Pradaxa

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
N/0148	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2023		Labelling	
II/0147/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2023	11/12/2023	SmPC, Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	C.I.7.a - Deletion of - a pharmaceutical form				
PSUSA/918/202303	Periodic Safety Update EU Single assessment - dabigatran	26/10/2023	n/a		PRAC Recommendation - maintenance
IA/0146	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	07/07/2023	n/a		
II/0144	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/06/2023	n/a		
IA/0143	A.7 - Administrative change - Deletion of manufacturing sites	16/02/2023	n/a		
IA/0142	A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS	16/12/2022	n/a		
PSUSA/918/202203	Periodic Safety Update EU Single assessment - dabigatran	27/10/2022	n/a		PRAC Recommendation - maintenance
N/0141	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/07/2022	23/01/2023	Labelling	
IB/0137/G	This was an application for a group of variations. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of	05/07/2022	n/a		

	a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0138	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/06/2022	n/a		
IA/0140/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/06/2022	n/a		
IB/0136	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	13/05/2022	n/a		
II/0133	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/01/2022	23/01/2023	PL	

II/0128	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021	20/01/2022	SmPC, Labelling and PL	
IB/0134/G	This was an application for a group of variations. B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/01/2022	23/01/2023	SmPC, Labelling and PL	
PSUSA/918/202103	Periodic Safety Update EU Single assessment - dabigatran	14/10/2021	09/12/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/918/202103.
IA/0135	A.7 - Administrative change - Deletion of manufacturing sites	24/11/2021	n/a		

II/0126/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/09/2021	n/a		
IA/0132	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	19/08/2021	n/a		
IA/0131	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	05/08/2021	n/a		
IB/0129	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	08/06/2021	n/a		
N/0127	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2021	09/12/2021	Labelling and PL	
IAIN/0125/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	15/02/2021	09/12/2021	Annex II and PL	

	manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
X/0122/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	12/11/2020	11/01/2021	SmPC, Annex II, Labelling and PL	

	significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(d) Change or addition of a new pharmaceutical form				
PSUSA/918/202003	Periodic Safety Update EU Single assessment - dabigatran	01/10/2020	n/a		PRAC Recommendation - maintenance
II/0123	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	14/05/2020	11/01/2021	SmPC and PL	

	data				
II/0118/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	16/12/2019	SmPC and PL	
IA/0121	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	07/10/2019	n/a		
PSUSA/918/201903	Periodic Safety Update EU Single assessment - dabigatran	03/10/2019	n/a		PRAC Recommendation - maintenance
IB/0119/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	19/09/2019	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites				
IA/0120	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	17/09/2019	n/a		
IAIN/0115	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/06/2019	16/12/2019	SmPC and PL	
IA/0117/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	14/06/2019	n/a		
II/0114	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/03/2019	13/05/2019	SmPC and PL	

IA/0113/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	05/12/2018	n/a		
PSUSA/918/201803	Periodic Safety Update EU Single assessment - dabigatran	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0108	Update of sections 4.2, 4.4. and 5.1 of the SmPC for Pradaxa 110 and 150 mg for the stroke prevention in atrial fibrillation, deep vein thrombosis and pulmonary embolism indications based on the results from study 1160.186: `A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110 mg and 150 mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0-3.0) plus clopidogrel or ticagrelor and aspirin in patients with non-valvular atrial fibrillation that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI)'In addition, the MAH took the opportunity to	26/04/2018	07/06/2018	SmPC and PL	Based on the results of Study 1160.186, the posology has been updated to reflect that patients with non valvular atrial fibrillation who undergo a percutaneous coronary intervention (PCI) with stenting can be treated with Pradaxa in combination with antiplatelets after haemostasis is achieved. Study 1160.186 was conducted in 2725 patients. Patients were randomized to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. The primary endpoint was a combined endpoint of major bleeds based on ISTH definition or clinically relevant non-major bleeding event. The incidence of the primary endpoint was 15.4 % (151 patients) in the dabigatran etexilate 110 mg dual-therapy

	correct in section 4.3 a contraindication that refers to concomitant treatment with heparin, based on the data assessed in the context of variation II/103 to reflect the fact that heparin is administered during ablation procedure at the same time as dabigatran etexilate. Section 4.5 is similarly updated. Section 4.8 is updated with a minor re-wording. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				group as compared with 26.9 % (264 patients) in the warfarin triple-therapy group (HR 0.52; 95% CI 0.42, 0.63; P<0.0001 for non-inferiority and P<0.0001 for superiority) and 20.2 % (154 patients) in the dabigatran etexilate 150 mg dual-therapy group as compared with 25.7 % (196 patients) in the corresponding warfarin triple-therapy group (HR 0.72; 95% CI 0.58, 0.88; P<0.0001 for non-inferiority and P=0.002 for superiority). As part of the descriptive analysis, TIMI (Thrombolysis In Myocardial Infarction) major bleeding events was lower in both dabigatran etexilate dual-therapy groups than in the warfarin triple-therapy group: 14 events (1.4%) in the dabigatran etexilate 110 mg dual-therapy group as compared with 37 events (3.8%) in the warfarin triple-therapy group (HR 0.37; 95% CI 0.20, 0.68; P=0.002) and 16 events (2.1%) in the dabigatran etexilate 150 mg dual-therapy group as compared with 30 events (3.9%) in the corresponding warfarin triple-therapy group (HR 0.51; 95% CI 0.28, 0.93; P=0.03). Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple-therapy group: 3 events (0.3%) in the 110 mg dabigatran etexilate dual-therapy group as compared with 10 events (3.8%) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.06) and 1 event (0.1%) in the 150 mg dabigatran etexilate dual-therapy group as compared with 8 events (1.0%) in the corresponding warfarin triple-therapy group (HR 0.12; 95% CI 0.02, 0.98; P=0.047). The incidence of the composite efficacy endpoint of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization in the two dabigatran etexilate dual-therapy groups combined was

					non-inferior to the warfarin triple-therapy group (13.7% vs. 13.4% respectively; HR 1.04; 95% CI: 0.84, 1.29; P=0.0047 for non-inferiority).There were no statistical differences in the individual components of the efficacy endpoints between either dabigatran etexilate dual-therapy groups and warfarin triple-therapy. This study demonstrated that dual-therapy, with dabigatran etexilate and a P2Y12 antagonist, significantly reduced the risk of bleeding vs. warfarin triple-therapy, with non-inferiority for composite of thromboembolic events, in patients with atrial fibrillation who underwent a PCI with stenting.
II/0111	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	13/05/2019	SmPC	
PSUSA/918/201709	Periodic Safety Update EU Single assessment - dabigatran	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0110/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	24/01/2018	n/a		

	material/intermediate/reagent - Tightening of specification limits				
R/0105	Renewal of the marketing authorisation.	09/11/2017	08/01/2018	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Pradaxa in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0109	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	20/12/2017	n/a		
IB/0107/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	15/12/2017	n/a		
II/0103	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	19/10/2017	SmPC	
PSUSA/918/201703	Periodic Safety Update EU Single assessment - dabigatran	28/09/2017	n/a		PRAC Recommendation - maintenance

II/0100	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/05/2017	n/a		
PSUSA/918/201609	Periodic Safety Update EU Single assessment - dabigatran	06/04/2017	n/a		PRAC Recommendation - maintenance
IB/0102/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/03/2017	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0101	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/03/2017	n/a		The information complements the data available from the phase III trials for a different population. Large phase III trials evaluating dabigatran compared to warfarin have allowed the description of the management of major bleeding events and associated outcomes before the availability of the dabigatran reversal agent, idarucizumab. Study 1160.162 did not assess which management options are associated with better outcomes and therefore, it is not possible to make conclusions on the appropriateness of the measures taken to manage the bleeding events or for the assessment of their effectiveness. However, it provides the characteristics of gastrointestinal or urogenital bleeding events in patients with non valvular atrial fibrillation taking dabigatran etexilate who present to emergency departments/rooms for management of such events; data

					from a real-world setting. Most patients in the present study 1160.162 had a successful resolution. Overall, results from this study do not warrant amendments to the product information.
II/0097	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/02/2017	19/10/2017	SmPC and Labelling	
II/0093	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		
IAIN/0098/G	This was an application for a group of variations. B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	28/11/2016	19/10/2017	SmPC, Labelling and PL	
IB/0096	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/10/2016	n/a		
PSUSA/918/201603	Periodic Safety Update EU Single assessment - dabigatran	29/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0095/G	This was an application for a group of variations.	21/07/2016	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0091/G	This was an application for a group of variations. Submission of a group of variations containing 1) the final clinical study report 1160.118 “Observational cohort study to evaluate the safety and efficacy of switching from Lovenox (enoxaparin) 40 mg to Pradaxa (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery” and consequent update of the RMP and 2) update of the timeline for availability of study 1160.144 report. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	n/a		
PSUSA/918/2	Periodic Safety Update EU Single assessment -	14/04/2016	n/a		PRAC Recommendation - maintenance

01509	dabigatran				
II/0092	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/04/2016	n/a		
II/0089	Update of sections 4.4 and 4.9 of the SmPC regarding the availability of the specific reversal agent for dabigatran (Praxbind). In addition, the MAH took the opportunity of this procedure to update the wording on coagulation factors in section 4.9. An updated RMP version 31.4, including the educational materials on the potential risk of bleeding during treatment, is proposed accordingly. The MAH took the opportunity to update the Product Information in line with the latest QRD template version 9.1 and implement minor editorial updates. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/01/2016	01/08/2016	SmPC, Annex II and PL	When rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to Pradaxa is available. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa treatment can be re-initiated 24 hours after administration of Praxbind (idarucizumab), if the patient is clinically stable and adequate haemostasis has been achieved. For peri-operative Pradaxa treatment discontinuation please refer to the Summary of Product Characteristics.
II/0081	Update of sections 6.5 and 6.6 in the SmPC regarding opening instructions and storage instructions. The Package Leaflet has been updated accordingly. To further support the update of the opening instructions of the blister, a pictogram will be printed on the folding box flap, which is part the labelling. In addition, a simplification of the description of the packaging material for the blister is implemented.	17/12/2015	01/08/2016	SmPC, Labelling and PL	N/A

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0088	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	20/10/2015	01/08/2016	SmPC	
PSUSA/918/201503	Periodic Safety Update EU Single assessment - dabigatran	08/10/2015	n/a		PRAC Recommendation - maintenance
IA/0087/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	24/09/2015	n/a		
II/0082	C.I.13 - Other variations not specifically covered	24/09/2015	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0079/G	This was an application for a group of variations. Submission of the final CSR of study 1160.84; an observational cohort study undertaken to evaluate the safety and efficacy of Pradaxa in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) undergoing elective total hip replacement surgery or total knee replacement surgery. The provision of the CSR addresses the post-authorisation measure MEA2 010.1. The application included an updated RMP version 31.0, which includes changes pertaining to the study report of study 1160.84, the update of due dates in Part III of the RMP for the provision of 14 study reports, and the inclusion of the outcome of 2 phase I studies (studies 1160.141 and 1160.142) following the CHMP assessment of variations II-46 and II-61. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the	24/09/2015	n/a		N/A

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0086/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	10/09/2015	n/a		
II/0080	Update of section 5.2 of the SmPC to implement bioavailability results from Study 1160.194. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	01/08/2016	SmPC	The oral bioavailability may be increased by 75 % after a single dose and 37 % at steady state compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (HPMC) capsule shell.
II/0066	Submission of the final CSR of Study 1160.86 (open label, non-comparative pharmacokinetic and pharmacodynamic study to evaluate the effect of Pradaxa on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment undergoing primary unilateral elective total knee or hip replacement surgery). An updated RMP version 28.6 was agreed	23/07/2015	n/a		N/A

	during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0084	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/06/2015	n/a		
PSUSA/918/201409	Periodic Safety Update EU Single assessment - dabigatran	10/04/2015	n/a		PRAC Recommendation - maintenance
IA/0078/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/02/2015	n/a		
IA/0077/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/02/2015	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0075	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2015	n/a		
II/0073	Update of data in section 4.8 and 5.1 (Pradaxa 110 and 150 mg) based on a targeted review of selected RE-LY data. In addition to some minor editorial changes of SmPC and Package Leaflet have been introduced. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	03/07/2015	SmPC and PL	
IA/0074	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	20/11/2014	n/a		
IB/0072/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the	04/11/2014	n/a		

	finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised				
PSUV/0069	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0063	Update of section 5.1 of the SmPC to include safety information from the RELY-ABLE study, a long-term extension of the RELY trial. In addition, upon request by the CHMP, the MAH took the opportunity to implement minor changes in section 4.2 of the SmPC of the orthopaedic VTE indication with regard to the initial dose in patients who should receive a lower dose. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	03/07/2015	SmPC	The RE-LY extension study (RELY-ABLE) provided additional safety information for a cohort of patients, which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43 months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5 years). There were 5897 patients enrolled, representing 49% of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86 % of RELY-ABLE -eligible patients. During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses 110

					mg b.i.d. and 150 mg b.i.d.. No new safety findings were observed. The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.
II/0058	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	25/09/2014	n/a		
IA/0071/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/08/2014	n/a		
II/0062	Submission of a revised RMP following the modification to the study 1160 – 144, post-authorization non-interventional study evaluating potential off-label use of dabigatran etexilate in Europe. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	24/07/2014	n/a		

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IAIN/0070	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	10/07/2014	03/07/2015	SmPC and PL	
II/0048/G	This was an application for a group of variations. Update of section 4.1 of the SmPC for 110mg and 150mg strengths in order to add the following two new related indications: (1) treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death (aVTEt), (2) prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death (sVTEp). Several sections of the SmPC for 75, 110 and 150mg strengths were proposed to be modified to include the data relevant for two new indications. The Package Leaflet was proposed to be updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/04/2014	03/06/2014	SmPC, Annex II and PL	Please refer to the CHMP AR for Pradaxa II/48/G.

II/0064	This type II variation concerns the provision of an updated protocol of the agreed study category 3: 1160.84: Observational cohort study to evaluate safety and efficacy of Pradaxa in patients with moderate renal impairment undergoing elective total hip replacement surgery or total knee replacement surgery. As a consequence, an updated RMP version 28.5 has been provided accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	22/05/2014	n/a		This study is being performed as a follow-up measure (MEA2 10.1) to better describe the benefit/risk profile of the 150mg dose of dabigatran in patients with renal impairment. The first patient was enrolled into the study in 2009. According to the planning at study start, the last study patient should have been recruited in 2010. However despite measures taken to improve enrolment (including increases in numbers of sites), recruitment is still slow. With this variation application, the applicant proposed to reduce the sample size from 500 to 425 patients to allow an earlier study termination in Q4 2014 (previously estimated to Q2 2015) and study report availability. This approach was agreed by the PRAC and CHMP.
IA/0068/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/05/2014	n/a		
IA/0067	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	21/05/2014	n/a		
IB/0059/G	This was an application for a group of variations.	30/04/2014	n/a		

	B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction				

II/0061	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	03/06/2014	SmPC and PL	
IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
PSUV/0057	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IA/0060/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	30/01/2014	n/a		
II/0056	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	23/01/2014	n/a		

II/0055	Update of section 4.3 of the SmPC (to change a contraindication for a concomitant use with tacrolimus to a non-recommendation) and section 4.5 of the SmPC (to change a non-recommendation for concomitant use with posaconazole to a cautionary statement) for both registered indications following the Assessment Reports for PSUR No 8 (012). Section 2 in the Package Leaflet was updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	18/12/2013	03/06/2014	SmPC and PL	Tacrolimus has been found in vitro to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors. Based on these data concomitant treatment with tacrolimus is not recommended. Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.
II/0052	Update of section 4.1 of the SmPC for 110 and 150 mg tablets, regarding the indication stroke and systemic embolism prevention in atrial fibrillation (SPAF) to a stroke risk assessment which does not exclude patients with atrial fibrillation < 65 years with just one additional risk factor for stroke following the shift in the updated Guideline of the European Society of Cardiology 2012. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/11/2013	18/12/2013	SmPC	Please, see CHMP AR for Pradaxa II/52.

IB/0054/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/11/2013	n/a		
IB/0053	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	18/10/2013	n/a		
II/0051	Update of section 4.4 of the for primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery indication in order to add a warning regarding the use of fibrinolytic medicinal products for the treatment of	19/09/2013	18/12/2013	SmPC	Independent from the indication, acute ischemic strokes can potentially occur in patients during anticoagulant treatment for SPAF (Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors) or pVTEp (Primary prevention of venous thromboembolic events in adult

	acute ischemic stroke in patients taking concomitantly dabigatran etexilate. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				patients who have undergone elective total hip replacement surgery or total knee replacement surgery) indication depending on the patients´s individudal risk factors. Only scarce data are available (18 adverse event case reports available, where fibrinolytics were concomitantly administered to dabigatran etexilate for the treatment of acute ischemic stroke) that do not allow indication-specific recommendations other than those formerly applied for SPAF indication only. Therefore it was agreed that the existing for SPAF indication recommendation for the use of fibrinolytic agents should be applied also for pVTEp.
II/0049	Update of section 4.8 of the SmPC in order to add the oesophageal ulcer to tabulated list of adverse reactions. Section 4.2 of the SmPC was updated consequently. Sections 3 and 4 of the Package Leaflet are updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	18/12/2013	SmPC, Annex II and PL	After the signal of disproportinate reporting for the PT ”oesophageal ulcer” all retrieved cases from postmarketing experience with dabigatran etexilate and from clinical trials with dabigatran etexilate/actice comparators were reviewed and evaluated. A causal association between oesophageal ulcers and the intake of dabigatran etexilate appeared. Therefore, the SmPC was modified to include the “oesophageal ulcer” into Section 4.8 of the SmPC and to modify the recommendations regarding swallowing of dabigatran etexilate in Section 4.2 of the SmPC.
IB/0050	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	20/08/2013	18/12/2013	SmPC and PL	
IAIN/0047/G	This was an application for a group of variations.	05/06/2013	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
II/0046	Update of sections 4.4, 4.5 and 5.2 of the SmPC in order to add the new information related to drug-drug interaction ticagrelor/dabigatran following the results of the study 1160-0141. In addition, sections 4.2, 4.4 and 4.5 were updated to make distinction between 'strong' and 'mild to moderated' P-glycoprotein inhibitors. The Package Leaflet was updated to include the text of the Patient Alert Card. Furthermore, the MAH proposed this opportunity to bring the PI in line with the QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	25/04/2013	15/07/2013	SmPC, Annex II, Labelling and PL	The study 1160.141 was investigating the concomitant intake of ticagrelor and Pradaxa in healthy volunteers. A pharmacokinetic interaction between ticagrelor and DE has been shown. Ticagrelor increased dabigatran exposure which is consistent with the hypothesis of P-gp inhibition by ticagrelor at the intestinal wall. The increases in gMean AUC0-∞ and Cmax were less than 2-fold in the loading situation and around 1.5-fold under steady state conditions of ticagrelor. Administration of single doses of 75 mg DE and the coadministration of single doses of 75 mg dabigatran with the ticagrelor loading dose and the multiple-dose regimen of ticagrelor was safe, i.e. it did not cause bleeding, in the healthy subjects. The increase in AUC is larger than 1.5-fold and warranted a warning in the SmPC.

	clinical, clinical or pharmacovigilance data				
II/0045	Update of section 4.8 of the SmPC in order to modify the frequency of the adverse drug reactions following the revision of the method for the calculation of frequency. The section 4 of the Package Leaflet was updated accordingly. Small linguistic changes were included in French, Finnish and Norwegian Annexes to bring them in line with the English version of the Product Information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	15/07/2013	SmPC and PL	The revised method for frequency calculation resulted in a downward shift in frequency category for a number of events, especially in the pVTEp indication. The licensed indications are markedly different both in terms of duration of treatment, nature of the indication and characteristics of the patient population. The new proposal does no longer distinguish between doses within each indication since this is simpler, more user-friendly and does not result in leaving out important information.
R/0041	Renewal of the marketing authorisation.	18/10/2012	17/01/2013	SmPC, Annex II, Labelling and PL	This is the first renewal to the Marketing Authorisation for Pradaxa. The overall cumulative experience with Pradaxa with respect to safety and efficacy data reported, collected and evaluated over the period covered (i.e. from March 18th, 2008 until June 1st 2012) was found to be consistent with the treated population of patients with nonvalvular atrial fibrillation or patients undergoing elective hip or knee replacement surgery and the known safety profile of Pradaxa. During the period covered, additional studies on bioequivalence, drug-drug interactions, PK-PD as well as preclinical/in vitro investigations and a genomic substudy have been performed and have added to the knowledge on Pradaxa. Relevant information arising from these studies has been sufficiently addressed in the SmPC in the previous procedures. Modification and strengthening of the wording

					of the SmPC has been performed based on these results as well as from post-marketing experience when considered relevant for the prescribers or physicians treating complications from Pradaxa. Adding together the evidence available at authorisation and the non-clinical and clinical data obtained since then including post-marketing experience, it is concluded that the benefits of Pradaxa in the approved indications continue to outweigh the harms. In light of the continued need to focus on the safety of Pradaxa following the authorisation of the prevention of stroke and systolic embolism in patients with atrial fibrillation indication in August 2011, especially with respect to major bleedings, the CHMP recommended one additional five-year renewal.
II/0044	Update of sections 4.3 and 5.1 of the SmPC in order to add a new contraindication in patients with prosthetic heart valves requiring anticoagulant treatment following the results of the REALIGN study. The Package Leaflet was updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	13/12/2012	21/01/2013	SmPC, Annex II and PL	RE-ALIGN was a phase II study that examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical heart valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin in the available results of this study. Therefore, a contraindication in patients with prosthetic heart valves requiring anticoagulant treatment was introduced in the SmPC for Pradaxa.
II/0043	Update of section 4.8 of the SmPC in order to add angiooedema and anaphylactic reaction as adverse	15/11/2012	21/01/2013	SmPC and PL	A review of the accumulated safety data on ‘angioedema’ revealed 195 ICSRs which were considered to represent

	drug reactions. In addition, traumatic haemorrhage and genitourological haemorrhage were added to section 4.8 of the primary venous thromboembolic prevention indication in line with the indication for stroke prevention in atrial fibrillation. The frequency category for bronchospasm in section 4.8 of the SmPC was corrected for the stroke prevention in atrial fibrillation indication. Small editorial corrections were added to section 4.8 of the SmPC. Section 4 of the Package Leaflet was updated accordingly. In addition the MAH proposed to correct various sections of the French translation of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				cases of possible angioedema under exposure to Pradaxa. There were no fatal cases due to angioedema, and the large majority of cases were assessed as non-serious in nature. The frequencies for all Pradaxa dosages translate into the EU SmPC defined frequency category ‘rare’. The review of the accumulated data on ‘anaphylactic reactions’ revealed 34 cases meeting the definition of such events. The 34 cases showed a gender distribution of 2:1 female to male. In approximately two-thirds of patients with information on time-to-onset available, the latency was less than 10 days. The frequencies for all Pradaxa dosages translate into the EU SmPC defined frequency category ‘rare’. In addition the correct frequency categories for ‘traumatic’ and ‘genitourological haemorrhage’ as well as for ‘bronchospasm’ were added to SmPC section4.8.
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
II/0032	Update of section 4.4 of the SmPC to include a warning not to use Pradaxa in patients with prosthetic valve disease. Annex II was updated in accordance. In addition, the MAH took the opportunity to make small editorial changes in Annex IIIA and IIIB, and to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	21/06/2012	30/08/2012	SmPC, Annex II, Labelling and PL	No reliable data are available regarding the efficacy and safety of Pradaxa in patients with a mechanical valve. The review of Pradaxa post-marketing experience data revealed that Pradaxa is sporadically used off-label for the treatment of patients with artificial heart valves. Within current variation the data from patients after heart valve replacement surgery receiving Pradaxa within the RE-LY trial as well as from the post marketing experience were assessed. The CHMP recommended addition of a warning not to use Pradaxa in patients with prosthetic heart valves.

	clinical, clinical or pharmacovigilance data				
II/0028	Update of sections 4.3, 4.4, 4.5 and 5.2 of the SmPC in order to contraindicate the concomitant use of dronedarone and dabigatran following the results of the phase 1 drug-drug interaction study. The Package Leaflet was proposed to be updated in accordance. Annex II (Conditions or restrictions with regards to the safe and effective use of the medicinal product) was updated to reflect the change in the key messages of the Prescribers Guide and Patient Alert Card. In addition, fluconazole was deleted from section 2 of the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	30/08/2012	SmPC, Annex II and PL	A phase 1 study conducted in healthy subjects, investigated the bioavailability and pharmacokinetic parameters of dabigatran etexilate in different settings of dronedarone co-administration. Overall bioavailability of dabigatran etexilate increased about 2-2.4 fold irrespective if dabigatran etexilate was administered at the same time as dronedarone or on-top of preexisting multiple dose treatment of dronedarone. Therefore it was agreed to contraindicate the concomitant use of dabigatran etexilate and dronedarone even if the post-marketing data did not confirm an increase in bleeding events in patients treated with both medicinal products. For further information please refer to the scientific conclusion: H-829-VAR-II-28-en.
IAIN/0040/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished	06/07/2012	30/08/2012	SmPC, Labelling and PL	

	product formulation - Change that affects the product information B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
II/0031	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. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	28/06/2012	SmPC and PL	This variation was submitted to update the product information for Pradaxa, to give clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding associated with this medicinal product. Bleeding is a well-known complication of all anticoagulant medicines and Pradaxa has therefore been kept under close review by the CHMP since its initial authorisation. The CHMP recommendation to update the product information followed the assessment of all available data, including from post-marketing surveillance. The Committee found that the frequency of occurrence of fatal bleedings with Pradaxa seen in post-marketing data was significantly lower than what was observed in the clinical trials that supported the authorisation of the medicine, but considered that this issue should nonetheless be kept under close surveillance. In the outcome a more precise wording of the contraindications was agreed as well as additional guidance to physicians on the medical management of the major bleedings associated with the use of Pradaxa.
IAIN/0038	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved	05/06/2012	n/a		

	manufacturer				
IAIN/0037/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	05/06/2012	26/07/2012	SmPC, Labelling and PL	
IAIN/0039	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	04/06/2012	n/a		
IAIN/0036	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	04/06/2012	n/a		
IAIN/0035/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a	01/06/2012	26/07/2012	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing				
II/0029	The MAH proposed the update of sections 4.9 and 5.2 of the SmPC to include the information about a study investigating the elimination of dabigatran by haemodialysis. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC	Section 4.9 and 5.2 of the SmPC were updated to include information about a phase 1 trial in patients with end stage renal disease without atrial fibrillation undergoing regular haemodialysis. In this study the elimination, pharmacokinetics, pharmacodynamic and safety of dabigatran etexilate before, during and after HD were investigated. Haemodialysis was shown to remove dabigatran etexilate without substantial redistribution. No deaths, serious adverse events, other significant adverse events, or adverse events of severe intensity were reported.
II/0026	The MAH proposed the update of sections 4.2 (110 and 150 mg strengths), 4.4 and 5.1 (75, 110 and 150 mg) of the SmPC in order to update the safety information regarding the tests that could be used to measure the anticoagulant activity of dabigatran etexilate. Further small editorial corrections were done in sections 4.4, 4.8, 5.1 and 5.2 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC and PL	Regression analysis from the RE-LY (Randomised Evaluation of Long Term Anticoagulant Therapy) study showed that major bleeding was correlated to trough aPTT and 80 seconds were shown to be the limit beyond which there is an increased risk of major bleeding events. Based on this analysis, the SmPC of Pradaxa was updated to include coagulation test thresholds at trough that may be associated with an increased risk of bleeding. In addition, during treatment with Pradaxa, the INR is relatively insensitive to the activity of dabigatran and is therefore not a good measure of anticoagulant activity associated with Pradaxa. Furthermore, false positive INR elevations have been reported in the RE-LY study and post-marketing.

					Therefore the information that the INR tests should not be performed was included in the SmPC.
WS/0255/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Description of Pharmacovigilance System (DDPS). C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	24/05/2012	24/05/2012		Changes to an existing pharmacovigilance system as described in the DDPS. The MAH update the Detailed Description of the Pharmacovigilance System (DDPS) for Aptivus, MicardisPlus, Mirapexin, Onduarp, Pradaxa, Sifrol, Trajenta, Twynsta and Viramune.
II/0025	The MAH proposed the update of sections 4.4 and 4.5 of the SmPC in order to include statements	15/03/2012	13/04/2012	SmPC and PL	The database of the RE-LY trial was evaluated in order to select patients concomitantly treated with Pradaxa and

	regarding the interactions with SSRIs (selective serotonin reuptake inhibitors)/SNRIs (selective serotonin norepinephrine re-uptake inhibitors), ticagrelor, fibrinolytics and further small editorial changes. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				SSRIs. This evaluation showed that the bleeding risk was increased in all treatment groups and therefore a statement was included into the SmPC that bleeding risk may be increased in patients concomitantly treated with SSRIs/SNRIs (selective serotonin re-uptake inhibitors or selective serotonin norepinephrine re-uptake inhibitors) and Pradaxa. Given that the most frequent adverse reaction associated with P2Y12 inhibitors like ticagrelor is bleeding, a careful evaluation in clinical settings is indicated where ticagrelor and dabigatran are to be used simultaneously. Therefore although not studied, a statement was included in section 4.5 of the SmPC. The most frequent adverse reaction associated with fibrinolytic agents is bleeding. A recommendation for treatment in case of an emergency situation was included in section 4.4 that the use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range.
II/0023	The MAH proposed the update of section 4.8 of the SmPC for all three strengths in order to update the safety information following the re-evaluation of the safety profile of the product after finalisation of RE-NOVATE II study that was submitted and assessed within FUM2 008.1. In addition, the MAH proposed to update section 4.8 of the 75 mg and 110mg strength for “Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery” to include the undesirable effect	15/12/2011	09/02/2012	SmPC, Annex II, Labelling and PL	The evaluation of the pooled safety data set from the RE-NOVATE II study did not give any information for new undesirable effects associated with the use of dabigatran not already known from earlier evaluations. Frequencies of four undesirable effects were however impacted by the RE-NOVATE II data. The frequencies have been updated and relevant modifications introduced in section 4.8 of the SmPC. Furthermore, the undesirable effect “haemoptysis” has been included in the indication "primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery" (for 75 mg and 110 mg

	“haemoptysis” based on the safety data from the RE-LY trial as it was done for 110 and 150 mg strengths for the indication “Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischemic attack, or systemic embolism (SEE); Left ventricular ejection fraction < 40 %; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension” within variation Pradaxa II/15. Section 4 of Package Leaflet was updated accordingly. Annexes IIB, Labelling and Section 3 of the Package Leaflet were updated for all three strengths with regards to the recommendation not to open the capsule. The section 4 of the Package Leaflet for 110 mg and 150 mg strengths was updated with regards to the information concerning the myocardial infarction in accordance to the wording of the SmPC. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8. Also, some minor corrections of the Bulgarian, German, Italian, Lithuanian and Swedish translations of various sections of Product Information were proposed to be implemented within this variation.				strengths). In addition package leaflet for 110 and 150 mg strengths has been updated in line with the SmPC with regards to the information that in a clinical trial the rate of heart attacks with dabigatran was numerically higher than with warfarin. The CHMP was also of the opinion that it is necessary to modify Annex IIB, Labelling and Package Leaflet in line with the SmPC section 4.2 the PL for all three strengths to include the recommendation for not opening dabigatran capsules as it may result in increased risk of bleeding. The Prescriber’s Guide and Patients Alert Card were also modified in this respect.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0022	Update of Section 4.2 of the SmPC and Annex II as a follow up to the safety FUM 028 on recent Japanese bleeding cases. In addition, Section 4.4 of the SmPC for the 110 and 150 mg dose strengths was modified to clarify that the referenced clinical trial data are from a study in AF patients and the dose recommendation apply to AF patients. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	22/12/2011	SmPC, Annex II and PL	This variation was to include in the SmPC the new recommendations to assess renal function in patients being considered for, or already being treated with Pradaxa. These recommendations follow an evaluation of reports of several cases of fatal bleeding in Japan. Some of these cases occurred in elderly patients with severe renal impairment, which constitutes a contraindication for Pradaxa treatment. Therefore: (1) renal function should be assessed in all patients prior to initiating Pradaxa therapy, (2) Pradaxa is contraindicated in patients with severe renal impairment, (3) While on treatment renal function should be assessed in clinical situations where a decline in renal function is suspected, (4) In elderly patients (> 75 years) or in patients with renal impairment the renal function should be assessed at least once a year.
IA/0027	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	16/12/2011	n/a		
IB/0024/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	30/11/2011	09/02/2012	SmPC, Labelling and PL	

	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)				
II/0020/G	This was an application for a group of variations. - To register an alternate active substance synthesis. The currently registrered active substance synthesis will be deleted. - To widen the acceptance criterion of one impurity for the final intermediate. - To add an alternative supplier for a starting material. - To update the analytical procedures for a starting material. - To tighten the acceptance criterion for an impurity. - To modify the analytical procedure for an intermediate. - To implement an alternative analytical procedure. - To modify analytical procedures for the final active substance. - To modify analytical procedures for the final active substance.	17/11/2011	n/a		

	- To extend the active substance retest period. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.b - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IA/0021	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/08/2011	n/a		
X/0013/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the	10/06/2011	01/08/2011	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion: Pradaxa H-C-829-X-13.

	medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the				

	approved specifications limits range for the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.I.c.3.z - Changes in the test procedure for the immediate packaging of AS - Other variation B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement				

	or addition of a site where batch control/testing takes place B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.e.3.z - Change in test procedure for the immediate packaging of the finished product - Other variation B.II.e.3.z - Change in test procedure for the immediate packaging of the finished product - Other variation B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0018	To update section 5.1 of the Annex I according to the results provided in the final phase III study report RE-NOVATE II (1160.64) following the recommendations given in FUM 008.1. To delete the duplication of information regarding paediatric population in section 4.2 of Annex I. To perform some minor grammar corrections in Annex I sections 4.2, 4.5, 4.8, 5.2 and Section 4 of Annex IIIB.	16/12/2010	21/01/2011	SmPC and PL	As requested in the assessment report for FUM 008.1, Section 5.1 of the SmPC was updated as per the results of RE-NOVATE II study with the following specifications: “Steady state (after day 3) geometric mean dabigatran peak plasma concentration, measured around 2 hours after 220 mg dabigatran etexilate administration, was 70.8 ng/ml, with a range of 35.2-162 ng/ml (25th – 75th percentile range). The dabigatran geometric mean trough concentration, measured at the end of the dosing interval (i.e. 24 hours after a 220 mg dabigatran dose), was on

	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				average 22.0 ng/ml, with a range of 13.0-35.7 ng/ml (25th – 75th percentile range) (see section 4.4)." It was agreed to delete subheading "children and adolescents" under heading "special patients populations" in section 4.2. In addition in the subsection on the paediatric population in section 4.2 it was added that Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2010	n/a	PL	
II/0016	The update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC and section 2 of the PL with new data regarding P-gp inhibitors and inducers based on interaction studies. The update concerning the drug-drug interaction of DE with quinidine was requested in the Assessment Report for PSUR3. In addition a version number of the pharmacovigilance system was deleted from the Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC, Annex II and PL	New data for drug-drug interactions of Pradaxa with P-gp inhibitors and inducers were obtained as part of the development of Pradaxa for long-term treatment. Specifically, this concerns the P-gp inhibitors quinidine and ketoconazole as well as the P-gp inducer rifampicin. An update concerning the drug-drug interaction of Pradaxa with quinidine was also requested in the Rapporteur´s Final Assessment Report for PSUR 3 (EMEA/H/C/829) which was issued on 9 February 2010. The update results in the following main changes: - Quinidine co-administration is no longer be contraindicated. Instead, in patients treated concomitantly with Pradaxa and quinidine, the dose of Pradaxa should be reduced to 150 mg once daily. In this situation Pradaxa should be taken concomitantly. - Concomitant treatment with Pradaxa and systemic ketoconazole is contraindicated. - Caution should be exercised with strong P-glycoprotein inhibitors (e.g. amiodarone, quinidine or verapamil).

					- The following P-glycoprotein inhibitors have not been studied and are therefore not recommended for concomitant treatment with Pradaxa: itraconazole, tacrolimus and cyclosporine. - Additional explicit warnings and precaution wording were introduced: Factors, such as decreased renal function (30-50 ml/min CrCL), age ? 75 years, or strong P-glycoprotein-inhibitor comedication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding and these patients should be closely clinically monitored (looking for signs of bleeding and anaemia) (see sections 4.2, 4.5 and 5.2). - Concomitant administration of Pradaxa with potent P-glycoprotein inducers should be avoided. - Carbamazepine was be added to the list of P-gp inducers, which are expected to reduce dabigatran plasma concentrations and thus should be co-administered with caution. - Effects on dabigatran exposure (AUC, Cmax) upon c
II/0015	C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data To update the section 4.8 Undesirable effects of the SPC (Annex I) as well as section 4 of the Package Leaflet (Annex IIIB) following the analysis of the safety database for possible undesirable effects after the completion of the pivotal trial RE-LY. All	23/09/2010	25/10/2010	SmPC and PL	In 2007, the Summary of Clinical Safety (SCS) summarizing all studies performed in the indication "Primary VTE prevention after hip or knee replacement surgery" was used to assess the safety profile of dabigatran etexilate (DE) and identify side effects for inclusion in section 4.8 of the SmPC as undesirable effects. During this evaluation some of the adverse events found in the SCS data set, especially those concerning the gastrointestinal tract such as nausea, vomiting, dyspepsia, etc., were,

	frequencies were calculated for adverse drug reactions as opposed to adverse events. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				based upon all available data, assessed as not related to treatment with DE and consequently were not classified as undesirable effects. At the time of assessment it was the opinion of the MAH that these events were more likely related to the underlying surgical intervention or other confounding factors. However, in 2009, after the completion of the pivotal clinical large scale trial RE-LY (18.113 patients with atrial fibrillation treated for stroke prevention), including more than 12,000 patients treated with DE, the respective safety data set was analysed for possible new undesirable effects. During data evaluation facts and evidence were found that several new adverse events especially concerning the gastrointestinal tract qualified for "new" side effects. For the evaluation MedDRA PTs were collapsed to relevant medical concepts and for these medical concepts frequencies were calculated following the principals described in the EC Guideline on Summary Product Characteristics. These side effects were included in section 4.8 of the SmPC submitted with the application of the new indication "Stroke prevention in patients with atrial fibrillation" (EMEA/H/C/000829/X/0013/G). Based on the results of evaluation of the RE-LY data, a re-evaluation of the data set used as the basics for the SCS was performed for the indication "Primary VTE prevention after hip or knee replacement surgery". The medical concepts which have been used for the RE-LY data set were also applied for a sea
II/0017	Introduction of changes in section 4.4 "Special warnings and precautions for use" of Annex I by inclusion of the statement regarding aPTT as a test	22/07/2010	26/08/2010	SmPC	Inclusion of a statement on the aPTT test for monitoring of dabigatran activity in section 4.4 was endorsed however the wording proposed by MAH was modified.

	to determine anticoagulant intensity of dabigatran, following the outcome of FUM 007.1 and FUM 007.2. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Section 4.4 should read: “The activated partial thromboplastin time (aPTT) test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding or at risk of bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution. If required, more sensitive quantitative tests such as calibrated diluted Thrombin Time should be performed.”
II/0014	Revision of PRADAXA product information for 75 mg and 110 mg hard capsules to include instruction for patients "not to open the capsule" following the results of the clinical trial 1160.87 that showed higher bioavailability of alternative oral formulations under investigation. Respective changes were included in ANNEX I sections 4.2 and 5.2 and ANNEX IIIB sections 2 and 3. To comply with the QRD template as published 10/2009, respective changes were included in ANNEX I sections 4.2, 4.6 and 5.1. To correct mistake in ANNEX IIIB section 2 where subheading "Taking other medicines" verapamil is mentioned in the paragraph headed "Amiodarone, verapamil" and was accidently not deleted in review under variation EMA/CHMP/829/II/0011. Furthermore, some minor grammar corrections were	20/05/2010	01/07/2010	SmPC and PL	DE is formulated as a capsule for use in adult patient population. For patients unable to swallow capsules – such as children, the elderly or disabled, two alternative formulations are under investigation, a reconstituted oral solution and pellets sprinkled on food, respectively. Study 1160.87 investigated the pharmacokinetics of a single dose of DE 150 g when administered as capsule, reconstituted oral solution and pellets sprinkled on food. The results showed a marked increased relative bioavailability when administered as reconstituted oral solution and pellets sprinkled on food when compared to capsules (60% and 80 % respectively). In order to ensure patient safety and minimise the risk of bleeding the CHMP therefore agrees on the inclusion of additional instruction for patients in section 4.2 of the SmPC, which however should be expanded to: “Patients should be instructed not to open the capsule as this may increase the risk of bleeding”.

	included in ANNEX I sections 4.2, 4.5 and 5.2 and ANNEX IIIB section 2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The EMA has waived the obligation to submit the results of studies with DE in all subsets of the paediatric population for the approved indication. Therefore a proposed wording to be included in section 4.2 and 5.1 of the SmPC is in agreement with the EMA guideline “A guideline on summary of product characteristics“ from September 2009 revision 2 and is therefore considered acceptable.
II/0011	Further to the assessment of FUM 006.1 and the completion of a drug-drug interaction study with verapamil, the CHMP requested the update of sections 4.2, 4.4 and 4.5 of the SPC to reflect the drug interaction with verapamil. The Package Leaflet has also been amended accordingly. Further changes to the list of local representatives for Hungary, Romania, Slovenia and Slovakia have been made in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	The concomitant use of verapamil with dabigatran etexilate can result in elevation of dabigatran plasma concentrations. Depending on dosing schedules this increase can differ remarkably. Verapamil is a strong P-glycoprotein (P-gp) inhibitor. Dabigatran etexilate is a P-gp substrate. Boehringer Ingelheim evaluated the effect of verapamil on dabigatran plasma concentrations under various dosing conditions in a Phase I trial in healthy volunteers. Multiple dosing of verapamil for several days elevated dabigatran concentrations 50-60%. However, the increase in dabigatran plasma concentrations was strongly dependent on the dose frequency and the relative timing of administration of the two drugs. Increases in dabigatran concentrations ranged from a low of a 12% (1.12-fold) to a high of 179% (2.79-fold). The CHMP concludes that concomitant use of verapamil with dabigatran etexilate can result in elevation of dabigatran plasma concentrations. Depending on dosing schedules this increase can differ remarkably. The greatest elevation of dabigatran exposure seems to happen in the first days after pre-dosing of an immediate release formulation of verapamil. The effect can be minimized by

					dosing dabigatran at least 2 hours before verapamil. The MAH submitted a procedure to update of sections 4.2, 4.4 and 4.5 of the SPC to reflect the drug interaction with verapamil. In addition, the Package Leaflet has also been amended accordingly. Further changes to the list of local representatives for Hungary, Romania, Slovenia and Slovakia have been made in the Package Leaflet.
II/0012	Update of the Detailed Description of the Pharmacovigilance System (DDPS) in order to include the change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. Changes to QPPV Update of DDPS (Pharmacovigilance)	23/07/2009	20/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 5.0 dt 9 October 2008) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) (Version 5.2 dt 9April 2009). Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0010	Update of section 4.8 of the SPC in order to include a more precise description of the term "major bleeding" and possible outcome. The package leaflet has also been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	The MAH applied to update section 4.8 of the SPC in order to include a more precise description of the term ´major bleeding´ and possible outcome. The package leaflet has also been updated accordingly. The text included in this sections is: "...Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes..."
II/0009	Update of Detail Description of the Pharmacovigilance System (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	22/01/2009	26/02/2009	Annex II and PL	The Marketing Authorisation Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS), this updated is Edition 5 dated 09 October 2008. . There have been no significant changes made to the MAH's pharmacovigilance systems. In addition, the MAH has also

					amended the name of the local representative in Austria in the Package Leaflet.
IB/0008	IB_33_Minor change in the manufacture of the finished product	22/10/2008	n/a		
II/0002	Quality changes to the manufacturing arrangements, process and controls of the drug product and intermediates. Quality changes	24/07/2008	04/08/2008		
II/0003	Quality changes to the manufacturing process, specifications and testing of the drug substance and intermediates. Change(s) to the manufacturing process for the active substance	26/06/2008	30/06/2008		
IB/0001	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	10/06/2008	n/a	SmPC, Labelling and PL	
IB/0007	IB_26_b_Change in the specification of immediate packaging - addition of new test parameter	09/06/2008	n/a		
IB/0005	IB_19_b_Change in specification of an excipient - addition of new test parameter	09/06/2008	n/a		
IA/0006	IA_26_a_Change in the specification of immediate packaging - tightening of specification limits	18/04/2008	n/a		

IA/0004	IA_39_Change/addition of imprints, bossing or other markings	18/04/2008	n/a		