Xarelto

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/0111	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/09/2024		PL	
II/0110/G	This was an application for a group of variations. Update of section 5.2 of the SmPC in order to update	27/06/2024	09/08/2024	SmPC, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	pharmacokinetic information based on in vitro study report PH-41585. In addition, the MAH took the opportunity to implement editorial changes in the SmPC. Update of sections 6.5 and 6.6 of the SmPC to mitigate the risk of misinterpretation regarding the volume of the suspension to be prepared. The Labelling and Package Leaflet are updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0109/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) 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) 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) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	07/12/2023	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release) 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)				
IA/0108	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	29/09/2023	n/a		
IA/0107	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	29/09/2023	n/a		
IB/0104	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/09/2023	n/a		
IA/0106/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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/09/2023	n/a		

IA/0105	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	21/08/2023	n/a		
PSUSA/2653/ 202209	Periodic Safety Update EU Single assessment - rivaroxaban	25/05/2023	26/07/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2653/202209.
IAIN/0103	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	13/04/2023	n/a		
IB/0102/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.I.z - Quality change - Active substance - Other variation B.I.z - Quality change - Active substance - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	13/04/2023	n/a		

	B.I.z - Quality change - Active substance - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.I.z - Quality change - Active substance - Other variation				
IAIN/0101/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect	27/02/2023	n/a		

	the product information				
IA/0100/G	This was an application for a group of variations. B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	17/02/2023	n/a		
II/0096	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2023	n/a		Submission of the final report from study 15786 (COMPASS LTOLE). This is a phase 3, multicenter, randomized, double-blind, double-dummy, active comparator, event-driven study, in which subjects were randomized 1:1:1 to rivaroxaban 2.5 mg bid/ASA 100 mg od, or rivaroxaban 5 mg bid, or ASA 100 mg od.

IAIN/0099	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	25/01/2023	n/a		
SW/0089	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0027 - Variation	15/09/2022	05/12/2022	SmPC, Annex II and PL	The PRAC considered it appropriate to summarise the key results from this imposed PASS program, which had been conducted in 3 EU countries and the UK, and which comprised more than 40,000 patients in the VTE-T indication and 162,000 patients in the NVAF indication, and reflect those in the SmPC, section 5.1 Pharmacodynamic properties of the product information. Furthermore, by finalisation of this category 1 study program, removal of the additional monitoring statement and the black triangle from the product information is warranted. Annex II of the product information should also be updated to remove this condition. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information and changes to the conditions of the marketing authorisation were warranted.
II/0097	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/10/2022	26/07/2023	SmPC and PL	
IB/0095	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	21/06/2022	n/a		
II/0093	Update of section 5.1 of the SmPC and subsequent changes in section 4.8, based on final results from	16/06/2022	05/12/2022	SmPC	Update of section 5.1 of the SmPC to add information on thromboprophylaxis in paediatric patients with congenital

	study 18226 (UNIVERSE); this is a prospective, open-label, active controlled, multicenter, 2-part study, designed to evaluate the single- and multiple-dose pharmacokinetic properties of rivaroxaban (Part A), and to evaluate the safety and efficacy of rivaroxaban when used for thromboprophylaxis for 12 months compared with acetylsalicylic acid (Part B) in children 2 to 8 years of age with single ventricle physiology who had the Fontan procedure. In addition, the MAH took the opportunity to introduce editorial changes to sections 4.8 and 4.9 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				heart disease after the Fontan procedure, based on the results from study 18226 (UNIVERSE). For more information, please refer to the Summary of Product Characteristics.
IA/0094	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	29/04/2022	n/a		
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021	05/12/2022	PL	
IA/0091/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	01/12/2021	n/a		

IA/0090	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	12/11/2021	n/a		
II/0081	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following the final results from the VOYAGER PAD study, a multicentre, randomised, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularization procedures. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/07/2021	26/08/2021	SmPC and PL	Please refer to Scientific Discussion for "Xarelto EMEA/H/C/000944/II/0081". For more information, please also refer to the Summary of Product Characteristics.
PSUSA/2653/ 202009	Periodic Safety Update EU Single assessment - rivaroxaban	22/04/2021	21/06/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2653/202009.
II/0079	Update to SmPC section 4.4 following the submission of the final report from the CASSINI study, an interventional phase III study comparing 10 mg rivaroxaban to placebo in the prevention of venous thromboembolism in ambulatory cancer patients. The package leaflet is being updated accordingly. C.I.13 - Other variations not specifically covered	17/06/2021	26/08/2021	SmPC and PL	Update of section 4.4 of the SmPC regarding patients with cancer: Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have

	elsewhere in this Annex which involve the submission of studies to the competent authority				been associated with an increased risk of bleeding during rivaroxaban therapy. In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated. For more information, please refer to the Summary of Product Characteristics.
IB/0088	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/04/2021	n/a		
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/03/2021	n/a		
IA/0086	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/02/2021	n/a		
X/0074/G	This was an application for a group of variations. Extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto 15 and 20 mg tablets. As a consequence, sections 4.2,4.4,4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated for all other dose strengths (2.5/10/ and 15/20 mg initiation packs) of Xarelto and corresponding sections of the Package Leaflet. Section 4.4 has been updated with regards to sodium	12/11/2020	21/01/2021	SmPC, Annex II, Labelling and PL	Please refer to the published assessment report Xarelto H-944-X-074-G: EPAR - Assessment Report – Variation.

	content according to Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668). The RMP version 12.4 has also been submitted. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0082/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 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	14/12/2020	n/a		
IAIN/0084	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply	11/12/2020	n/a		

	with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
II/0080	Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include data from the pooled analysis of paediatric studies P170 (sitagliptin/metformin) and P289 (sitagliptin/metformin extended release). The package leaflet is revised accordingly, and update of the product information is performed to comply with QRD Version 10.1. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/10/2020	n/a		
IAIN/0078	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	01/07/2020	n/a		
IB/0077	B.II.z - Quality change - Finished product - Other variation	29/04/2020	n/a		
PSUSA/2653/ 201909	Periodic Safety Update EU Single assessment - rivaroxaban	17/04/2020	n/a		PRAC Recommendation - maintenance
SW/0076	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0024 - Maintenance	12/03/2020	12/03/2020		The risk-benefit balance of medicinal products containing the active substance rivaroxaban concerned by the PASS final report remains unchanged.

II/0068	Update of section 5.1, of the SmPC based on results from the pantoprazole/placebo randomization part of the COMPASS study; this is part of a double-blind, double-dummy randomized trial in which pantoprazole is being compared with placebo in patients participating in the trial who are not receiving a proton-pump inhibitor. In addition, an amendment to the COMPASS Clinical Study Report is submitted to correct values caused by a programming error in the statistical outputs in this study. No changes on the approved label are proposed due to this correction. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/11/2019	28/08/2020	SmPC	In a study in patients with Coronary or Peripheral Artery Disease but without a continuous need for treatment with a proton pump inhibitor the use of pantoprazole 40 mg once daily in addition to antithrombotic study medication showed no benefit in the prevention of upper gastrointestinal events (i.e. composite of upper gastrointestinal bleeding, upper gastrointestinal ulceration, or upper gastrointestinal obstruction of perforation); the incidence rate of upper gastrointestinal events was similar in the pantoprazole 40 mg once daily group and the placebo group.
IB/0071	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	07/11/2019	n/a		
IB/0072	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2019	28/08/2020	SmPC, Annex II and Labelling	
IA/0073/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	11/10/2019	n/a		

	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size				
IA/0070/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/08/2019	n/a		
IAIN/0069	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2019	28/08/2020	SmPC	
II/0064	Submission of the final report from an interventional phase III study (COMMANDER HF, 2.5 mg rivaroxaban compared to placebo). Safety information and the main efficacy results from this study are included in Sections 4.4 and 5.1 of the SmPC. The package leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/07/2019	28/08/2020	SmPC and PL	Study data indicate that amongst coronary artery disease patients those with severe symptomatic heart failure may benefit less from treatment with rivaroxaban.

PSUSA/2653/201809	Periodic Safety Update EU Single assessment - rivaroxaban	26/04/2019	01/07/2019		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2653/201809.
IAIN/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/06/2019	28/08/2020	SmPC and PL	
IA/0066	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/04/2019	n/a		
IA/0063/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/12/2018	n/a		
SW/0061	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0012	28/06/2018	27/08/2018	Annex II	Considering that this study as part of the study programme outlined in Annex II is finalised, the PRAC considered it relevant to state the details of the remaining data from the programme expected in the coming years. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted.
II/0058	Extension of Indication to include prevention of atherothrombotic events in adult patients with	26/07/2018	23/08/2018	SmPC, Annex II, Labelling	Please refer to the published assessment report Xarelto H-

	coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events for Xarelto 2.5 mg co-administered with acetylsalicylic acid; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data. Furthermore, the PI for all dose strengths is brought in line with the latest QRD template version 10. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			and PL	944-II-058: EPAR - Assessment Report – Variation.
PSUSA/2653/ 201709	Periodic Safety Update EU Single assessment - rivaroxaban	26/04/2018	02/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2653/201709.
R/0060	Renewal of the marketing authorisation.	22/03/2018	22/05/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xarelto in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0055	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2017	n/a		

IB/0057/G	This was an application for a group of variations. 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.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.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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.1.e - Replacement or addition of a	22/11/2017	22/05/2018	Annex II and PL	

	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.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.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.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing 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.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.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
IB/0056/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms 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	22/11/2017	22/05/2018	SmPC, Labelling and PL	

	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 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				
II/0052/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 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 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.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new	14/09/2017	19/10/2017	SmPC, Labelling and PL	In the Phase III EINSTEIN CHOICE study, rivaroxaban 20 mg and 10 mg once daily were superior to acetylsalicylic acid (ASA) 100 mg once daily for the extended treatment of recurrent venous thromboembolism (VTE) with no significant differences in bleeding rates. Patients treated with rivaroxaban 20 mg and 10 mg had comparable efficacy and safety outcome rates. Both rivaroxaban groups had a favorable net clinical benefit over the ASA group with comparable results for the two rivaroxaban groups. Following completion of at least 6 months of treatment for deep vein thrombosis (DVT) or pulmonary embolism (PE), rivaroxaban 10 mg provides an additional option for extended treatment to the approved rivaroxaban 20 mg dose. The additional rivaroxaban treatment option may allow patients and physicians to adapt the individual rivaroxaban dose for extended treatment based on the individual risk profile. Apart from the results from the EINSTEIN CHOICE study, a possible interaction of clinical importance has also been

	container - Solid, semi-solid and non-sterile liquid pharmaceutical forms C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				examined for rivaroxaban regardless of indication. As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with selective serotonin re-uptake inhibitor (SSRIs) or selective serotonin norepinephrine re-uptake inhibitor (SNRIs). When concomitantly used in the rivaroxaban clinical program, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.
II/0050	Update of sections 4.2, 4.4 and 5.1 of the Summary of Product Characteristics (SmPC) to reflect information on posology in patients with non valvular atrial fibrillation and information on safety and efficacy in patients who undergo PCI (percutaneous coronary intervention) with stent placement based on the final results of study 16523 (PIONEER AF-PCI): An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose- Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention. The package Leaflet is updated accordingly. In addition, the marketing authorisation holder took the opportunity to update the telephone number of local representatives for UK in the Package Leaflet. Correction was also made in Annex IIIA to remove the recording of blood type in the patient alert card. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	20/07/2017	22/08/2017	SmPC, Labelling and PL	There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement. Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited. No data are available for such patients with a history of stroke/TIA. The results of this study were reflected in section 5.1 of the SmPC. In addition, section 4.2 and 4.4 were updated to include the dosing regimen used in the study and its limitations, respectively.

	data				
PSUSA/2653/201609	Periodic Safety Update EU Single assessment - rivaroxaban	21/04/2017	23/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2653/201609.
T/0054	Transfer of Marketing Authorisation	05/04/2017	08/05/2017	SmPC, Labelling and PL	
IAIN/0053/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.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/03/2017	08/05/2017	Annex II and PL	
IA/0051	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	27/02/2017	n/a		

IAIN/0049	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	07/02/2017	08/05/2017	SmPC, Annex II, Labelling and PL	
II/0042/G	This was an application for a group of variations. Update of section 5.1 of the SmPC following the submission of a prospective, single-arm, non-interventional, open-label cohort study was conducted to investigate the safety and effectiveness in a real-world setting, XANTUS (SN 15914), for strengths 15 mg film-coated tablets, 20 mg film-coated tablets. Update of section 5.1 of the SmPC following the submission a prospective, non-interventional, open-label cohort study was conducted in patient with acute DVT to investigate the safety and effectiveness in a real-world setting, XALIA (SN 15915), for strengths 15 mg film-coated tablets, 20 mg film-coated tablets, and treatment initiation pack. In addition the EU-RMP is updated (version 9.1) to include information from the completed PASS observational studies XANTUS and XALIA. Additionally the final CSRs of X-TRA (SN 16320, phase IIIb) and VENTURE-AF (SN 15694, phase IIIb) were also included in the RMP. Furthermore there is a minor editorial change in the list of representatives in the package leaflets of 15 mg film-coated tablets, 20 mg film-coated tablets, 10 mg film-coated tablets, 2.5 mg film-coated tablets strengths. The Bayer affiliate in Portugal	15/09/2016	08/05/2017	SmPC and PL	Update of section 5.1 of the SmPC following the submission of a prospective, single-arm, non-interventional, open-label cohort study was conducted to investigate the safety and effectiveness in clinical practice, XANTUS (SN 15914). 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean CHADS2 and HAS-BLED scores were both 2.0 in XANTUS, compared to a mean CHADS2 and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years. These observations in clinical practice are consistent with the established safety profile in this indication. Update of section 5.1 of the SmPC following the submission a prospective, non-interventional, open-label cohort study was conducted in patient with acute DVT to investigate the safety and effectiveness in clinical practice, XALIA (SN 15915). 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient

	changed from Bayer Portugal, S.A. to Bayer Portugal, Lda. All other information remains the same. 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				baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted hazard ratios comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 1.50), 0.91 (95% CI 0.54 1.54) and 0.51 (95% CI 0.24 1.07), respectively. These results in clinical practice are consistent with the established safety profile in this indication.
IB/0046	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	14/09/2016	08/05/2017	SmPC, Labelling and PL	
IA/0043/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.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of	26/05/2016	n/a		

	specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits 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.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.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)				
IAIN/0045	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	25/05/2016	06/07/2016	SmPC, Labelling and PL	
IAIN/0044	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	25/05/2016	06/07/2016	SmPC, Labelling and PL	
PSUSA/2653/ 201509	Periodic Safety Update EU Single assessment - rivaroxaban	14/04/2016	n/a		PRAC Recommendation - maintenance
PSUSA/2653/ 201503	Periodic Safety Update EU Single assessment - rivaroxaban	08/10/2015	n/a		PRAC Recommendation - maintenance

IB/0040/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms 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	06/07/2015	06/07/2016	SmPC, Labelling and PL	
II/0037	Update of section 4.4 of the SmPC with information regarding the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, and section 4.8 of the SmPC with the ADRs 'Cholestasis' and 'Hepatitis (incl. hepatocellular injury)' as well as 'Thrombocytopenia', observed during post-marketing experience. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	28/07/2015	SmPC and PL	To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, the pharmacokinetic profile of rivaroxaban should be considered. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Please also refer to the Summary of Product Characteristics for strength-specific additional recommendations regarding the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture.
PSUSA/2653/ 201409	Periodic Safety Update EU Single assessment - rivaroxaban	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0038	Submission of study results (EINSTEIN cancer analysis) and literature data on the efficacy and safety of rivaroxaban in the treatment of DVT,	26/03/2015	n/a		

	treatment of PE and prevention of recurrent DVT and PE (VTEp) in patients with active cancer as requested by CHMP in Dec 2014 during variation II-33. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0034	Update of Annex II to reflect that a post-authorisation study program that addresses the safety of rivaroxaban in the secondary prevention of Acute Coronary Syndrome outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all population and particularly in patients at increased risk of bleeding, should be conducted. Consequently the RMP has been updated in order to reflect this imposed mandatory additional pharmacovigilance activity. 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	26/02/2015	28/07/2015	Annex II	
II/0033	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	28/07/2015	SmPC and PL	

II/0035	Submission of the final results of a phase II interventional study (X-PLORER) C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/10/2014	n/a		
PSUV/0032	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0030	Update of sections 4.2 and 4.3 of the SmPC in order to provide further guidance related to switching anticoagulant therapy to/from Xarelto. 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	26/06/2014	31/07/2014	SmPC	This variation was requested by the CHMP with the aim to update the wording in the SmPC in order to minimise the risk of medication errors, the background being reports on bleedings in patients switching anticoagulant treatment to Xarelto. Following the CHMP assessment of relevant cases in relation to medication errors when switching anticoagulant therapy, appropriate changes have been implemented in the SmPC to further increase readability and to emphasize the need of discontinuation of other anticoagulant while converting to rivaroxaban. The benefit/risk balance remains unchanged by this variation.
II/0031	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	28/07/2015	SmPC and PL	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/06/2014	31/07/2014	Labelling	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/04/2014	31/07/2014	PL	
PSUV/0026	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance

II/0024/G	This was an application for a group of variations. Update of section 4.2, 4.4, 4.5, 4.8, 5.2 of the SmPC in order to provide information based on new study results and update of the CCDS. The Package Leaflet is updated accordingly. A.6 - Administrative change - Change in ATC Code/ATC Vet Code 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/11/2013	31/07/2014	SmPC and PL	Addition of crushed tablets as alternative way of administration to the PI of Xarelto as requested by the PRAC (March 2013) is introduced in section 4.2. As requested by the PRAC, inclusion of new drug-drug interaction data in section 4.4 in patients with mild, moderate and severe renal impairment concomitantly treated with a moderate CYP3A4 inhibitor is introduced for the higher strenghts of Xarelto (15 and 20 mg). A minor update is introduced in the 2.5mg, 5mg, 10mg. Furthermore, the MAH introduced amendment of existing wording on CYP3A4 inducers in section 4.5 of the SmPC as requested by the CHMP and addition of Allergic Oedema and Angioedema in section 4.8. Introduction of updated PK data in Section 5.2 related to absorption following results of study 10924 (intestinal absorption site PK study). Harmonisation of wording across all strengths and minor corrections are also introduced. Finally the ATC code in also harmonised for all strengths.
IAIN/0025/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	07/11/2013	31/07/2014	SmPC, Labelling and PL	

II/0023	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	27/06/2013	05/08/2013	SmPC and PL	Please refer to assessment report H-C-000944-II-0023
R/0022	Renewal of the marketing authorisation.	21/03/2013	22/05/2013	SmPC, Annex II, Labelling and PL	
X/0017	Annex I_2.(c) Change or addition of a new strength/potency	21/03/2013	22/05/2013	SmPC, Annex II, Labelling and PL	For further information please refer to the scientific conclusion: H-000944-X-0017
IAIN/0021/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 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	28/11/2012	22/05/2013	SmPC, Labelling and PL	
II/0018	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/10/2012	15/11/2012	SmPC, Annex II, Labelling	Please refer to assessment report H-C-000944-II-0018

				and PL	
IB/0020/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	07/06/2012	29/10/2012	Annex II and PL	
II/0016/G	This was an application for a group of variations. Update of sections 4.4, 4.8, 5.1, 5.2 of the SmPC in relation to updated information either requested by the CHMP or proposed by the MAH. Furthermore, an update of the PI is introduced in order to harmonise the PI for all strengths and to provide the most recent information for Xarelto 10	19/04/2012	25/05/2012	SmPC, Labelling and PL	Update of section 4.4 to introduce an additional risk factor for bleeding risk for patients with bronchiestasis or history of pulmonary bleeding following a Complete Company Core Data sheet review by the MAH with new clinical data. Specific safety-related changes in section 4.8 'Undesirable effects' in particular a reclassification of the frequency of wound secretion as common requested by the CHMP in PSUR 4 is also introduced.

	mg film-coated tablets. In addition, the MAH introduced an update of the PI in line with the latest QRD template version 8 and an update of the list of local representatives in the patient leaflet and minor corrections for translations in Czech, Spanish, Lithuanian, Maltese, Polish and Slovenian product information. The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet. 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Update of sections 4.4, 5.1 and 5.2 of the SmPC is also introduced to address the post authorisation commitment FU2 14.4 for Xarelto. Information to prescribers is introduced to clarify that there is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests.
IAIN/0019/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	20/04/2012	n/a		

	the pharmacovigilance system 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				
X/0010	Annex I_2.(c) Change or addition of a new strength/potency	22/09/2011	09/12/2011	SmPC, Annex II, Labelling and PL	
II/0012	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/09/2011	09/12/2011	SmPC, Annex II, Labelling and PL	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet to introduce a new indication in the prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (SPAF) with one or more risk factors has been granted as follows: Prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ? 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. The application is based on one large pivotal study and one supportive study as follows: " pivotal global Phase III study (11630), referred to as ROCKET study (Rivaroxaban Once-daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation) " supportive Phase III study(11620) conducted in Japanese subjects, referred to as J-ROCKET study. The above extension of indication applies to the oral 15mg and 20 mg tablet only (parallel procedure EMEA/H/C/000944/X/0010).

IA/0014/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release 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	19/08/2011	n/a	SmPC, Annex II, Labelling and PL	
IB/0013/G	This was an application for a group of variations. 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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	14/04/2011	n/a	Annex II and PL	

	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.z - Change in the manufacturing process of the finished product - Other variation				
II/0007	Update of Summary of Product Characteristics, Annex II and Package Leaflet Update of section 4.4 of the Summary of Product Charateristics (SmPC) to include information on precautionary measures to reduce the risk of gastrointestinal bleeding by using gastroprotective co-medication. Update of section 4.8 of the SmPC based on information from clinical trials. The Package Leaflet (PL) has been updated accordingly. The MAH also took the opportunity to update the Product Information in line with the current version of the SmPC guideline/QRD templates and also updated the list of Local Representatives in the PL. Furthermore, the annex II is updated to remove the version number of the DDPS. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC, Annex II and PL	Based on a consensus paper and data from the MAH's clinical and safety databases, the MAH proposed to include information on precautionary measures to reduce the risk of gastrointestinal bleeding by using gastroprotective co-medication in section 4.4 of the SmPC. The PL has been updated accordingly. Based on the information provided by the completed and ongoing trials and the mode of action of rivaroxaban, a revision of section 4.8 of the SmPC was considered necessary to reflect the most recent knowledge on this product. Furthermore, the observed frequency of some of the adverse reactions has been changed based on the compiled clinical study data. Changes in frequency of some ADRs have been made as well as the inclusion of the new ADRs pseudoaneurysm formation following percutaneous intervention, compartment syndrome secondary to a bleeding, renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion have been included. The PL has been updated accordingly.

IA/0011/G	This was an application for a group of variations. 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.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	12/01/2011	n/a		
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/11/2010	n/a	PL	
IA/0008/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.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	03/11/2010	n/a		

	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				
IG/0009/G	This was an application for a group of variations. 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 C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV 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	18/06/2010	n/a	Annex II	
IA/0006/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	26/05/2010	26/05/2010	SmPC, Labelling and PL	

	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				
N/0005	The Marketing Authorisation Holder took the opportunity to update details of all local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/04/2010	n/a	PL	
IA/0004	To add Stegemann Lohnverpackackung & Logistischer Service e.K. as an additional manufacturing site. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/02/2010	n/a		
II/0003	Update of the Detailed Description of Pharmacovigilance System (DDPS). Consequently, Annex II has been updated with the new version number of the agreed DDPS (version 9.7). Update of DDPS (Pharmacovigilance)	24/09/2009	21/10/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 9.7) to reflect the integration of the companies' pharmacovigilance systems (Bayer and Schering AG). Consequently, Annex II has been updated with the standard text including new version number of the agreed DDPS.
T/0001	Transfer of Marketing Authorisation	11/03/2009	02/04/2009	SmPC, Annex II, Labelling and PL	

IA/0002	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	09/03/2009	n/a	Annex II and PL	