Eliquis

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
IB/0096	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/04/2025		SmPC, Labelling and PL	
PSUSA/226/202405	Periodic Safety Update EU Single assessment - apixaban	30/01/2025	28/03/2025	SmPC and PL	Anticoagulant-related nephropathy (ARN): In view of available data including 6 relevant, biopsy-confirmed cases of ARN indicating a possible association with apixaban, a

[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).

					pharmacological class effect (ARN is already listed for other DOACs rivaroxaban and edoxaban), and pathophysiological plausibility, the PRAC considers a causal relationship between apixaban and ARN is at least a reasonable possibility. The PRAC concludes that the product information of products containing apixaban should be amended accordingly.
IA/0095	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	22/08/2024	n/a		
IB/0093	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	31/07/2024	n/a		
X/0089/G	This was an application for a group of variations. Extension application to: 1) Introduce a new pharmaceutical form (granules in single-dose container) associated with a new strength (0.15 mg). 2) Introduce a new pharmaceutical form (coated granules in sachet) associated with 3 new strengths (0.5 mg, 1.5 mg and 2 mg) Extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim analysis from Study CV185325; this is an open-label, multi-centre, randomized, active controlled trial to provide PK data	30/05/2024	26/07/2024	SmPC, Annex II, Labelling and PL	Please refer to the Assessment Report Eliquis EMEA-H-C-002148-X-0089-G

	and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children who require anticoagulation for a venous thromboembolism; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPCs are updated. The Package Leaflet and Annex II are updated in accordance. Version 21.3 of the RMP has also been submitted. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(c) Change or addition of a new strength/potency 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				
IAIN/0092	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	07/03/2024	06/05/2024	Annex II and PL	
IB/0090	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/11/2023	n/a		
IA/0091/G	This was an application for a group of variations.	21/09/2023	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				
II/0088	Update of sections 4.2 and 5.1 of the SmPC in order to update efficacy and safety information in the paediatric population based on results of the paediatric studies performed in compliance with the paediatric investigation plan (PIP), including studies CV185155 and CV185362. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/05/2023	06/05/2024	SmPC	Please refer to Scientific Discussion 'Eliquis-H-C-002148-II-0088' For more information, please refer to the Summary of Product Characteristics.
IAIN/0087/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.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 B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging	08/09/2022	31/03/2023	Annex II and PL	

	site				
IA/0086/G	This was an application for a group of variations. 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.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	04/07/2022	n/a		
IAIN/0085/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	16/02/2022	31/03/2023	Annex II and PL	

	finished product, including quality control sites (excluding manufacturer for batch release)				
PSUSA/226/202105	Periodic Safety Update EU Single assessment - apixaban	16/12/2021	16/02/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/226/202105.
IA/0084	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/09/2021	n/a		
IB/0082/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.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	07/05/2021	n/a		
II/0080	Update of section 4.4 of the SmPC in order to update the existing warning regarding patient with active cancer in line with the final results of the study CARAVAGGIO (NCT03045406), which is a randomized open-label non-inferiority clinical trial assessing apixaban for the treatment of acute proximal DVT and/or PE in ambulatory patients with active cancer or history of cancer. In addition, the MAH took the opportunity to make a correction to section 5.1 of the SmPC and to remove	15/04/2021	16/02/2022	SmPC	

	the list of local representatives from the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/226/202005	Periodic Safety Update EU Single assessment - apixaban	28/01/2021	31/03/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/226/202005.
IA/0081	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		
R/0077	Renewal of the marketing authorisation.	12/11/2020	11/01/2021	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 Eliquis in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0079	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/12/2020	n/a		
N/0078	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2020	11/01/2021	PL	
IB/0075	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/08/2020	11/01/2021	SmPC	
IAIN/0074/G	This was an application for a group of variations.	23/04/2020	11/01/2021	Annex II and	

	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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			PL	
II/0064	Update of sections 4.2, 4.4, 4.5 and 5.1 of the SmPC in order to update the safety information based on the final results from study CV185316 (AUGUSTUS), an open-label, randomised, controlled clinical trial to evaluate the safety of apixaban in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2020	11/01/2021	SmPC	A study in patients with non-valvular atrial fibrillation who had acute coronary syndrome and/or had undergone percutaneous coronary showed that acetylsalicylic acid significantly increased the risk of major or clinically relevant non-major (CRNM) bleeding when added to anticoagulation (either apixaban or Vitamin K antagonist) on top of a background therapy with a P2Y12 inhibitor. Apixaban was superior to Vitamin K antagonist for adjudicated major and CRNM bleeding events.
IB/0073/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/03/2020	n/a		
PSUSA/226/201905	Periodic Safety Update EU Single assessment - apixaban	12/12/2019	17/02/2020	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/226/201905.
IA/0072	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/01/2020	n/a		
IAIN/0071	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/01/2020	n/a		
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2019	11/01/2021	PL	
IAIN/0070	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	16/12/2019	n/a		
IA/0069	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	03/12/2019	n/a		
IAIN/0067	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	20/11/2019	n/a		
II/0063	Update of sections 4.4 and 4.9 of the SmPC in order	03/10/2019	17/02/2020	SmPC,	For situations when reversal of anticoagulation is needed

	to reflect the availability of a reversal agent for apixaban following the recent approval of andexanet alfa in the EU; the Package Leaflet and Labelling are updated accordingly. The RMP version 20.1 has also been submitted, with updates due to the availability of a reversal agent and implement the revised GVP template Rev.2. As a result, the list of safety concerns has been updated and a number of safety concerns listed as missing information have been reclassified and have been removed from the RMP. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to update the information in the SmPC and Package Leaflet in accordance with the most recent guidance on labelling of excipients of medicinal products for human use. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			Labelling and PL	due to life-threatening or uncontrolled bleeding, a reversal agent for the anti- factor Xa activity of apixaban is available.
IA/0066/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 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		

	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				
IB/0062	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	01/07/2019	17/02/2020	SmPC and PL	
II/0059	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/05/2019	01/07/2019	SmPC and PL	
IAIN/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/06/2019	17/02/2020	SmPC and PL	
IAIN/0060	A.1 - Administrative change - Change in the name and/or address of the MAH	07/03/2019	02/04/2019	SmPC, Labelling and PL	
PSUSA/226/201805	Periodic Safety Update EU Single assessment - apixaban	29/11/2018	n/a		PRAC Recommendation - maintenance
IA/0058	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	15/10/2018	n/a		
IAIN/0056	C.I.z - Changes (Safety/Efficacy) of Human and	03/08/2018	02/04/2019	SmPC and PL	

	Veterinary Medicinal Products - Other variation				
II/0050	Update of sections 4.2 and 5.1 of the SmPC in order to update the posology, efficacy and safety information for patients undergoing cardioversion based on the final results from the post-authorisation efficacy study EMANATE. The package leaflet and the RMP (version 19.0) are updated accordingly. In addition, the marketing authorisation holder (MAH) took the opportunity to update their address in the product information and the list of local representative in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	31/05/2018	SmPC, Labelling and PL	Posology for patients undergoing cardioversion: Apixaban can be initiated or continued in non-valvular atrial fibrillation (NVAF) patients who may require cardioversion. For patients not previously treated with anticoagulants, at least 5 doses of apixaban 5 mg twice daily (2.5 mg twice daily in patients who qualify for a dose reduction (see recommendation for Dose reduction and Renal impairment)) should be given before cardioversion to ensure adequate anticoagulation. If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see recommendation for Dose reduction and Renal impairment). The administration of the loading dose should be given at least 2 hours before cardioversion. Confirmation should be sought prior to cardioversion that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account. Clinical efficacy and safety information for patients undergoing cardioversion: EMANATE, an open-label, multi-center study, enrolled 1500 patients who were either oral anticoagulant naïve or pre-treated less than 48 hours, and scheduled for cardioversion for NVAF. Patients were randomized 1:1 to apixaban or to heparin and/or VKA for the prevention of cardiovascular

					events. Electrical and/or pharmacologic cardioversion was conducted after at least 5 doses of 5 mg twice daily apixaban (or 2.5 mg twice daily in selected patients or at least 2 hours after a 10 mg loading dose (or a 5 mg loading dose in selected patients if earlier cardioversion was required. In the apixaban group, 342 patients received a loading dose (331 patients received the 10 mg dose and 11 patients received the 5 mg dose). There were no strokes (0%) in the apixaban group (n= 753) and 6 (0.80%) strokes in the heparin and/or VKA group (n = 747; RR 0.00, 95% CI 0.00, 0.64). All cause death occurred in 2 patients (0.27%) in the apixaban group and 1 patient (0.13%) in the heparin and/or VKA group. No systemic embolism events were reported. Major bleeding and CRNM bleeding events occurred in 3 (0.41%) and 11 (1.50%) patients, respectively, in the apixaban group, compared to 6 (0.83%) and 13 (1.80%) patients in the heparin and/or VKA group. This exploratory study showed comparable efficacy and safety between apixaban and heparin and/or VKA treatment groups in the setting of cardioversion.
II/0051	Update of section 4.8 of the SmPC in order to reflect all adverse drug reactions for all indications with the correct calculated frequency based on clinical trials data. 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	17/05/2018	02/04/2019	SmPC and PL	
IA/0055/G	This was an application for a group of variations.	02/05/2018	n/a		

	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				
IAIN/0054/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 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	16/04/2018	n/a		
IA/0053	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	26/03/2018	n/a		

IA/0052	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	05/02/2018	n/a		
II/0048	Submission of the final report from study (B0661073) listed as a category 4 study in the RMP. This is a non-interventional post-authorisation safety study (PASS) of the utilisation patterns of apixaban in Denmark. In addition, a revised RMP (version 18.0) is submitted. 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		The drug utilisation study (DUS) (B0661073) is a descriptive, retrospective, cross-sectional study that uses electronic healthcare data from the Danish national registries to describe the utilisation patterns of apixaban in Denmark. The study was conducted to estimate the proportion of apaxiban users in the outpatient settings who received the drug for the approved indications at the time of the study, and to describe the characteristics of patients who were prescribed apixaban for on-label or off-label indications. The results of this study indicated that apixaban was mostly (82.6%) used for on-label indications, with the majority of patients using apixaban for non-valvular atrial fibrillation (NVAF). The proportion of on-label apixaban use reported was similar to that of a previous Swedish DUS study (86.4% on-label), and to the proportion on-label use reported in the literature for other non-vitamin K oral anticoagulants (NOACs) (80-90% on-label use). Off-label use was found in nearly 11% of patients. The proportion of off-label use reported was comparable to that reported in previous similar DUS study in Sweden (7.7% off-label use). These results did not warrant an update of the product information.
PSUSA/226/201705	Periodic Safety Update EU Single assessment - apixaban	30/11/2017	n/a		PRAC Recommendation - maintenance

II/0049/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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	16/11/2017	n/a		
II/0047	Update of section 4.5 of the SmPC to include clarithromycin as one of the active substances which are not considered strong inhibitors of both CYP3A4 and P-gp and which are expected to increase apixaban plasma concentration to a lesser extent based on the final results from study CV185547. The final study report of study CV185547 (an open-label, non-randomised, single-sequence, crossover study in healthy subjects to determine the effect of multiple-dose clarithromycin on the single-dose pharmacokinetics of apixaban) is also submitted. In addition, the MAH took the opportunity to make some corrections in the SmPC and to update the labelling in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/10/2017	31/05/2018	SmPC and Labelling	Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and Cmax, respectively. No dose adjustment is required.
II/0043	Submission of the final report from study (CV185-365) listed as a category 3 study in the RMP. This is	01/09/2017	n/a		The results of the PASS CV185-365 suggest that use of the risk minimisation tools appears to have positive impact

	a post authorisation safety study which evaluates the effectiveness of Eliquis (apixaban) risk minimisation tools in the European Economic Area countries. A RMP (version 17.0) has also been submitted to reflect the completion of the study CV185-365. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				upon knowledge, comprehension, and behaviour among health care professionals and patients/caregivers regarding Eliquis treatment and associated bleeding risk. Although distribution and utilisation were not optimal, they are consistent with findings from similar effectiveness evaluation studies of risk minimisation tools. At present, the MAH does not propose any modifications to the content of the risk minimisation tools. The results are consistent with study objectives and support the effectiveness of the risk minisation tools for their intended purpose.
IB/0044/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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	09/08/2017	n/a		
IA/0045	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	17/07/2017	n/a		
IB/0042	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/04/2017	n/a		
PSUSA/226/201605	Periodic Safety Update EU Single assessment - apixaban	15/12/2016	16/02/2017	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/226/201605.

IAIN/0041/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.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	08/12/2016	16/02/2017	Annex II and PL	
II/0040	Submission of the final study report of the AEGEAN study (CV185-220) which assess the education and guidance programme for Eliquis (apixaban) adherence in non-valvular atrial fibrillation patients. The updated risk management plan is also submitted to reflect the results of the study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/10/2016	n/a		
II/0037/G	This was an application for a group of variations. Submission of final study reports of two drug utilisation studies (DUS) in Sweden (Study B0661017) and in the Netherlands (Study B0661018) to fulfil post-approval measures listed in	15/09/2016	n/a		

	the risk management plan (RMP) which has also been submitted. The RMP has been updated to reflect the data from the two completed post-authorisation safety studies examining the utilisation pattern of apixaban in Sweden and in the Netherlands, to reflect ongoing DUS in Denmark (Study B0661073), to reflect updated approved SmPC with regard to administration as a crushed tablet (EMEA/H/C/002148/II/030) and prothrombin complex concentrates (EMEA/H/C/002148/II/029), and minor updates to various postmarketing commitment studies. The group of variations leads to amendments to the Risk Management Plan (RMP). 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				
IA/0038/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	21/07/2016	n/a		

	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.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)				
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/03/2016	16/02/2017	PL	
IB/0035	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	25/02/2016	n/a		
R/0034	Renewal of the marketing authorisation.	19/11/2015	14/01/2016	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Eliquis continues to be favourable. The CHMP was of the opinion that an additional five-year renewal is required, on the basis of pharmacovigilance grounds.
PSUSA/226/201505	Periodic Safety Update EU Single assessment - apixaban	03/12/2015	n/a		PRAC Recommendation - maintenance
II/0030	Update of sections 4.2 and 5.2 of the SmPC for Eliquis 2.5 mg and 5 mg film-coated tablets, to provide recommendations regarding the use of alternative methods of administration of apixaban tablets, based on the results from clinical	24/09/2015	14/01/2016	SmPC and PL	For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Eliquis tablets may be crushed and

	pharmacology studies CV185292 and CV185111. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Eliquis tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of apple puree, the Cmax and AUC were 20% and 16% lower, respectively, when compared to administration of 2 whole 5 mg tablets. The reduction in exposure is not considered clinically relevant. Following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of D5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose. Given the predictable, dose-proportional pharmacokinetic profile of apixaban, the bioavailability results from the conducted studies are applicable to lower apixaban doses.
II/0029	Update of sections 4.9 and 5.1 of the SmPC based on the study results from study CV185156 evaluating the ability of prothrombin complex concentrates (PCCs) to reverse the anticoagulant effect of apixaban in healthy subjects. The provision of the study report addresses the post approval measure MEA 016.1. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and the Package Leaflet.	17/09/2015	14/01/2016	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/226/201411	Periodic Safety Update EU Single assessment - apixaban	25/06/2015	20/08/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/226/201411.
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2015	14/01/2016	PL	
IA/0031	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	29/05/2015	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2015	20/08/2015	Labelling	
PSUV/0022	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IA/0024	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	03/12/2014	n/a		
IA/0023/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	30/10/2014	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IA/0021	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	12/08/2014	n/a		
II/0014/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one 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	26/06/2014	28/07/2014	SmPC, Annex II, Labelling and PL	
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/06/2014	28/07/2014	PL	
PSUV/0018	Periodic Safety Update	12/06/2014	n/a		PRAC Recommendation - maintenance
II/0017	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	28/07/2014	SmPC	Update section 4.4 and 5.1 to update the Summary of Product Characteristics (SmPC) as follows: •Section 4.4: to replace the term 'Rotachrom anti-FXa assay' with 'a calibrated quantitative anti-FXa assay' •Section 5.1: to include the apixaban plasma concentration data (ng/mL) along with the already

					approved anti-Xa activity data (IU/mL). The application is based on a study report study report testing 4 different chromogenic anti-FXa assays: (Rotachrom Heparin Assay , Liquid Anti-Xa Assay, Coamatic Heparin Assay and Technochrom Anti-Xa Assay.
II/0016	Update of sections 4.2 and 4.4 of the SmPC C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	28/07/2014	SmPC	The applicant submited a sub-analysis from the ARSITOTLE study in patients who have undergone cardioversion (743 cardioversions in 540 patients). The incidence of systemic embolism, stroke, death, major bleedings and myocardial infarctions are comparable in the apixaban and the warfarin administered groups. Therefore in this variation a recommendation in section 4.2, that patients undergoing cardioversion can be maintained on apixaban, with a cross reference in section 4.4 are introduced.
IB/0019	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	16/04/2014	28/07/2014	SmPC, Labelling and PL	
IA/0015	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	26/11/2013	n/a		
II/0011/G	This was an application for a group of variations. Amendments to the Summary of Product Characteristics, annex II, labelling and Package leaflet.	19/09/2013	15/11/2013	SmPC, Annex II, Labelling and PL	Update of sections 4.4, 4.9 and 5.2 of the SmPC following routine assessment of the Company Core Data Sheet (CCDS) and submission of a final study report in special populations. The proposed labelling revisions provide additional clarity that apixaban should not be used in patients with prosthetic heart valves and information in

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				subjects with End Stage Renal Disease. This update - includes a recommendation that apixaban should not be used in patients with prosthetic heart valves (section 4.4) following a routine assessment of the Company Core Data Sheet (CCDS). - provides updated information in sections 4.9 and 5.2 following results of a special population study: "Single-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Apixaban in Subjects on Haemodialysis" (CV185087). The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 9. Additionally, correction of some errors has been implemented such as the addition of Haemoptysis as uncommon undesirable effect in section 4.8.
PSUV/0012	Periodic Safety Update	27/06/2013	26/08/2013	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0012.
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2013	15/11/2013	PL	
IB/0010/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	05/08/2013	n/a		

	manufacturer 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.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 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 currently approved batch size 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 currently approved batch size				
IA/0009	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/04/2013	n/a		
IA/0008	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	12/02/2013	26/08/2013	SmPC	
IAIN/0007	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		

X/0004/G	This was an application for a group of variations. 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.(c) Change or addition of a new strength/potency 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	20/09/2012	19/11/2012	SmPC, Annex II, Labelling and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/03/2012	19/11/2012	PL	
IA/0005	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	26/10/2011	n/a		
II/0003/G	This was an application for a group of variations. To register a NIR method for releasing apixaban tablets 2.5 mg (real time release testing, RTRT) at the currently approved finished product manufacturing site To register a second finished product manufacturing site for apixaban tablets 2.5 mg and To register the same NIR method for releasing	20/10/2011	20/10/2011		

	apixaban tablets 2.5 mg (RTRT) at the second finished product manufacturing site B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product 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				
IB/0002	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	09/09/2011	n/a		
IA/0001/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	04/07/2011	n/a		