~~Renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min)].~~

~~While on treatment renal function should be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).~~"

4.3 Contraindications

"

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2) or when UHF is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)
- ~~Organic lesion at risk of bleeding~~
- ~~Spontaneous or pharmacological impairment of haemostasis~~
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)"

4.4 Special warnings and precautions for use

Haemorrhagic risk

"As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of drugs affecting haemostasis by inhibition of platelet aggregation. 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."

« In a study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, ~~D~~dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux ~~requiring proton pump inhibitors (PPI) or histamine 2 (H_2) blocker treatment~~ increase the risk of GI bleeding. In these atrial fibrillationpatients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in section 4.2 be followed. The administration of a PPI can be considered to prevent GI bleeding. »

"Table 1 summarises factors which may increase the haemorrhagic risk. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) ~~(strong P-gp inhibitors are contraindicated, see section 4.3 and 4.5)~~ Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis • ~~Other anticoagulants should not be used unless in switch situations are contraindicated except in switch situations (see section 4.3)~~
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • ~~Active ulcerative GI disease~~ • ~~Recent GI bleeding~~ • Recent biopsy, major ~~trauma or head injury~~ • ~~Recent ICH~~ • ~~Brain, spinal or ophthalmic surgery~~ • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Pradaxa should only be given if the benefit outweighs bleeding risks.

4.5 Interaction with other medicinal products and other forms of interaction

"Anticoagulants and antiplatelet aggregation agents

"There is no or only limited experience with the following treatments ~~have not been studied and~~ which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic agents, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and platelet aggregation agents such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone~~, rivaroxaban, and vitamin K antagonists~~ (see section 4.4).

"From the limited data collected in the phase III study RE LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3)."

"UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section~~s~~ 4.3~~4.2 and 4.4~~)."

Clopidogrel and ASA: From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of antiplatelets, ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin (see section 4.4). ~~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 (see section 4.4). The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin."~~

"~~From the data collected in the phase III study RE-LY (see section 5.1) 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 (see section 4.4). The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin~~"

4.9 Overdose

"Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. 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 should be given according to the physician's judgement.
Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings"

5.1 Pharmacodynamic properties

"The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin."

Table 14: Hazard Ratio and 95 % CI for major bleeds by subgroups

Endpoint	Dabigatran etexilate	Dabigatran etexilate

	110 mg twice daily vs. Warfarin	150 mg twice daily vs. Warfarin
Age (years)		
< 65	0.33 (0.19, 0.59)	0.36 (0.21, 0.62)
65 ≤ and < 75	0.70 (0.56, 0.89)	0.80 (0.64, 1.00)
≥ 75	1.01 (0.83, 1.23)	1.18 (0.98, 1.43)
≥ 80	1.12 (0.84, 1.49)	1.35 (1.03, 1.77)
CrCL(ml/min)		
30 ≤ and < 50	1.00 (0.77, 1.29)	0.94 (0.72, 1.21)
50 ≤ and < 80	0.76 (0.61, 0.93)	0.89 (0.73, 1.08)
≥ 80	0.59 (0.43, 0.82)	0.84 (0.62, 1.13)
ASA use	0.85 (0.68, 1.05)	0.92 (0.75, 1.14)
Clopidogrel use	0.88 (0.56, 1.37)	0.95 (0.62, 1.46)

Pradaxa 150 mg

4.2 Posology and method of administration

"For the following two groups the recommended daily dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups, the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

See further down and sections 4.4, 4.5, 5.1 and 5.2."

"Assessment of renal function (SPAF):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

Additional requirements in patients with mild to moderate renal impairment and in patients aged over 75 years:

- Renal function should be assessed during treatment with Pradaxa at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]}\ (\times 0.85 \text{ if female})}{\text{serum creatinine [μmmol/l]}}$$

- For creatinine in mg/dl:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]}\ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dl]}}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment."

"Renal impairment (SPAF)

Treatment with Pradaxa in patients with severe renal impairment (CrCL < 30 ml/min) is contraindicated (see section 4.3).

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of Pradaxa is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of Pradaxa to 220 mg taken as one 110 mg capsule twice daily should be considered (see sections 4.4 and 5.2). Close clinical surveillance is recommended in patients with renal impairment.

~~Renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min)].~~

~~While on treatment renal function should be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).~~"

4.3 Contraindications

"

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2) or when UHF is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)
- ~~Organic lesion at risk of bleeding~~
- ~~Spontaneous or pharmacological impairment of haemostasis~~
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)"

4.4 Special warnings and precautions for use

Haemorrhagic risk

"As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of drugs affecting haemostasis by inhibition of platelet aggregation. 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."

« In a study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, ~~D~~dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux ~~requiring~~

~~proton pump inhibitors (PPI) or histamine 2 (H_2) blocker treatment~~ increase the risk of GI bleeding. In these atrial fibrillationpatients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in section 4.2 be followed. The administration of a PPI can be considered to prevent GI bleeding. »

"Table 1 summarises factors which may increase the haemorrhagic risk. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) ~~(strong P-gp inhibitors are contraindicated, see section 4.3 and 4.5)~~ Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis • ~~Other anticoagulants should not be used unless in switch situations are contraindicated except in switch situations (see section 4.3)~~
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • ~~Active ulcerative GI disease~~ • ~~Recent GI bleeding~~ • Recent biopsy, major ~~trauma or head injury~~ • ~~Recent ICH~~ • ~~Brain, spinal or ophthalmic surgery~~ • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Pradaxa should only be given if the benefit outweighs bleeding risks.

4.5 Interaction with other medicinal products and other forms of interaction

"Anticoagulants and antiplatelet aggregation agents

"There is no or only limited experience with the following treatments ~~have not been studied and~~ which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic agents, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and platelet aggregation agents such as GPIIb/IIIa receptor

antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone~~, rivaroxaban, and vitamin K antagonists~~ (see section 4.4).

"From the limited data collected in the phase III study RE LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3)."

"UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section~~s~~ 4.3~~4.2 and 4.4~~)."

Clopidogrel and ASA: From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of antiplatelets, ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin (see section 4.4). ~~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 (see section 4.4). The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin."~~

"~~From the data collected in the phase III study RE-LY (see section 5.1) 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 (see section 4.4). The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin~~"

4.9 Overdose

"Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. 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 should be given according to the physician's judgement.
Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings"

5.1 Pharmacodynamic properties

"The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin."

Table 14: Hazard Ratio and 95 % CI for major bleeds by subgroups

Endpoint	Dabigatran etexilate 110 mg twice daily vs. Warfarin	Dabigatran etexilate 150 mg twice daily vs. Warfarin
Age (years)		
< 65	0.33 (0.19, 0.59)	0.36 (0.21, 0.62)
65 ≤ and < 75	0.70 (0.56, 0.89)	0.80 (0.64, 1.00)
≥ 75	1.01 (0.83, 1.23)	1.18 (0.98, 1.43)
≥ 80	1.12 (0.84, 1.49)	1.35 (1.03, 1.77)
CrCL(ml/min)		
30 ≤ and < 50	1.00 (0.77, 1.29)	0.94 (0.72, 1.21)
50 ≤ and < 80	0.76 (0.61, 0.93)	0.89 (0.73, 1.08)
≥ 80	0.59 (0.43, 0.82)	0.84 (0.62, 1.13)
ASA use	0.85 (0.68, 1.05)	0.92 (0.75, 1.14)
Clopidogrel use	0.88 (0.56, 1.37)	0.95 (0.62, 1.46)

The consecutive changes were introduced into the Annex IIIB and were agreed by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

In December 2011 the CHMP requested the MAH to provide the tabulated description of all fatal bleeding cases associated with Pradaxa use, in light of the significant increase in the number of fatal bleeding events associated with the use of Pradaxa since the completion of variation Pradaxa EMEA/H/C/000829/II/0022. The MAH was asked to provide an in-depth analysis and discussion of whether the occurrence of fatal bleedings events in the real-world setting observed so far is higher than expected from the RE-LY study results. In addition, a recent meta-analysis by Ken Uchino and Adrian V Hernandez was published (Circulation. 2011; 124: A15500) where it was suggested that Pradaxa is associated with an increased risk of myocardial infarction/acute coronary syndrome. The MAH was requested to provide its view on the meta-analysis. The assessment of these responses was done within the ARs for FUM 029 and for FU2 029.1. In addition an Ad Hoc Experts Group meeting on Pradaxa was convened on 6th March 2012 to advise the CHMP in particular on the possible improvement in prevention and medical management of bleeding events related to the use of Pradaxa. Current variation was submitted to update the SmPC with regards to the contraindications and warnings related to haemorrhagic risk factors and to respond to additional questions as requested in the ARs for FUM 029 and FU2 029.1.

Following the assessment of all the information provided by the MAH the CHMP concluded that the benefit-risk for Pradaxa remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation accepted		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.3, 4.4, 4.5, 4.9 (all 3 strengths) and 5.1 (110 and 150 mg strengths) of the SmPC in order to minimise the risk related to bleeding events in patients treated with Pradaxa following the AR for FUM 029. The Package Leaflet was proposed to be updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.