EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Angiox

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
PSUSA/421/201709	Periodic Safety Update EU Single assessment - bivalirudin	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0075/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	05/01/2018	n/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).

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	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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IA/0074/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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	05/01/2018	n/a		
PSUSA/421/201609	Periodic Safety Update EU Single assessment - bivalirudin	07/04/2017	n/a		PRAC Recommendation - maintenance
IB/0070	To amend the product information section 4.4 of the SmPC - correction of a value provided for the half life. To amend Section 4.8 (Table 1) the adverse reaction of "INR Increased" from the current listing under the System Organ Class of Blood and Lymphatic System Disorders to add it in the Investigations SOC.	25/10/2016	14/09/2017	SmPC and PL	

	- re-ordering of ADRs in the Cardiac Disorders SOC so that they appear in order of seriousness and to amend the details of the local representative in Spain. In addition, the MAH has made minor administrative changes to the SmPC and patient information leaflet in the different languages. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0068	Submission of the drug utilization study Eurovision 2. The RMP has been amended to refine the additional risk minimisation measures in line with the findings 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		
IB/0069/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of 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.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	27/09/2016	n/a		

	corresponding test method				
PSUSA/421/201509	Periodic Safety Update EU Single assessment - bivalirudin	14/04/2016	n/a		PRAC Recommendation - maintenance
II/0063	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	25/02/2016	n/a		
II/0062	Update of sections 4.2 and 4.4 of the SmPC in order to update posology instructions and update warning of use of bivalirudin in case of haemorrhage. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representative for Portugal in the Package leaflet. The RMP version 13.1 was agreed. 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	19/11/2015	16/12/2015	SmPC and PL	The recommended dose of bivalirudin for patients undergoing PCI is an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion of 1.75 mg/kg body weight/hour may be continued for up to 4 hours post-PCI and at a reduced dose of 0.25 mg/kg body weight/hour for an additional 4 – 12 hours as clinically necessary. In STEMI patients the infusion of 1.75 mg/kg body weight/hour should be continued for up to 4 hours post-PCI and continued at a reduced dose of 0.25 mg/kg body weight/hour for an additional 4 – 12 hours as clinically necessary (see section 4.4). Prolonged post PCI infusions of bivalirudin at recommended doses have not been associated with an increased rate of bleeding. Acute stent thrombosis (<24 hours) has been observed in patients with STEMI undergoing primary PCI and has been managed by Target Vessel Revascularisation (TVR) (see sections 4.8 and 5.1). The majority of these cases were non-fatal. This increased risk of acute stent thrombosis was observed during the first 4 hours following the end of the

					procedure among patients who either discontinued the infusion of bivalirudin at the end of the procedure or received a continued infusion at the reduced dose of 0.25 mg/kg/h.
IB/0065	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/10/2015	n/a		
II/0058	Submission of completed study report TMC-BIV-07-01 "Exposure and Adverse Event Assessment (EAEA) for Angiomax Protocol Bivalirudin (Angiomax) as a Procedural Anticoagulant in the Paediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease". Update sections of the 4.2, 5.1 and 5.2 of the SmPC with data on paediatric population (clinical study TMC-BIV-07-01). In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version V9.1. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	16/12/2015	SmPC, Annex II and PL	Update sections of the 4.2 and 5.1 of the SmPC with data on paediatric population (clinical study TMC-BIV-07-01 "Exposure and Adverse Event Assessment (EAEA) for Angiomax Protocol Bivalirudin (Angiomax) as a Procedural Anticoagulant in the Pediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease"). In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version V9.1. The requested variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and Annex II.
IB/0064	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	03/09/2015	n/a		

PSUSA/421/201409	Periodic Safety Update EU Single assessment - bivalirudin	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0061	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/04/2015	n/a		
IA/0060/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 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	20/03/2015	n/a		
IB/0056/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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.4 - Administrative change - Change in the name	19/02/2015	n/a		

	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.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites 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.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition				
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/02/2015	16/12/2015	Labelling and PL	
IA/0055/G	This was an application for a group of variations.	29/10/2014	n/a		

	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
R/0052	Renewal of the marketing authorisation.	25/04/2014	23/06/2014	SmPC, Annex II, Labelling and PL	The efficacy of bivalirudin has been demonstrated in studies which are presented within the EU product information. The known and potential risks are not unexpected for the patient population and expected actions of the drug and are adequately reflected in the RMP and SmPC. The important identified risk of medication errors with bivalirudin includes the practice of bolus dosing without subsequent infusion. An inappropriate dosing pattern was associated with an increase in ischaemic outcomes in the ImproveR study and is not recommended. Medication errors are subject to additional risk minimisation as described in the RMP and the SmPC. No new data on this subject has been identified during the current renewal period. A simple large retrospective survey is on-going to gather more information regarding effectiveness of the risk minimisation. The CHMP recommends that the renewal be granted with unlimited validity.
IA/0054	A.7 - Administrative change - Deletion of	12/06/2014	n/a		

	manufacturing sites				
PSUV/0051	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0050	Update of sections 4.2 and 5.2 of the SmPC in order to reflect the re-evaluation of the appropriate role of activated clotting time (ACT) during administration of bivalirudin as requested in assessment report for PSUR 10. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.3. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/03/2014	23/06/2014	SmPC, Annex II, Labelling and PL	Further information regarding the utility of activated clotting time (ACT) testing during bivalirudin treatment was assessed. The limitations of the ACT test were noted. However, it was agreed that an increase in ACT indicates that the bivalirudin dose has been successfully delivered to the patient. Furthermore, additional data from the REPLACE-2 study in patients undergoing PCI suggest that patients with ACT <225s at 5 minutes post-bolus who received a second bolus dose had a lower incidence of thrombotic complications than patients with similar ACT values who did not receive a second bolus. Therefore, it was concluded that the information currently provided on ACT values where a second bolus dose would be appropriate should be retained in the SmPC. In addition, a sentence was added to alert the physician to the possibility of medication errors in the event that ACT does not rise as expected. The addition of the sentence advising that the i.v. infusion line should be primed with bivalirudin to ensure continuity of drug treatment was agreed. Finally, it was agreed that the recommendation to monitor ACT during the procedure in patients with renal insufficiency may be deleted. Instead a sentence to remind physicians that patients with renal insufficiency in particular should be monitored for clinical signs of bleeding was added to the SmPC.
IAIN/0049/G	This was an application for a group of variations.	04/01/2013	n/a		

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV				
II/0047	Update of Annex II of the SmPC following the CHMP recommendations from the AR for FUM 17 in order to include key information related to the educational materials. In addition, Annex II was brought in line with the latest QRD template version 8 rev. 2. Minor editorial corrections were included in the PL. The requested variation proposed amendments to the Annex II and IIIB. 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	15/11/2012	20/11/2013	Annex II and PL	This variation was submitted to update Annex II of the product information to include the key elements of the educational materials following the assessment of the Drug Utilisation Study (DUS) EUROVISION. As a result of the issues identified with the EUROVISION DUS, the educational materials were recommended to be updated and the re-education of HCPs to be undertaken. The initial and re-training of the health care providers will cover issues of medication errors and the importance of an infusion dose following the bolus dose.
IB/0048/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.b.2.e - Change in test procedure for AS or	22/10/2012	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IA/0046	A.7 - Administrative change - Deletion of manufacturing sites	17/07/2012	n/a		
IB/0045	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	14/06/2012	n/a		
A20/0042	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of Committee for Medicinal Products for Human Use (CHMP) on measures necessary to ensure the quality and the safe use of Angiox further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/562/A-20/0042
II/0037	The MAH proposed the update of section 4.8 of the SmPC in order to update the safety information with regards to myocardial infarction, cardiac tamponade, arterio-venous fistula and compartment syndrome	19/01/2012	21/02/2012	SmPC and PL	With this variation the terms: cardiac tamponade, arterio-venous fistula, catheter thrombosis, myocardial infarction and compartment syndrome were included in Section 4.8 of the SmPC. Although several of these terms could be

	following the assessment report of PSURs 7 and 8. In addition separate adverse drug reaction tables for three clinical trials were merged into one table as per current SmPC Guideline. The Package Leaflet was proposed to be updated in accordance. Furthermore, small corrections were introduced in sections 4.8, 5.1, 5.2, 6.2 and 10 of the SmPC. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The requested variation proposed amendments to the SmPC 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				considered to be associated with the procedure undergone by the patient, it was agreed that bivalirudin treatment as an anticoagulant is likely to worsen these effects, and detailing them in Section 4.8 provides the physician with a more complete understanding of the adverse reactions likely to occur during bivalirudin treatment. In addition, it was decided to modify the overall current layout of Section 4.8 of the SmPC that included three separate tables of adverse drug reactions for the three clinical trials. A single table of adverse drug reactions was created instead as per SmPC Guideline whilst also retaining the necessary additional text regarding the three trials.
IB/0043	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	17/02/2012	n/a		
IB/0041	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/02/2012	n/a		
IB/0044/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the	02/02/2012	n/a		

	manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
IA/0040/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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	14/12/2011	n/a		

	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/08/2011	n/a	PL	
IB/0038/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	10/06/2011	n/a		

	or addition) for the AS or a starting material/intermediate 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				
IA/0036	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	22/02/2011	n/a	Annex II and PL	
IA/0035	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	21/01/2011	n/a		
IA/0034	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/10/2010	n/a		
IA/0033	To delete one presentation B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	11/06/2010	n/a	SmPC, Labelling and PL	
II/0024	Extension of the current indication to include patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI. Sections 4.1, 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC have been updated and the package leaflet has been updated accordingly. The	22/10/2009	20/11/2009	SmPC, Annex II and PL	Please refer to the Assessment Report (Angio-H-562-II-24-AR).

	local representative contact details for Greece, Spain, Portugal and France have also been updated in the package leaflet. In addition, Annex II has been updated to reflect the latest RMP version (version 8) agreed with CHMP. Extension of Indication				
II/0032	changes to the manufacturing process of the active substance. Quality changes	22/10/2009	12/11/2009		
II/0027	amendment to the subcontractor used for the microbial contamination testing of the active substance. Quality changes	24/09/2009	06/10/2009		
IA/0031	IA_13_a_Change in test proc. for active substance - minor change	19/08/2009	n/a		
IA/0029	IA_07_a_Replacement/add. of manufacturing site Secondary packaging site	18/08/2009	n/a		
IA/0030	IA_09_Deletion of manufacturing site	07/08/2009	n/a		
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/08/2009	n/a		
II/0025	Update of Summary of Product Characteristics	29/05/2009	02/07/2009	SmPC and PL	

	Quality changes				
R/0026	Renewal of the marketing authorisation.	23/04/2009	18/06/2009	SmPC, Annex II and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Angiox remains positive but recommends a second renewal, based on pharmacovigilance grounds. The request of an additional five-year renewal is due to limited exposure in the recently approved indication expanding the use of Angiox to the potentially higher risk ACS population and under more acute conditions. In the light also of the possibility of further expanding its use to STEMI patients (if the type II variation application, under review is granted), a further opportunity to assess of the benefit:risk bivalirudin in the future through an additional renewal is considered necessary. This is further supported by the fact that additional potential risks, such as stent thrombosis have been identified following data from the HORIZONS-AMI study (the pivotal study for the STEMI indication). Therefore, based upon the safety profile of Angiox which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit 1 additional renewal application in 5 years time.
IA/0023	IA_01_Change in the name and/or address of the marketing authorisation holder	03/12/2008	n/a	SmPC, Annex II, Labelling and PL	
II/0016	Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	29/07/2008	SmPC and PL	Update of sections 4.4 and 4.8 of the SPC following the assessment of the 5th PSUR. The review comprised of all available data relating to the potential for Angiox to cause an increase in INR (International Normalised Ratio) as well

					as data relating to a possible warfarin interaction leading to a raised INR and update to include serious haemorrhagic events as an undesirable effect. The Package Leaflet has also been updated accordingly.
IA/0022	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	09/07/2008	n/a		
IA/0021	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	09/07/2008	n/a		
IA/0020	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	09/07/2008	n/a		
IA/0019	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	09/07/2008	n/a	Annex II and PL	
II/0015	Change to the manufacturing process for the finished product Change(s) to the manufacturing process for the finished product	30/05/2008	11/06/2008		
IA/0018	IA_13_a_Change in test proc. for active substance - minor change	09/06/2008	n/a		
IA/0017	IA_13_a_Change in test proc. for active substance - minor change	23/05/2008	n/a		
II/0008	Extension of indication in acute coronary syndromes (UA/NSTEMI).	15/11/2007	10/01/2008	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Angiox-AR-H-562-II-08

	Extension of Indication				
IB/0013	IB_33_Minor change in the manufacture of the finished product	04/12/2007	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/07/2007	n/a	PL	
IB/0011	IB_38_c_Change in test procedure of finished product - other changes	22/05/2007	n/a		
II/0007	Update of Summary of Product Characteristics, Labelling and Package Leaflet	25/01/2007	07/03/2007	SmPC, Labelling and PL	Update section 4.8 Undesirable Effects with regards to post-marketing reports of intracranial haemorrhage after the assessment of the 3rd PSUR.
IA/0010	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/02/2007	n/a		
IA/0009	IA_13_a_Change in test proc. for active substance - minor change	11/01/2007	n/a		
II/0006	Update of Summary of Product Characteristics	27/07/2006	01/09/2006	SmPC	Update of Section 4.8 of the SPC following the assessment of the 2nd PSUR. Addition of "urticaria" and "haematoma" following post-marketing reports.
II/0005	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		
IB/0004	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	20/10/2005	n/a	SmPC	
IB/0002	IB_17_a_Change in re-test period of the active substance	26/08/2005	n/a		

IA/0003	IA_06_a_Change in ATC code: Medicinal products for human use	22/08/2005	n/a	SmPC, Labelling and PL	
IB/0001	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	27/10/2004	27/10/2004	SmPC, Labelling and PL	