11 April 2013
EMA/PRAC/212356/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

PSUR assessment report

dabigatran etexilate

Procedure No: EMEA/H/C/000829/PSU034

Period covered by the PSUR: 19 March 2012 to 18 September 2012

Note

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

Following the PRAC recommendation on this PSUR, the Committee for Medicinal Products for Human Use (CHMP) adopted an opinion. This opinion's annex IV "Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation can be found under the Assessment history tab of the EPAR.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

List of abbreviations

ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
AERS	Adverse Event Reporting System
AF	Atrial Fibrillation
AGEP	Acute Generalised Exanthematous Pustulosis
ALT	Alanine-Aminotransferase
BI	Boehringer Ingelheim
BI GDSD	BI Global Drug Safety Database
bid	*bis in die* (twice a day)
CaseID	Case Identification
CCDS	Company Core Data Sheet
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
CrCl	Creatinine Clearance
DLP	Data Lock Point
DVT	Deep Vein Thrombosis
EBGM	Empirical Bayesian Geometric Mean
EEA	European Economic Area
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
EU	European Union
FDA	Food and Drug Administration
GDSD	Global Drug Safety Database
GI	Gastrointestinal
HP	Healthcare Professional
HR	Hazard Ratio
ICH	International Conference on Harmonisation (of technical Requirements for Registration of Pharmaceuticals for Human Use)
ILD	Interstitial Lung Disease
IMS	Intercontinental Marketing Services
INR	International Normalised Ratio
IP	Interstitial Pneumonia
KFDA	Korea Food and Drug Administration

LLT	Lowest Level Term
MAH	Marketing Authorisation Holder
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health Labour and Welfare
MIDAS	Multinational Integrated Data Analysis
NI	No information
NS	Non-Serious
PE	Pulmonary Embolism
PFP	Product Familiarisation Programme
P-gp	P-glycoprotein
PK	Pharmacokinetic
PL	Package Leaflet
PMDA	Pharmaceutical and Medical Devices Agency
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Preferred Term
pVTEp	Primary Venous Thromboembolism prevention
RE-LY	Randomized Evaluation of Long term anticoagulant therapy
RD	Risk Difference
RI	Reporting Index
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDR	Signal of Disproportionate Reporting
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPAF	Stroke Prevention in Atrial Fibrillation
TEN	Toxic Epidermal Necrolysis
TIA	Transient Ischaemic Attack
TTO	Time to onset
ULN	Upper Limit of Normal
US	United States
VTE	Venous Thromboembolism
WebVDME	Web Visual Data Mining Environment

1. Steps taken for the assessment

This is the assessment of PSUR received for dabigatran etexilate with a DLP 18 September 2012 as follows:

MAH	Marketing authorisation concerned	Submission date
Boehringer Ingelheim	Pradaxa (EU/1/08442/001-019)	20 November 2012

The steps taken for the procedure were:

Start of procedure:	13 December 2012
PRAC Rapporteur's preliminary assessment report circulated on:	13 February 2013
MAH comments on the Rapporteur preliminary assessment report received on:	13 March 2013
PRAC Rapporteur's updated assessment report circulated on:	03 April 2013
PRAC recommendation:	11 April 2013

2. PSUR Data

2.1. Introduction (executive summary)

This is the eighth PSUR for dabigatran etexilate (DE). The report updates safety information on dabigatran etexilate given as mesilate for the period 19 Mar 2012 to 18 Sep 2012. Pradaxa was authorized in the EU on 18 March 2008.

Pradaxa is available as a hard hydroxypropylmethylcellulose capsule containing DE as active substance in the dose strengths 75 mg, 110 mg and 150 mg. DE is the oral pro-drug of the active moiety dabigatran. Dabigatran is a potent, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the thrombus development. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In the EU, the authorised indications for DE use are:

• Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

• Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- o Previous stroke, transient ischemic attack (TIA), or systemic embolism
- o Left ventricular ejection fraction <40%
- o Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- o Age ≥75 years

o Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

In addition, the substance is currently under investigation in the following indications:

- Acute venous thromboembolism (VTE) treatment
- Secondary prevention of VTE
- Prevention of stroke, systemic embolism and valve thrombosis in patients with mechanical heart valves (development discontinued end of 2012).

During the update period, the MAH received 9238 case reports (7437 [healthcare-professional] HP-confirmed; 1801 non-HP-confirmed) including 15 689 ADRs (11 947 HP-confirmed; 3742 non- HP-confirmed). In addition, late-breaking information (19 Sep 2012 to 18 Oct 2012) on 1700 cases (1420 HP-confirmed, 280 non-HP-confirmed) was considered. In general, the vast majority of ADRs received were assessed as already listed side effects for Pradaxa, reported terms describing the mode of action of Pradaxa or alternative explanations were reported.

As expected, bleeding events were the most often reported ADRs. In 43.2% of all HP-confirmed cases received during the update period, at least one bleeding event or an event associated to bleeding was reported. In 238 (7.4%) of the cases for the update period, bleeding was associated with fatal outcome. The percentage of bleeding events from all reported events (43.2%) was comparable with that observed in the previous reporting period (44.5%).

Furthermore, in the current PSUR the following topics were investigated without giving rise to new safety concerns:

- Agranulocytosis/leucopenia
- Myocardial infarction
- Hepatotoxicity
- Renal function
- Haemorrhage

The current PSUR did not reveal any new safety issues and as such no particular issues need to be addressed except routine pharmacovigilance. The benefit-risk balance remains positive for the authorised indications.

Next PSUR

Submission of next PSUR is planned within 70 days after the DLP of 18 Mar 2013.

2.2. Worldwide marketing authorisation status

DE was first authorised in all member states of the European Economic Area (EEA) via centralised procedure. The IBD for dabigatran etexilate is 18 Mar 2008.

Dabigatran etexilate is currently authorised and/or marketed in 96 countries under the trade names Pradaxa®, Pradaxar®, Pradax® or Prazaxa®. On 07 Sep 2012 on request of the Canadian Health Authority, BI changed the local trade name for Pradax® to Pradaxa® in Canada.

2.3. Overview of exposure and safety data

2.3.1. Actions taken in the reporting interval for safety reasons

During the update period, there were:

- no marketing authorisation withdrawals, revocations or suspensions
- no failures to obtain a marketing authorisation renewal
- no restrictions on distribution
- no clinical trial suspensions
- no dosage modifications
- no changes in target population or indications
- no formulation changes
- no urgent safety restrictions
- no Dear Doctor Letters

2.3.2. Changes to reference safety information

The reference safety information for this PSUR valid at DLP of this PSUR, is the company core data sheet (CCDS)/ 0266 version 08, dated 03 Jul 2012. The current CCDS covers two indications and three dose strengths (75 mg, 110 mg and 150 mg). During the update period, the following updates were made to the CCDS:

CCDS 07 to CCDS 08 (03 July 2012)
Side effects

- Addition of new side effects angioedema and anaphylactic reaction under the SOC 'Immune system disorders'.
- Change of side effect term traumatic haematoma into traumatic haemorrhage under the SOC 'Injury, poisoning and procedural complications'.

Meaningful differences between CCDS and SmPC:
The SmPC variations implementing wording according to CCDS 0266 versions 5 and 7 were completed within the reporting period and did not result in meaningful differences to the CCDS. The CCDS 0266 version 6 item 'Addition of data from drug/drug interaction study dronedarone/dabigatran etexilate (1160.112) and recommendation against co-medication of dabigatran etexilate and dronedarone' was implemented in the SmPC (EMEA/H/C/000829/II/0028) in the form of a contraindication on EMA request. In the context of FUM 29 the SmPC and package leaflet were updated with procedure EMEA/H/C/000829/II/0031. The main label updates introduced by this variation pertained to a more precise specification and clarification of already approved contraindications and to the section on overdose, to which information on bleeding management has been added. As the updates to both sections were in line with the CCDS, changes to the CCDS were not foreseen. Approvals of the EU variation applications pertaining to CCDS 05, CCDS 06 and CCDS 07 were obtained within the review period. Variation EMEA/H/C/000829/II/0043 pertaining to CCDS 08 was obtained on 21 January 2013.

2.3.3. Patient exposure

The patient exposure to DE during the update period as per BI's standard method was estimated at 417 449 patient-years. During the update period, 8 clinical trials and 7 observational studies were ongoing, exposing patients to DE. Two clinical trials were reported during the update period (1160.85; 1160.88). A total of 17 558 subjects were treated in these trials and observational studies.

2.3.4. Adverse reactions

Frequently reported serious and non-serious adverse events

A total of 9238 cases were received during the update period of this PSUR with a total of 15 689 ADRs. Of these, 11 947 (76.1%) were HP-confirmed. The most frequently reported HP confirmed ADRs related to the SOCs 'gastrointestinal disorders' (3555 ADRs, 29.8%) and 'nervous system disorders' (1257 ADRs, 10.5%).

ID	MedDRA SOC	Serious		Non-serious		Total	
		n (%)					
14	Gastrointestinal disorders	1217	(10.2)	2338	(19.6)	3555	(29.8)
08	Nervous system disorders	918	(7.7)	339	(2.8)	1257	(10.5)
22	General disorders & admin. site cond.	326	(2.7)	576	(4.8)	902	(7.6)
23	Investigations	228	(1.9)	656	(5.5)	884	(7.4)
12	Vascular disorders	438	(3.7)	383	(3.2)	821	(6.9)
16	Skin & subcutaneous tissue disorders	73	(0.6)	626	(5.2)	699	(5.9)
24	Injury, poisoning & procedural complic.	247	(2.1)	424	(3.5)	671	(5.6)
13	Respiratory, thoracic & mediastinal dis.	275	(2.3)	376	(3.1)	651	(5.4)
18	Renal & urinary disorders	253	(2.1)	370	(3.1)	623	(5.2)
11	Cardiac disorders	368	(3.1)	56	(0.5)	424	(3.5)
03	Blood & lymphatic system dis.	157	(1.3)	96	(0.8)	253	(2.1)
17	Musculoskeletal, conn. tissue & bone dis.	51	(0.4)	183	(1.5)	234	(2.0)
01	Infections & infestations	122	(1.0)	58	(0.5)	180	(1.5)
06	Metabolism & nutrition dis.	59	(0.5)	76	(0.6)	135	(1.1)
09	Eye disorders	25	(0.2)	102	(0.9)	127	(1.1)
07	Psychiatric disorders	29	(0.2)	84	(0.7)	113	(0.9)
02	Neoplasms benign & malignant	104	(0.9)	6	(0.1)	110	(0.9)
15	Hepatobiliary disorders	56	(0.5)	37	(0.3)	93	(0.8)
20	Reproductive system & breast dis.	23	(0.2)	64	(0.5)	87	(0.7)
25	Surgical & medical procedures	21	(0.2)	32	(0.3)	53	(0.4)
04	Immune system disorders	4	(0.0)	28	(0.2)	32	(0.3)
10	Ear & labyrinth disorders	2	(0.0)	20	(0.2)	22	(0.2)
26	Social circumstances	8	(0.1)	5	(0.0)	13	(0.1)
05	Endocrine disorders	4	(0.0)	1	(0.0)	5	(0.0)
21	Congenital & familial/ genetic dis.	2	(0.0)	1	(0.0)	3	(0.0)
	Total	**5010**	**(41.9)**	**6937**	**(58.1)**	**11947**	**(100.0)**

In order to place the number of reported ADRs in perspective with the volume of marketed goods, reporting indices (RIs) were calculated per MedDRA SOC. The calculated reporting indices from the table do not represent exact incidences of ADRs. They can only be considered an estimate of reaction

incidences and may be used to compare the ADR profile across different PSURs. Overall, reporting indices for the current PSUR reporting decreased with respect to cumulative (PSUR 1 to 6) figures in the range of -29.1% to -84.1% (except for the SOC 'neoplasms benign & malignant' and 'social circumstances', where a small increase of 8.9% and 7.2%, respectively, was observed). Reporting indices also decreased for all SOCs when compared with the previous reporting period (PSUR 7) in the range of -6.3% to -78.3%, except for the SOC 'social circumstances' (increase of 29.3%). For this SOC, comparably small absolute number of ADRs (n=13) were received in the update period; therefore, minor changes of case counts already had an impact on the reporting index.

PSUR	**1-6**	**7**	**8**
Period **SOC**	**18 Mar 2008 to 18 Sep 2011**	**19 Sep 2011 to 18 Mar 2012**	**19 Mar 2012 to 18 Sep 2012**
Infections & infestations	**8.6**	7.9	4.3
Neoplasms benign & malignant	2.4	**3.3**	2.6
Blood & lymphatic system disorders	**10.7**	8.4	6.0
Immune system disorders	**1.7**	1.1	0.8
Endocrine disorders	**0.2**	0.2	0.1
Metabolism & nutrition disorders	**6.5**	4.5	3.2
Psychiatric disorders	**6.6**	4.8	2.7
Nervous system disorders	**45.3**	42.4	30.0
Eye disorders	**5.6**	4.6	3.0
Ear & labyrinth disorders	**1.1**	0.8	0.5
Cardiac disorders	**14.3**	11.8	10.1
Vascular disorders	**43.0**	27.9	19.6
Respiratory, thoracic & mediastinal dis.	**39.1**	23.5	15.6
Gastrointestinal disorders	**186.9**	138.9	85.0
Hepatobiliary disorders	**4.4**	2.9	2.2
Skin & subcutaneous tissue disorders	**31.8**	22.3	16.7
Musculoskeletal, conn. tissue & bone dis.	**14.1**	9.1	5.6
Renal & urinary disorders	**26.1**	20.5	14.9
Pregnancy, puerperium & perinatal cond.	0.0	**0.0**	0.0
Reproductive system & breast disorders	**3.5**	3.0	2.1
Congenital & familial/ genetic disorders	**0.5**	0.3	0.1
General disorders & admin. site conditions	**45.9**	30.2	21.6
Investigations	**56.3**	31.7	21.1
Injury, poisoning & procedural complic.	**33.4**	23.1	16.1
Surgical & medical procedures	**3.5**	1.4	1.3
Social circumstances	0.3	0.2	**0.3**
Total	**591.8**	424.8	285.7

All figures denoted in **bold** highlight the highest reporting index calculated for the SOC.

CASES WITH FATAL OUTCOME

Of the 7437 HP-confirmed cases received during the update period, 590 were reported with fatal outcome. The number of fatal cases per MedDRA SOC is shown in the table below.

SOC	Cases per SOC	
	n	%
General disorders and administration site conditions	128	21.7%
Nervous system disorders	105	17.8%
Gastrointestinal disorders	90	15.3%
Cardiac disorders	75	12.7%
Vascular disorders	54	9.2%
Infections and infestations	35	5.9%
Respiratory, thoracic and mediastinal disorders	33	5.6%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29	4.9%
Injury, poisoning and procedural complications	23	3.9%
Renal and urinary disorders	10	1.7%
Blood and lymphatic system disorders	3	0.5%
Hepatobiliary disorders	3	0.5%
Skin and subcutaneous tissue disorders	1	0.2%
Social circumstances	1	0.2%
Total	**590**	**100.0%**

Looking at treatment indications, the majority of cases with a fatal outcome concerned patients treated for the SPAF indication (n=386) followed by primary venous thromboembolism prevention ([pVTEp] n=14). Eleven patients were treated for off-label indications. In the remaining 179 cases, the indication was not reported. The below table shows primary cause of death in all patients with fatal outcome treated for SPAF:

Cause of death	n	%
Haemorrhage*	113	29.3
Cardiac event**	64	16.6
Ischaemic stroke	29	7.5
Thromboembolic event	2	0.5
Other	103	26.7
Not reported	75	19.4
Total	386	100.0

* Including intracranial haemorrhage (haemorrhagic stroke)

** Cardiac events included but were not limited to the following PTs: Heart failure myocardial infarction, cardiac arrest, ischaemic heart disease, arrhythmia, heart condition

The below table shows primary cause of death in all patients with fatal outcome treated for SPAF:

Table 11 Primary cause of death in all patients with fatal outcome treated for SPAF (19 Mar 2012 to 18 Sep 2012)

Cause of death	n	%
Haemorrhage*	113	29.3
Cardiac event**	64	16.6
Ischaemic stroke	29	7.5
Thromboembolic event	2	0.5
Other	103	26.7
Not reported	75	19.4
Total	386	100.0

* Including intracranial haemorrhage (haemorrhagic stroke)
** Cardiac events included but were not limited to the following PTs: Heart failure myocardial infarction, cardiac arrest, ischaemic heart disease, arrhythmia, heart condition

Selected cases containing new or relevant safety information by SOC

Agranulocytosis/leukopenia

A total of 18 cases were received during the update period. Of these 8 were serious cases reporting ADRs coding to the MedDRA PTs 'agranulocytosis' (n=5) and 'pancytopenia' (n=3).

Hepatobiliary disorders

The safety information received for this SOC was analysed regarding the topic 'hepatotoxicity'. 280 HP-confirmed case reports were received fulfilling the SMQ criteria. 124 case reports described an isolated elevation of coagulation parameters, which is in line with the mode of action of Pradaxa. In 58 cases originating from the SMQ search isolated elevation of liver enzymes were reported. This event is an already listed adverse drug reaction of Pradaxa. In 15 case reports retrieved from the SMQ search for the reporting period of this PSUR the outcome was fatal. In 4 of these 15 cases, a hepatic event was reported as cause of death or as contributory factor. In conclusion, the safety data on hepatobiliary events that came to the attention of the company during the update period of this PSUR did not reveal relevant new information concerning the safety profile of Pradaxa.

Renal and urinary disorders

A total of 10 fatal cases were reported for this SOC. Two hundred and twenty two cases of the total of 386 cases of this SOC were containing haemorrhagic events (6 fatal). The most frequently reported haemorrhagic event of this SOC was haematuria (88.3%, N=196 and urinary bladder haemorrhage (4.5%, N=10).

Haemorrhage

At case level, a total of 7437 HP-confirmed ADR case reports were received by BI during the update period. In 3214 (43.2%) of these cases, at least one bleeding event was reported, which is similar to the previous reporting period (44.5%, PSUR 7). The haemorrhagic events were distributed as follows to the various anatomical systems: gastrointestinal 47.1%; urogenital 10.4%; intracranial 8.1%; skin 6.6%; wound 1.5%; other locations 15.1% and no location reported 11.3%. This is very similar to the last update period. To assess the effect of potential drug interactions on the frequency of bleeding events, the occurrence of these events in patients concomitantly treated with P-gp inhibitors and/or anticoagulants was evaluated for all cases received during the update period and shown in the below table.

	No bleeding	Bleeding	Serious bleeding event	Fatal bleeding fatal event	All cases
	N (%)	N (%)	N (%)	N (%)	N (%)
Total (all ICSRs)	5399 (100.0)	3853 (100.0)	1762 (100.0)	272 (100.0)	9252 (100.0)
P-gp Inhibitors [1]	252 (4.7)	222 (5.8)	99 (5.6)	11 (4.0)	474 (5.1)
Anticoagulants [2]	390 (7.2)	409 (10.6)	244 (13.9)	43 (15.8)	799 (8.6)
P-gp inhibitors + Anticoagulants	44 (0.8)	61 (1.6)	38 (2.2)	6 (2.2)	105 (1.1)

[1] Drug class 'P-gp inhibitors' consisted of: amiodarone, clarithromycin, dronedarone, ketoconazole, nelfinavir, quinidine, reserpine, ritonavir, saquinavir, verapamil, tacrolimus, and cyclosporin.
[2] Drug class 'anticoagulants' included the following groups (WHO DD ATC 4 level): vitamin K antagonists, heparin group, other antithrombotic agents, and platelet aggregation inhibitors excl. heparin

A cumulative evaluation of all haemorrhagic events received from spontaneous reporting (spontaneous and health authority cases) since first launch in March 2008 was performed in the current PSUR. Comparing reporting rates for serious and fatal bleeding events observed under market conditions, the following can be concluded:

- Generally, reporting rates are lower than what would be expected from experience of the RE-LY trial (incidence rates); under-reporting has to be considered.
- Monthly cumulative reporting rates for fatal bleeding were stable during the PSUR update period; for serious bleeding events there is a trend for a decrease of monthly cumulative reporting rates in the update period.
- There does not appear to be a clinically meaningful difference between patients experiencing serious or fatal bleedings in terms of most patient characteristics. The percentage of patients ≥75 years of age may be slightly higher in the fatal subgroup; however, it needs to be taken into account that age information has not been reported for 36.3% and 38.3% of serious and fatal bleeding cases respectively.
- Especially for the comparison of the patient populations with fatal bleeding events the interpretation of data is difficult due to often limited information on single case level and relatively low case numbers, so that only limited conclusions can be drawn from the data available.
- No new risk factors have been detected by thorough analysis of market data available so far.

MAH response to question in previous PSUR 7

PSUR Question 2 of 3:

MAH mentions possible underreporting as a general issue. In the next PSUR MAH is asked to discuss whether actions should be taken to increase awareness and reporting of ADR for Pradaxa. The MAh responded that the safety profile of Pradaxa was investigated in well controlled clinical trials and based on the results of these trials frequencies for side effects have been calculated and are provided in the EU SmPC. It is well known that reporting rates of adverse drug reactions from post marketing experience are lower than reporting incidences calculated from well controlled clinical trials. However, spontaneous reporting rates might be influenced by published reports or programs which increase the public awareness of a product. Compared to products marketed for many years such as warfarin, which is also used in the SPAF indication, it is expected that the reporting rates for Pradaxa are higher. Reason for the higher reporting rate of adverse drug experiences observed in association with the use of Pradaxa compared to warfarin is the introduction of a new therapeutic principal (oral thrombin inhibitor) into the market. Heightened awareness is further stimulated by media and authority communications. This is not comparable with the reporting situation of warfarin which is available on

the market for more than five decades. The MAH has established educational programs for treating physicians including tools such as the prescriber guides for the various treatment indications and the patient alert card. Both are updated and distributed whenever new information becomes available. Based on the above it is considered that no further actions to increase the awareness of Pradaxa and to improve the reporting of ADRs are necessary.

Question from previous PSUR regarding pericardial effusion, pericardial hemorrhage and cardiac tamponade.

A relatively large number of cases of pericardial effusion, pericardial haemorrhage and cardiac tamponade have been found in one of the MSs Pharmacovigilance databases. Several cases have alternative aetiologies (e.g. recent cardiac surgery/cardioversion) however there are also cases without clear confounders. The SmPC includes mentioning of pericardial bleeding in the context of major bleeding, and it appears that the numbers of cases have increased more rapidly recently (since ~Nov 2011) and therefore may be related to the new indication in AF and use in patients at greater risk. The MAH is requested to review this subject with a view to identifying any additional risk factors, and to inclusion of these terms in the main table in section 4.8 of the SmPC if appropriate, given the potential severity of these events.

MAH response

In parallel to an increase in exposure, the MAH can confirm the observation of an increasing number of reports of 'Pericardial effusion', 'Pericardial hemorrhage' and 'Cardiac tamponade' from 2011. The MAH created a search algorithm comprised of the MedDRA PTs 'Pericardial effusion', 'Pericardial hemorrhage' and 'Cardiac tamponade' and identified 117 individual case safety reports in the MAH's global safety database from beginning of operation to database lock point on 23 Jul 2012. 37 of the 117 cases reported a clearly hemorrhagic origin of the event, 15 cases reported a clearly non-hemorrhagic origin and for the remaining 65 cases, no origin was reported or could be identified from the provided information.

Evaluation of the case series with effusions and tamponade of clearly hemorrhagic origin only:

Conclusive alternative explanations were reported for 32 of the 37 events. For some of the cases, more than one plausible alternative explanation was reported. Remarkably for several cases, identified and listed contraindications have not been respected (e.g., severe renal impairment) or Pradaxa was used in an unapproved indication ('anticoagulation in catheter ablation'). Especially the latter potential clinical use is being investigated for safety and efficacy in the DAPPAR-AF (Dabigatran for Peri Procedural Anticoagulation during Radiofrequency Ablation of Atrial Fibrillation) study by Allan Skanes (BI-study ID: 1160.125; ClinicalTrials.gov identifier: NCT01468155).

Evaluation of the case series with effusions and tamponade of clearly hemorrhagic and unknown origin:

This case series comprises 102 cases of effusions / tamponade of clearly non-hemorrhagic (N= 37) and unknown (N= 65) origin. 61 of 102 cases are considered to report conclusive alternative explanations for the occurrence of the selected events. Some reports contain more than 1 alternative explanation. In a total of 38 of these 61 cases, the events were reported together with invasive cardiac procedures. No alternative explanation was reported in 41 cases. In 35 of these, a causal association was considered 'not fully assessable' because of missing essential information with regards to temporal sequence of events or concomitant diseases / medication.

Evaluation of the case series with effusions and tamponade of clearly nonhemorrhagic and unknown origin:

This case series comprises 80 cases of effusions / tamponade of clearly non-hemorrhagic (N= 15) and unknown (N= 65) origin. In 40 cases (27 of these with a total daily dose of 300 mg), 'Atrial fibrillation' or equal terms were reported as indication. For all cases with dosing information available, predominantly 300 mg total daily dose was reported (33 of 80). The MAH considers the observation of an increased number of spontaneous reports as indicator of the increasing clinical use of Pradaxa in a per-se more vulnerable patient population with regards to cardiac events after market authorization for 'stroke prevention in patients with non-valvular atrial fibrillation'. The increasing number of reports from clinical trials in 2012 however, is reflecting the current phase II development program RE-ALIGN (A Randomized, Phase II Study to Evaluate the sAfety and Pharmacokinetics of oraL dabIGatran Etexilate in Patients after Heart Valve replacemeNt; Study-ID: 1160-113), which started in October 2011. All clinical trials cases in 2012 were reported from this single open-label study.

Evaluation of the clinical study database RE-ALIGN:
Exposing a particularly vulnerable patient population, the MAH evaluated the clinical database of the ongoing RE-ALIGN study (Study-ID: 1160.113: A Prospective, Randomised, Open label, Blinded Endpoint phase II study to Evaluate the sAfety of oraL dabIGatran etexilate in patients after heart valve replacemeNt) for case reports of the selected PTs. A total of 28 cases could be identified with date of 05th Oct, 2012. On a PT level, “pericardial effusion” was reported in 19 cases, “pericardial hemorrhage” in 8 cases, and “cardiac tamponade” was reported once. 18 cases were reported in the dabigatran treatment arms, 8 cases in the active control arm with warfarin and 2 cases were reported for patients in screening phase, who were not randomized and thus, not exposed to study drug.

Overall conclusion by MAH
The sequential evaluation of the initial case series derived from the MAH’s safety database was considered appropriate to account for the different risk factors and pathophysiological mechanism of serous and hemorrhagic pericardial effusions / tamponades. Due to the large number of spontaneous reports in the entire case series as well as in all subgroups, the data quality was generally limited or even poor. Several cases could not be assessed with regards to causal association; some could not even be assessed for a temporal sequence of drug administration and onset of the respective event. In several cases, Pradaxa may well have contributed to the extent of the – most frequently hemorrhagic effusion / tamponade. In the majority of these cases, the common pattern was identifiable that an invasive cardiac procedure was reportedly or at least highly likely responsible to have set the initial lesion. Effective anticoagulation in this situation is well able to increase the extent of bleeding regardless of the anticoagulant used. The above mentioned patient populations and risk factors however, have already been identified and are reflected in the appropriate section of the SmPC. In addition, a prescriber's guide has been distributed. 'Hemorrhage' is also a major topic in the Risk Management Plan. In addition to this, the MAH cannot identify previously unrecognized risk factors, neither for the subgroup of serous nor for hemorrhagic effusions / tamponades in the post-marketing data. The MAH considers the increase in reports seen from 2011 onwards as consequence of the increasing clinical use of Pradaxa in a patient population that is per-se at greater risk for cardiac events due to the underlying disease, atrial fibrillation.

2.3.5. Studies

Newly analysed studies
During the update period, the following studies containing important safety information were analyzed:

Phase IV trial 1160.85
The European Medicines Agency (EMA) requested that a post-approval study be conducted as a follow-

up measure (FUM011) to evaluate the risk of bleeding in the more general population of patients with an increased risk of bleeding. Study 1160.85 was conducted to address this issue. The aims were to assess the safety (major bleeding events [MBEs]) and efficacy (symptomatic venous thromboembolism [VTE]) of DE 220 mg once daily, in accordance with the European product label in defined subgroups of patients from the general population (with potentially an increased risk) who were undergoing elective total hip replacement (THR) surgery or elective total knee replacement (TKR) surgery in a routine clinical setting.

Summary: DE administered to patients undergoing hip or knee replacement surgery in accordance with the current European label, in a routine clinical setting, was safe and well tolerated. The pattern of AE reporting was similar to that observed in the corresponding phase III studies (RE-MODEL, RE-NOVATE, RE-NOVATE II). However, the overall incidence of treatment-emergent AEs (which included bleeding events and efficacy outcome events), drug-related AEs, and SAEs was lower. The incidences of any bleeding events were also lower.

Phase I trial 1160.88:
The pharmacokinetics and pharmacodynamics of DE administered twice daily for three consecutive days (total 6 doses) were assessed in nine stable adolescents (12 to <18 years).

Phase IIIb trial 1160.71:
This study is a rollover trial from RE-LY, in which subjects treated with DE were allowed to continue the double-blind dose to which they had been randomised. In the RELY-ABLE study period, the annualised event rate of subjects with stroke/SEE was numerically higher for DE 110 (1.60%) compared to DE 150 (1.46%). The hazard ratio for stroke/SEE for DE110 vs. DE150 was 1.10 with a 95% CI of 0.83-1.46. All categories of bleeding generally occurred more frequently in the DE 150 group compared to the DE 110 group. The risk of major bleeds was significantly lower for DE 110 treatment [0.79, 95% CI (0.65, 0.96) p=0.0168]. Annualised rates were 2.99% and 3.74% for the DE110 and DE 150.

Phase II trial 1160.113:
The majority of patients included in this PK interim snapshot belonged to the “recent surgery group” (Population A). The main finding of this preliminary analysis was that a higher number of patients than initially predicted presented with dabigatran trough levels below the predefined target of 50 ng/mL. It appeared that higher dosages of dabigatran etexilate may be required in the early post-operative period to achieve an exposure comparable to chronic treatment remote from surgery. The exact reasons for these findings are not yet fully understood.

Targeted New Safety Studies
No new targeted safety studies are currently under evaluation.

Published safety studies
No new targeted safety studies are currently under evaluation.

2.3.6. Other information

Efficacy-related information

The search with the MedDRA SMQ 'Lack of efficacy/ effect' identified 53 case reports and the MedDRA SMQ 'Embolic and thrombotic events' identified 860 case reports. 33 cases were found in both SMQs, so that in total 880 case reports were included in the evaluation. In 114 (13.0%) of these, a fatal outcome on case level was reported.

Indication: SPAF

The most important events related to lack of efficacy in patients treated for SPAF (n=479) were 'cerebrovascular accident' (n=85; 17.7%), 'ischaemic stroke' (n=18; 3.8%) and 'transient ischemic attack' (n=26; 5.4%) followed by 'cerebral infarction' (n=14, 2.9%), 'myocardial infarction' (n=17; 3.5%),'acute myocardial infarction' (n=11; 2.3%), 'embolic stroke' (n=11; 2.3%), 'deep vein thrombosis' (n=10; 2.1%), 'pulmonary embolism' (n=9; 1.9%), and 'thrombosis' (n=9; 1.9%). The remaining reported events (≥1%) were: 'embolism' (n=6, 1.3%),'Atrial thrombosis' (n=5; 1%), and 'Haemorrhagic stroke' (n=9; 1.9%). In 78 (16.2%) of the 482 case reports, a fatal outcome was reported.

Indication: Primary VTE prevention

The most frequently reported event in patients treated for pVTEp (n=56) was 'Pulmonary embolism' (n=17; 30.4%), and 'Deep vein thrombosis' (n=17; 30.4%). The remaining reported event (≥1%) were: 'Drug ineffective' (n=2; 3.6%), and 'Ischaemic stroke' (n=2; 3.6%); all following events were reported just once each, equalling 1.8%: 'Arterial thrombosis limb', 'Basilar artery occlusion' , 'Cerebral infarction', 'Drug effect decreased', 'Cerebrovascular accident', 'Embolism venous', 'Haemorrhagic stroke', 'Hypersensitivity', 'Acute myocardial infarction', 'Swelling', 'Shock haemorrhagic', 'Intracardiac thrombus', 'Cardiogenic shock', 'Myocardial infarction', ' No therapeutic response', 'Stress cardiomyopathy', 'Infarction', 'Thrombophlebitis superficial', 'Transient ischaemic attack', 'Venous thrombosis', 'Venous thrombosis limb', 'Venous thrombosis', 'Drug ineffective'.

Unspecified indications (n=306) and off-label use (n=39):

The following events (≥1%) were reported: 'Cerebrovascular accident' (n=96; 27.8%), 'Ischaemic stroke' (n=19; 5.5%), 'Deep vein thrombosis' (n=17; 4.9%), 'Thrombosis' (n=17; 4.9%), 'Transient ischaemic attack' (n=16; 4.6%), 'Haemorrhagic stroke' (n=14; 4.1%), 'Cerebral infarction' (n=13; 3.8%), 'Myocardial infarction' (n=13; 3.8%), 'Pulmonary embolism' (n=13; 3.8%), 'Drug ineffective' (n=7; 2.0%), 'Embolic stroke' (n=8; 2.3%), 'Atrial thrombosis' (n=7; 2.0%). Six serious, non-fatal cases of off-label use in the context of valvular atrial fibrillation were identified.

MAH response to question in previous PSUR 7:

PSUR Question 1 of 3:

Treatment with Pradaxa prior to planned DC-cardioversion in patients with atrial fibrillations is common in clinical practice. MAH is in the next PSUR asked to comment upon this approach. Are there any studies documenting the efficacy of this approach? Any safety concerns? How long after DS conversion should treatment be given?

MAH response:

In the RELY study cardioversion on randomied treatment was permitted. Precardioversion transoesophageal echocardiography was encouraged. Data from before, during and 30 days after cardioversion were analysed and are meanwhile published (Nagarakanti et al 2011; P 11-00277). In total, 1983 cardioversions were performed in 1270 patients: 647, 672 and 664 in the De 110, DE 150 and warfarin groups, respectively. For D110, D150, and warfarin, transesophageal echocardiography was performed before 25.5%, 24.1%, and 13.3% of cardioversions, of which 1.8%, 1.2%, and 1.1% were positive for left atrial thrombi. Continuous treatment with study drug for >3 weeks before cardioversion was lower in D110 (76.4%) and D150 (79.2%) compared with warfarin (85.5%; P<0.01 for both). Stroke and systemic embolism rates at 30 days were 0.8%, 0.3%, and 0.6% (D110 versus warfarin, P=0.71; D150 versus warfarin, P=0.40) and similar in patients withand without

transesophageal echocardiography. Major bleeding rates were 1.7%, 0.6%, and 0.6% (D110 versus warfarin, P=0.06; D150 versus warfarin, P=0.99). In conclusion, the frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transesophageal echocardiography guidance. These data were acknowledged in the registration process and the current label for Pradaxa states the following:

- Patients can stay on dabigatran etexilate while being cardioverted.

Also the most recent *ESC clinical practice guidelines* acknowledged that RELY provides currently the largest cardioversion database including the fact of the evaluation of DE as first novel oral anticoagulant in this setting. The updated *ESC clinical practice guidelines* from 2012 therefore state as follows:

- For patients with AF of 48 hour duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2–3 or dabigatran) is recommended for 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological)
- In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2–3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion

2.3.7. Late-breaking information

Late-breaking information (19 Sep 2012 to 18 Oct 2012) on 1700 cases (1420 HP-confirmed, 280 non-HP-confirmed) was considered. No information affecting the overall assessments provided in this PSUR was identified.

2.3.8. Risk Management Plan

The EU Risk Management Plan (EU-RMP) Pradaxa is being updated and will be submitted to the relevant regulatory authorities without undue delay (version 25). The currently approved version is version 23, dated 28 Mar 2012. The RMP was assessed in the separate AR.

2.3.9. Overall safety evaluation

Drug interactions

A total of 44 cases were received, 31 serious including 7 fatal cases. Of the 44; 31 cases (70.4%) were reported as serious and 13 (-29.5 %) cases were reported as non serious. In one of the fatal cases, patient died due to stroke (Phenprocoumon/Pradaxa, overlapping with low-molecular-weight heparin). In the other 6 cases, the interaction was reported as responsible for a fatal bleeding event. In these 6 patients, the drug combination with Pradaxa was: Aspirin (2), unspecified NSAID (1), Clopidogrel and aspirin (1), Dronedarone (1) and Erythromycin (1). The majority (4) of the bleeding cases may not describe a true interaction but rather side effects that are known for both drugs. Of the 44 cases, a total of 19 (43.1%) non-fatal serious cases involved bleeding events. A summary of drugs suspected for drug interaction with Pradaxa for cases with bleeding events is provided in the below table.

Drugs	Event, case ID and outcome
Antiplatelet drugs and Anticoagulants drugs (currently included in the CCDS)	
Acetylsalicylic acid	Hemorrhage; Fatal Shock haemorrhagic and anaphylactic shock due to oesomeprazol & Insulin; Fatal Haematuria Gingival haemorrhage; Recovered

	Rectorrhagia; Recovered
Acetylsalicylate lysine	Haemorrhage Digestive; Patient discharged.
NSAIDs	Gastrorrhagia; Fatal
Ibuprofen	Vaginal haemorrhage; Recovered
Phenprocoumon (Marcumar)	Low GI bleeding; NYR
P-gp inhibitors (currently included in the CCDS)	
Verapamil	Haemorrhagic Stroke; Recovered
Amiodarone	Gastric Haemorrhage; NYR
	Cerebral haematoma, anal bleeding; Recovered
	Rectorrhagia; Recovered
	Rectorrhagia; Recovered
	Vaginal haemorrhage; Outcome not reported
Dronedarone	Subdural haematoma; Fatal
	Hemopericardium; Recovered
Propafenone	Digestive haemorrhage; Recovered
Erythromycin (one dose) *	GI haemorrhage patient with stigmata of bleeding peptic ulcer and severe renal failure. The patient received one dose of IV Erythromycin before Upper-endoscopy in order to stop the bleeding ulcer. Pradaxa® was contraindicated. Fatal
Clarithromycin *	Rectal bleeding; Recovered
Fluconazol	Melena; Recovered
Substrate for P- glycoprotein	
Clopidogrel	GI haemorrhage. Aspirin/Clopidogrel; Unknown age patient with congestive heart failure, low ejection fraction who had experienced MI (Angioplasty and Stent placement) 4 days before the bleeding; Fatal
	Gingival bleeding; Recovered
	Subconjunctival haemorrhage; NYR
	Loperamide* Haematuria in patient with prostate cancer and urinary tract infection; Recovered

*Not included in the CCDS NYR= not yet recovered

Overdose

A total of 55 cases (including 5 non-HP confirmed cases) involving overdose were received during the reporting period. Overall, the pattern of reported events in cases concerning overdose does not provide grounds to amend the CCDS.

Drug abuse or misuse

Six cases (4 HP-confirmed, 2 non-HP-confirmed) that involved abuse or misuse of Pradaxa were received during the reporting period. One case of intentional overdose in suicidal intention is described, also involving other drugs. The remaining case reports concern wrong dosages or dosage regimens and rather constitute off-label use or compliance problems.

Pregnancy and lactation

Only one case has been reported in the current PSUR period. It was reported that at gestational week 37, the patient delivered a healthy female baby weighing 2.570 Kg. No events were reported.

Special patient groups

Use in children

A total of 2 cases (both HP-confirmed) of Pradaxa use in children (age below 18 years) were received during the reporting period. In both cases age is uncertain, and especially describing a 7 year old male patient with concomitant medication including amlodipine, aspirin, bisoprolol, flucloxacillin, gliclazide, lisinopril, metformin, metronidazole and simvastatin strongly suggest that that a reporting error has

been the case.

Off label use
Information on indication was available for 4401 HP-confirmed cases (59.2% of all HP-confirmed cases); in total 4991 indication terms were reported. In 51 (1.0%) of the 4991 indication terms, off-label use indications were reported. The frequency of reported off-label use in the current PSUR period is low and similar to the frequency observed in the previous PSUR 7, where off-label use was reported in 1.4%.

Effects of long term treatment
The available data from clinical trials and post marketing experience regarding long-term treatment with Pradaxa® show a similar safety profile compared to short-term treatment. Overall, the effects of long-term treatment observed so far, do not provide grounds to amend the reference safety information.

MAH response to question in previous PSUR 7
Question 3 of 3:
Are there any plans of long-term follow-up on the patients in the RE-LY trial? This could be extremely important for many of the safety issues raised. The MAH is requested to comments on this in the next PSUR.
MAH Response:
The RELY-ABLE study which is the follow up trial of RE-LY has included > 5800 patients. Patients were eligible if they completed RE-LY still receiving double-blind DE. Enrolled patients continued to receive the same double-blind dabigatran dose in RELY-ABLE. The primary outcomes are the occurrence of major ischemic and haemorrhagic outcomes as well as death and net clinical benefit. An interims analysis has been completed and is described in more detail in PSUR 8. In summary, the overall goal of RELY-ABLE was to provide further description of the long-term efficacy and safety of two doses of dabigatran 110 and 150 mg twice daily in patients completing RE-LY still receiving dabigatran. Patients were eligible for RELY-ABLE if they were participating in RE-LY, randomized to double-blinded dabigatran study medication and not permanently discontinued from study medication at the time of the final RE-LY study visit. There were 5851 patients studied. Mean follow up was 4.25 years. During RELY-ABLE, rates of stroke or systemic embolism were 1.60 and 1.46 %/year on dabigatran 110mg and 150 mg bid, respectively (hazard ratio (HR) 0.91, 95% confidence interval (CI), 0.69-1.20). Rates of major hemorrhage were 2.99 and 3.74%/year on dabigatran 110 and 150 mg (HR 1.26, 95% CI, 1.04-1.53). Rates of total death were 3.10 and 3.0 %/year (HR 0.97; 95% CI0.94-1.22). Rates of hemorrhagic stroke were very low; 0.14 and 0.13%/year. Rates of stroke, major bleeding and death on dabigatran during RELY-ABLE were similar to rates in RE-LY; relative effects of the two dabigatran doses on these outcomes were also consistent with RE-LY.

2.4. Modifications to the contraindications and the drug-drug interaction profile of DE (sections 4.2, 4.3 and 4.5).

Within the PSUR procedure the MAH was requested to discuss the below issues and to modify the SmPC accordingly:

a) Section 4.3, contraindications relating to lesions or conditions at significant risk of major bleeding

Requested changes (additions in **bold**; deletions in ~~strikeout~~)

• Lesion or condition, **if considered a** ~~at~~ significant risk **factor for**~~of~~ major bleeding. **This may include** ~~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

Rationale for requested change

It has been suggested that the contraindication now in place for Pradaxa and other oral anticoagulants are too strict, especially with regard to the prevention of VTE in surgery indications where, for example, an AV malformation or an aneurysm should not necessarily exclude a patient from receiving one of the new anticoagulants. This concern is acknowledged. Therefore, it is requested that the contraindication about lesions and conditions is revised slightly allowing the prescribing physician some more room for clinical judgment on when to consider the listed lesions and conditions as absolute contraindications.

MAH response

The PRAC comment is acknowledged and the MAH agrees to the suggested changes.

PRAC comment

The MAH has accepted the requested changes and the PRAC considered the issue as resolved (see Annex I to this AR).

b) Section 4.5, drug-drug interactions, posaconazole

The MAH was asked to discuss and consider downgrading concomitant treatment with posaconazole from a non-recommendation to a caution.

Rationale for request

No DDI studies have been conducted. There is conflicting information, but it is agreed that posaconazole is not as strong a P-gp inhibitor as ketoconazole. Posaconazole is a strong CYP3A4 inhibitor, but this is not relevant for Pradaxa. Considering the lack of robust in vitro and in vivo data, a non-recommendation (current wording) or even a caution for Pradaxa may be appropriate.

MAH response

The CHMP and PRAC comment is acknowledged and the MAH agrees to downgrade posaconazole from the current “non-recommendation” to a cautionary statement. The following wording (in bold) is suggested for Annex I section 4.5 ‘(see also response to Question 2 d):

~~*Neither clinical nor in vitro test results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa.*~~

The following P-gp inhibitors have not been studied: Posaconazole and tacrolimus. Both medicinal products are only weak P-gp inhibitors and not expected to interact in a clinically meaningful manner. Nevertheless, close clinical surveillance is recommended.

PRAC comment

The MAH has not provided any discussion on whether a caution or non-recommendation is warranted. A brief summary of the available data on the P-gp inhibitory potential of posaconazole and a discussion

of its implications for Pradaxa should be provided. The issue was considered not resolved and will be further assessed within procedure LEG2 12.1 after finalisation of this PSUR.

c) Section 4.5, drug-drug interactions, voriconazole

Request

The MAH is requested to discuss the interaction potential with voriconazole and insert a non-recommendation or a caution in the SmPC.

Rationale for request

No DDI studies have been conducted. There is conflicting information, but it is agreed that voriconazole is a P-gp inhibitor, but not as strong as ketoconazole. Voriconazole is a strong CYP3A4 inhibitor, but this is not relevant for Pradaxa. Considering the lack of robust in vitro and in vivo data, a non-recommendation or a caution for Pradaxa may be appropriate.

MAH response

Voriconazole has not been reported to be a strong P-gp inhibitor. In contrast, in a clinical trial with the prototypic P-gp substrate digoxin, voriconazole comedication did not affect the PK of digoxin [R13-0765]. In this study, the ratios for Cmax and AUC were reported as 109.8% [90% confidence interval (CI) 97.1, 124.1] and 100.5% [90% CI 91.4, 110.5], respectively. This information is also reflected in the interaction table (page 13) of the VFEND Summary of Product Characteristics. Further, in the recent FDA Draft Guidance for Industry "Drug Interaction Studies- Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations", voriconazole is listed as a strong CYP3A4 inhibitor and a Non-P-gp Inhibitor (Table 8). In summary, voriconazole is not a P-gp inhibitor and therefore the interaction potential with dabigatran etexilate is considered very low. A non-recommendation or a caution for Pradaxa seems not justified.

R13-0765 Purkins, L.; Wood, N.; Kleinermans, D.; Nichols, D. Voriconazole does not affect the steady-state pharmacokinetics of digoxin. Br. J. Clin. Pharmacol. 2003, 56 (Suppl. 1), 45–50)

PRAC comment

The MAH has provided documentation that voriconazole is unlikely to be a P-gp inhibitor of a significance that would alter the pharmacokinetics of dabigatran etexilate to a clinically relevant degree. Hence, there appears to be no need to include a caution or a non-recommendation. The issue was considered resolved.

d) Section 4.5, drug-drug interactions, tacrolimus

Request

The MAH is asked to discuss and consider downgrading concomitant treatment with tacrolimus from a contraindication to a non-recommendation or a caution.

Rationale for request

No DDI studies have been conducted. There is conflicting information, but it is agreed that tacrolimus is not as strong a P-gp inhibitor as ketoconazole. For Pradaxa a contraindication appears too restrictive, and a non-recommendation or even a caution may be more appropriate.

MAH response

The PRAC comment are acknowledged and the MAH agrees to downgrade tacrolimus from the current contraindication to a cautionary statement. The following changes (shown below in bold) are suggested for Annex I sections 4.3 and 4.5 '(see also response to Question 2 b):

Section 4.3 Contraindications

- *Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazol~~e~~, ~~tacrolimus~~ and dronedarone (see section 4.5)*

Section 4.5 Interaction

Systemic ketoconazole, cyclosporine, itraconazole, ~~tacrolimus~~ and dronedarone are contraindicated (see section 4.3). Caution should be exercised with other strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil) (see sections 4.2 and 4.4).

[…]

The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected:

Itraconazole, ~~tacrolimus~~ and cyclosporine, which are contra-indicated (see section 4.3).

[…]

The following P-gp inhibitors have not been studied: Posaconazole, tacrolimus. Both medicinal products are only weak P-gp inhibitors and not expected to interact in a clinically meaningful manner. Nevertheless, close clinical surveillance is recommended.

PRAC comment

The MAH has not provided any discussion on whether a caution or non-recommendation is warranted or whether the current contraindication should be kept. A brief summary of the available data on the P-gp inhibitory potential of tacrolimus and a discussion of its implications for Pradaxa should be provided. The issue was considered not resolved and will be further assessed within procedure LEG2 12.1 after finalisation of this PSUR.

e) Section 4.2 and 4.5, posology and drug-drug interactions, amiodarone

Request

Taking into account all available data, the MAH is asked to discuss the appropriateness of the current recommended dose reduction for the pVTE indications in patients treated concomitantly with amiodarone.

Rationale for request

In light of the modest increase in dabigatran exposure with amiodarone and the fact that amiodarone treatment is not in itself reason for dose reduction in the SPAF indication, the current recommended dose reduction for Pradaxa in the pVTE indications could be challenged.

MAH response

With the responses to the Day 180 List of Outstanding Issues during the registration process for pVTEp in 2007 the MAH agreed to a dose adjustment of dabigatran when co-treated with amiodarone. Since then, no additional meaningful data were further generated which would justify a dose increase. The RENOVATE II study (1160.64, U10-1392-01 submitted with eCTD sequence 0005) which was completed after first registration did only investigate a daily dose of 220 mg/day and therefore had to

exclude patients on co-treatment with amiodarone. The FUM trial 1160.85 (U12-1556-01, submitted with eCTD sequence 0085) which was recently completed only included a very low number of patients with concomitant therapy of P-gp inhibitors; there were only 3 patients with concomitant treatment of amiodarone, so no firm conclusions can be drawn. The postmarketing surveillance data do not reliably allow a differentation between the two registered indications to assess bleed rates with or without amiodarone for pVTEp. Moreover, based on postmarketing experience those data are highly dominated by AE reports coming from the SPAF indication. As patient population and clinical setting for pVTEp and SPAF are different incl. a wound healing process in case of pVTEp a dose increase is not justifyable by the MAH.

PRAC comment

No significant new information is available to justify a change in the current dose recommendations for the pVTE indications when co-treating with amiodarone. The company response is acceptable. Issue resolved.

f) Section 4.2 and 4.5, posology and drug-drug interactions, quinidine

Request

Taking into account all available data, the MAH is asked to discuss the appropriateness of the current recommended dose reduction for the pVTE indications in patients treated concomitantly with quinidine.

Rationale for request

In light of the modest increase in dabigatran exposure with quinidine and the fact that quinidine treatment is not in itself reason for dose reduction in the SPAF indication, the current recommended dose reduction for Pradaxa in the pVTE indications could be challenged.

MAH response

During the registration process for pVTEp in 2007 a contraindication for dabigatran when cotreated with quinidine was agreed in the frame of the CHMP opinion. After trial 1160.90 which was submitted via type II variation EMA/H/C/000829/II/0016 (eCTD sequence 0011) this quinidine contraindication was changed to a dose adjustment. Since then, no additional meaningful data were further generated which would justify a dose increase of dabigatran for co-treatment with quinidine in pVTEp. The RENOVATE II study (1160.64, U10-1392-01 submitted with eCTD sequence 0005) which was completed after first registration had to exclude patients on co-treatment with quinidine. The FUM trial 1160.85 (U12-1556-01, submitted with eCTD sequence 0085) which was recently completed only included a very low number of patients with concomitant therapy of P-gp inhibitors; none of the patients received co-treatment with quinidine, so no firm conclusions can be drawn. As patient population and clinical setting for pVTEp and SPAF are different incl. a wound healing process in case of pVTEp a dose increase is not justifyable by the MAH.

PRAC comment

No significant new information is available to justify a change in the current dose recommendations for the pVTE indications when co-treating with quinidine. The company response is acceptable. Issue resolved.

g) Section 4.5, drug-drug interactions, clarithromycin

Request

The MAH is asked to discuss and consider removing the caution regarding concomitant treatment with clarithromycin.

Rationale for request

A 1.2-fold increase in dabigatran exposure may be considered too insignificant to warrant a caution.

MAH response

With the responses to the Day 180 List of Outstanding Issues during the registration process for pVTEp in 2007 the MAH agreed to include a cautionary statement for co-treatment with clarithromycin. Furthermore, with the Letter of Undertaking dated 22 Jan 2008 the MAH agreed to conduct “A drug drug interaction study with steady state concentrations of a specific P-gp inhibitor (clarithromycin)” as a Follow-up measure (FUM006). Upon assessment of the study report, the CHMP asked for rephrasing of the SmPC, which was handled in the frame of type II variation EMA/H/C/000829/II/0011. Since then, no new clinical meaningful data were generated which would allow the MAH to remove this caution. The FUM trial 1160.85 (U12-1556-01, submitted with eCTD sequence 0085) which was recently completed only included a very low number of patients with concomitant therapy of P-gp inhibitors not allowing firm conclusions.

PRAC comment

No new clinical data is available. Even if a 1.2-fold increase in dabigatran exposure may be considered insignificant, the company prefers to maintain the caution. This is acceptable. Issue resolved.

2.5. Conclusions of the MAH

During the update period, the MAH received 9238 case reports (7437 HP-confirmed; 1801 non-HP-confirmed) including 15 689 ADRs (11 947 HP-confirmed; 3742 non- HP-confirmed). In addition, late-breaking information (19 Sep 2012 to 18 Oct 2012) on 1700 cases (1420 HP-confirmed, 280 non-HP-confirmed) was considered. In general, the vast majority of ADRs received were assessed as already listed side effects for Pradaxa, reported terms describing the mode of action of Pradaxa or alternative explanations were reported. As expected, bleeding events were the most often reported ADRs. In 43.2% of all HP-confirmed cases received during the update period, at least one bleeding event or an event associated to bleeding was reported. In 238 (7.4%) of the cases for the update period, bleeding was associated with fatal outcome. The percentage of bleeding events from all reported events (43.2%) was comparable with that observed in the previous reporting period (44.5%). The pattern of bleeding ADRs evaluated in patients treated in the granted indications is similar to that known from well-controlled clinical trials and past PSURs. The cumulative review of all haemorrhagic case reports allows to conclude that reporting rates of spontaneous data are lower than it would be expected from experience of the RE-LY trial; under-reporting needs to be considered. No new risk factors have been detected by thorough analysis of market data available. During the reporting period, cumulative reporting rates for serious bleeding events have slightly decreased from 56.2 events per 10 000 patient years (February 2012) to 51.5 events per 10 000 patient-years (August 2012). The reporting rate for fatal bleeding events remained stable with 7.3 events per 10 000 patient-years (February 2012) and 7.3 events per 10 000 patient-years (August 2012). The information received during the reporting period concerning the monitoring topics 'hepatotoxicity' and 'myocardial infarction' did not reveal any new relevant medical safety information. The number of case reports received for these topics is considered to be low. The evaluation of events associated with renal impairment did not result in any change of the assessment provided in the last PSUR 7. However the MAH will continue to monitor this topic.

2.6. Discussion and conclusions on the PSUR data

During the period under review the SmPC was updated with a contraindication recommendation against co-medication of Pradaxa and dronedarone (EMEA/H/C/000829/II/0028). In addition, the SmPC and package leaflet were updated with more precise specifications and clarification of already approved contraindications (EMEA/H/C/000829/II/0031). Furthermore, the section overdose was likewise updated with information on bleeding management (also EMEA/H/C/000829/II/0031). Based on a review of the safety data related to the RE-ALIGN study, the SmPC section 4.3 has been updated with the following contraindication: Prosthetic heart valves replacement requiring anticoagulant treatment (EMEA/H/C/829/II/44)

During the current PSUR 8 period the market exposure for Pradaxa was 417 449 patient years. During the update period, the MAH received 9238 case reports with a total of 15 689 ADRs. The far most frequent ADR was haemorrhagic events with a total of 7437 HP-confirmed ADR case reports during the update period. In 3214 (43.2%) of these cases, at least one bleeding event was reported, which is similar to the previous reporting period (44.5%, PSUR 7). In contrast to warfarin treatment no specific antidote exists for Pradaxa. However, an antibody is under development.

Overall, reporting indices for the current PSUR reporting decreased with respect to cumulative (PSUR 1 to 6) figures in the range of -29.1% to -84.1% (except for the SOC 'neoplasms benign & malignant' and 'social circumstances', where a small increase of 8.9% and 7.2%, respectively, was observed). Reporting indices also decreased for almost all SOCs when compared with the previous reporting period (PSUR 7) in the range of -6.3% to -78.3%.

The MAH stated that the information received during the reporting period concerning the monitoring topics 'hepatotoxicity' and 'myocardial infarction' did not reveal any new relevant medical safety information. The number of case reports received for these topics was considered to be low. However, as mentioned in the RMP assessment the cumulative reporting rate for myocardial infarction is 3.1 per 10 000 patient-years, in the previous PSUR period the reporting rate was 2.6 events per 10 000 patient-years (stated in the previously submitted RMP with the previous PSUR period). The MAH provided response and it was assessed within updated RMP AR. The evaluation of events associated with renal impairment did not result in any change of the assessment provided in the last PSUR 7. However the company will continue to monitor this topic.

No new safety issues were detected in the current PSUR period. The obvious question of a possible role underreporting was the topic of a specific question to MAH following the previous PSUR where MAH was asked to discuss whether actions should be taken to increase awareness and reporting of ADR for Pradaxa. MAH has established educational programmes for treating physicians including tools such as the prescriber guides for the various treatment indications and the patient alert card. Both are updated and distributed whenever new information becomes available. Thus, the question has been answered satisfactorily.

In the previous PSUR, the MAH was requested to comment on the large number of pericardial effusion, pericardial hemorrhage and cardiac tamponade and whether or not these cases are reflected in the SmPC. MAH presented a thorough review of the topic “pericardial effusion, pericardial hemorrhage and cardiac tamponade.” It was in general accepted that the increase seen reflects an increased use of Pradaxa in patients with an increased risk for bleedings. It was also agreed upon, that these patient populations and risk factors have been identified and are reflected in the appropriate section of the SmPC. However, it is worrying that many of the bleeding events described are due to improper use of

the drug, either because of use despite contraindications or because of off-label use. In the next PSUR, MAH is asked to discuss whether more intensive information to prescribing physicians about proper indications and especially contraindications should be encouraged.

It should be noted that an interim report on RE-ALIGN study (referenced in the company response) recently resulted in a new contraindication (prosthetic heart valves requiring anticoagulant treatment) due to an excess of pericardial bleedings as well as ischaemic events in patients treated with dabigatran etexilate compared to patients treated with warfarin. Currently, the inclusion of a warning regarding patients undergoing cardiac surgery is being discussed in another procedure (LEG036).

Regarding long-term treatment the MAH was asked to address the follow-up trial RELY-ABLE in more than 5800 patients with a mean follow-up of 4.3 years. Rates of stroke, major bleeding and death on dabigatran during RELY-ABLE were similar to rates in RE-LY; relative effects of the two dabigatran doses on these outcomes were also consistent with RE-LY. Also, this question has been addressed to a satisfactory extend. A third question regarding Pradaxa treatment during cardioversion was also answered and addressed in the SmPC.

Overall, the current PSUR reflects solid data collection and reporting. No new safety issues have been raised.

3. Signal and risk evaluation

As the PSUR has been submitted in the old format, due to the transitional period, this section is omitted.

4. Benefit evaluation

As the PSUR has been submitted in the old format, due to the transitional period, this section is omitted, and section 5 has been adjusted to include the accompanying benefit-risk evaluation, which has another format, than in the new PSUR format.

5. Benefit-risk balance

Benefit-Risk analysis for the SPAF indication:

The clinical relevance of the results from the RE-LY study is high. For the first time, a significantly decreased major bleed rate compared to well-controlled warfarin could be demonstrated. Moreover, the significantly reduced risk of intracranial bleeds for both tested doses of DE is considered to represent major therapeutic progress increasing the overall acceptance of anticoagulant therapy. When risk and benefit were considered both dabigatran doses had smaller risk ratios compared to warfarin. Risk reduction for DE 110 mg bid and DE 150 mg bid were 8% and 10%, respectively with corresponding p values of 0.100 and 0.037. Yearly event rates were 7.08%, 6.89% and 7.62% for DE 110 mg bid, DE 150 mg bid mg and warfarin groups, respectively. The table below shows an overview of the clinically most relevant favourable and undesirable effects of DE as observed in the indication of prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors.

Table 20 Overview of the clinically most relevant favourable and undesirable effects of dabigatran etexilate in patients treated for SPAF

	Effect	Description
Favourable effects	Significant reduction of stroke	For the primary efficacy endpoint, stroke/SEE, non-inferiority for both doses of dabigatran with warfarin was established (p <0.0001 for both comparisons) and dabigatran etexilate 150 mg bid was superior to warfarin (p=0.0002).
	Significant reduction of intracranial hemorrhage	Intracranial hemorrhage risk decreased 71% for dabigatran etexilate 110 mg bid compared to warfarin (p<0.0001) and 59% for dabigatran etexilate 150 mg bid compared to warfarin (p<0.0001).
Undesirable effects	Increase incidence of GI bleed	Subjects treated with dabigatran etexilate 150 mg bid had a higher incidence of major bleeding events within the gastrointestinal tract when compared with warfarin (1.5% per year versus 1.0%) per year.
	Numerically higher rate of MIs	In comparison to warfarin the annual myocardial infarction rate for dabigatran etexilate was increased from 0.64 % (warfarin) to 0.82 % (dabigatran etexilate 110 mg twice daily) / 0.81 % (dabigatran etexilate 150 mg twice daily)
	GI events such as dyspepsia, stomach discomfort, gastritis nausea, diarrhoea	The constellation of dyspepsia/stomach discomfort/gastritis was twice as frequent for dabigatran as for warfarin. Nausea and diarrhea were also more frequent for dabigatran compared to warfarin.

Benefit-Risk analysis for the pVTEp indication:

It is considered that the benefit to risk ratio at the recommended oral dosages of DE is at least as good as the current injectable gold standard. It is concluded that the totality of efficacy and safety data are positive for DE in the indication VTE prophylaxis in major orthopaedic surgery. The table below shows an overview of the clinically most relevant favourable and undesirable effects of DE as observed in the indication of primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Table 21 Overview of the clinically most relevant favourable and undesirable effects of dabigatran etexilate in patients treated for pVTEp

	Effect	Description
Favourable effects	Prevention of VTE/ PE	Dabigatran etexilate was demonstrated to be non-inferior to the gold standard therapy, enoxaparin, in preventing total VTE and all cause mortality.
Undesirable effects	Bleeding	Bleeding events are the most often reported adverse reactions for dabigatran etexilate. Major or severe bleeding events may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.
	Hypersensitivity	Hypersensitivity reaction may occur as pruritus, rash, urticaria, bronchospasm, angioedema or anaphylactic reactions.

6. Final assessment conclusions and actions

This is the eighth PSUR for Pradaxa. The report updates safety information on DE given as mesilate for the period 19 Mar 2012 to 18 Sep 2012. During the update period, the MAH received 9238 case reports with a total of 15 689 ADRs. The far most frequent ADR was haemorrhagic events with a total of 7437 HP-confirmed ADR case reports during the update period. In 3214 (43.2%) of these cases, at least one bleeding event was reported, which is similar to the previous reporting period (44.5%, PSUR 7). In contrast to warfarin treatment no specific antidote exists for Pradaxa. However, an antibody is under development.

During the period under review the SmPC was updated with a contraindication recommendation against co-medication of Pradaxa and dronedarone. In addition, the SmPC and package leaflet was updated with more precise specifications and clarification of already approved contraindications. Furthermore; the section overdose was likewise updated with information on bleeding management. Based on a review of the safety data related to the RE-ALIGN study (excess of hemorrhagic pericardial effusions in patients receiving dabigatran etexilate), the SmPC section 4.3 has been updated with the following contraindication: Prosthetic heart valve replacement (EMEA/H/C/829/II/44).

The information received during the reporting period concerning the monitoring topics 'hepatotoxicity' and 'myocardial infarction' did not reveal any new relevant medical safety information. The number of case reports received for these topics is considered to be low. However, as mentioned in the RMP assessment the cumulative reporting rate for myocardial infarction is 3.1 per 10 000 patient-years, in the previous PSUR period the reporting rate was 2.6 events per 10 000 patient-years (stated in the previously submitted RMP with the previous PSUR period). This issue was assessed in the RMP AR and considered resolved.

The evaluation of events associated with renal impairment did not result in any change of the assessment provided in the last PSUR 7. However the MAH will continue to monitor this topic.

Many of the bleeding events described are due to improper use of the drug, either because of use despite contraindications or because of off-label use. In the next PSUR, MAH was asked to discuss whether more intensive information to prescribing physicians about proper indications and especially contraindications should be encouraged.

The benefit-risk balance remains positive for DE for the indication prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (SPAF) with one or more risk factors as well as for the indication VTE prophylaxis in major orthopaedic surgery (elective total hip replacement surgery or total knee replacement surgery). No new safety issues have arisen that would recommend changes to the SmPC or RMP.

Scientific motivation to modify section 4.3 of the SmPC:

The contraindication in lesion or condition at significant risk for major bleeding which is now in place for Pradaxa does not allow for medical judgement, especially with regard to the prevention of VTE in surgery indications where, for example, an AV malformation or an aneurysm should not necessarily exclude a patient from receiving one of the new anticoagulants. This concern was viewed in perspective of safety profile of Pradaxa during PSUR period and was acknowledged by PRAC (a decreasing trend of cumulative reporting rates for serious bleedings). Therefore, the contraindication about lesions and conditions is revised slightly allowing the prescribing physician some more room for clinical judgment on when to consider the listed lesions and conditions as absolute contraindications.

In addition, the MAH was asked to discuss the need to introduce changes to sections 4.2, 4.3 and 4.5 regarding drug-drug interaction profile (see discussion in section 2.4). The issues regarding drug-drug interaction for posaconazole, tacrolimus and rifampicin will be further assessed within procedure LEG2 12.1 after finalisation of this PSUR.

7. Request for supplementary information

As mentioned in the RMP assessment (see separate document) the cumulative reporting rate for myocardial infarction is 3.1 per 10 000 patient-years, in the previous PSUR period the reporting rate was 2.6 events per 10 000 patient-years (stated in the previously submitted RMP with the previous PSUR period). The MAH was asked to comment on this increase. This issue was assessed in the RMP AR and considered resolved.

8. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers by consensus that the risk-benefit balance of medicinal products containing the active substance dabigatran etexilate remains favourable but recommends that the terms of the marketing authorisation should be varied as follows:

Update of Section 4.3 of the SmPC regarding the contraindication to use Pradaxa in patients with lesion or condition, if considered at significant risk factor for major bleeding.

The amendments recommended to be introduced to the product information are detailed in Annex 1.

In addition, the MAH is required to submit by 03 June 2013 the following additional information (LEG2 012.1)

- The MAH has not provided any discussion on whether a caution or non-recommendation is warranted for posaconazole. A brief summary of the available data on the P-gp inhibitory potential of posaconazole and a discussion of its implications for Pradaxa should be provided.

- The MAH has not provided any discussion on whether a caution or non-recommendation is warranted or whether the current contraindication should be kept for tacrolimus. A brief summary of the available data on the P-gp inhibitory potential of tacrolimus and a discussion of its implications for Pradaxa should be provided.

- Regarding the information on the interaction with rifampicin (and other P-gp inducers) and the ~66% reduction in dabigatran exposure with concomitant use, the MAH is asked to consider whether a contraindication is appropriate in this case given the information gained from the dose-response studies described in the EPAR for dabigatran. In these studies, a dose-response relationship was observed with respect to VTE rate, and the dabigatran exposure in an orthopaedic patient receiving concomitant rifampicin could be expected to be lower than the lowest equivalent (daily) dose included in the dose response study.

In addition, the MAH should also address the following issues in the next PSUR:

- It is worrying that many of the bleeding events described are due to improper use of the drug, either because of use despite contraindications or because of off-label use. In the next PSUR, MAH is asked to discuss whether more intensive information to prescribing physicians about proper indications and especially contraindications should be encouraged.

In addition, the MAH should submit an updated RMP together with next PSUR in order to address the following issues:

1. The MAH is asked to provide and update in the RMP on recruitment for study 1160.129 when submitting a RMP in connection with the next PSUR.
2. A continuous update of the development of an antidote is expected with each RMP update.

9. List of annexes

ANNEX 1

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

The following changes to the product information of medicinal products containing the active substance dabigatran etexilate are recommended:

Summary of product characteristics

- Section 4.3

A contraindication should be revised as follows:

(additions in **bold**; deletions in ~~strikeout~~)

- Lesion or condition, **if considered a** ~~at~~ significant risk **factor for**~~of~~ major bleeding. **This may include** ~~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.

ANNEX 2

RECOMMENDED CHANGES TO THE CONDITIONS OF THE MARKETING AUHTORISATION

None.