Firazyr

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
II/0061	Update of section 4.6 based on final results from the Icatibant Outcome Survey (IOS) registry listed as a category 3 study in the RMP; this is a prospective, observational disease registry. The RMP version 8.1 is acceptable. In addition, the MAH took the opportunity to implement editorial changes to the PI	04/09/2025		SmPC	SmPC new text Pregnancy There is no or limited data from the use of icatibant in pregnant women. Animal studies showed effects on uterine implantation and parturition (see section 5.3), but the potential risk for

[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).

	and to bring the PI in line with the latest QRD template version 10.4. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				humans is unknown. Firazyr should be used during pregnancy only if the potential benefit justifies the potential risk for the foetus (e.g for treatment of potentially life threatening laryngeal attacks). For more information, please refer to the Summary of Product Characteristics.
PSUSA/1714/ 202407	Periodic Safety Update EU Single assessment - icatibant	13/02/2025	n/a		PRAC Recommendation - maintenance
IB/0059/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.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	19/12/2023	n/a		

	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)				
IA/0058	A.7 - Administrative change - Deletion of manufacturing sites	20/09/2023	n/a		
IB/0057	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	20/04/2023	14/03/2024	PL	
IAIN/0056/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.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	19/10/2022	15/05/2023	SmPC, Annex II, Labelling and PL	
II/0054/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or	22/09/2022	n/a		

	replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2022	15/05/2023	PL	
PSUSA/1714/202107	Periodic Safety Update EU Single assessment - icatibant	10/03/2022	n/a		PRAC Recommendation - maintenance
IAIN/0053/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 A.7 - Administrative change - Deletion of manufacturing sites	16/11/2021	15/05/2023	Annex II and PL	
T/0051	Transfer of Marketing Authorisation	13/08/2021	25/10/2021	SmPC, Labelling and PL	
IB/0050/G	This was an application for a group of variations.	19/10/2020	25/10/2021	SmPC, Annex II, Labelling	

	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			and PL	
IAIN/0049/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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	13/03/2020	n/a		
II/0047	Update of Risk Management Plan (RMP) in order to reflect the finalisation of the paediatric study HGT-FIR-086, update the main safety concerns following results of the paediatric study HGT-FIR-086 and remove study HGT-FIR-086 as an additional PV activity. In addition the RMP was reformatted to comply with the requirements of the new EU RMP template. The requested variation proposed amendments to the Risk Management Plan (RMP). 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	16/05/2019	n/a		In total, there were seven shifts in reproductive hormones categories at any time point, most of them transient. Three of the seven shifts occurred in testosterone levels in pubertal/post-pubertal males after the second and third exposures. In this subgroup, shifts were noted both from normal to low (n=1) and from low to normal range values (n=2). Thus, there were no clear trends in the observed shifts. The shifts observed in other reproductive hormones were transient. It is considered that the changes in reproductive hormones in the study are not clinically relevant, and do not raise any concern. The number of subjects in the study was however low, especially in the second phase, and furthermore, there were a substantial number of missing values for reproductive hormones. In summary, even though no clinically meaningful shifts in reproductive hormones were seen in the study, no firm conclusions could be made due to the low number of observations. No medication errors were reported in the

					study, neither with administration by health care personnel or by the subject's caregiver. Based on these results no update on the information already reflected in section 5.1 was deemed necessary. The RMP was updated to reflect the fulfilment of Study HGT-FIR 086. Furthermore, the RMP was updated according to the new EU RMP format and to include update of exposure data, update of the safety concerns "Effect on reproductive hormone levels in pubertal/ post-pubertal children" and "Medication Errors" and addition of data from a preclinical study.
II/0046	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	14/03/2019	n/a		
II/0043/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	28/02/2019	18/12/2019	SmPC	
PSUSA/1714/ 201807	Periodic Safety Update EU Single assessment - icatibant	17/01/2019	n/a		PRAC Recommendation - maintenance
IAIN/0045	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	04/01/2019	18/12/2019	Annex II and PL	

IAIN/0044/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible 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)	28/11/2018	n/a		
T/0041	Transfer of Marketing Authorisation	06/07/2018	23/08/2018	SmPC, Labelling and PL	
PSUSA/1714/201707	Periodic Safety Update EU Single assessment - icatibant	22/02/2018	26/04/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1714/201707.
IA/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	20/03/2018	n/a		
II/0034/G	This was an application for a group of variations. Extension of Indication to include adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency, for the use of Firazyr for	14/09/2017	19/10/2017	SmPC and PL	Please refer to the Scientific Discussion Firazyr EMEA/H/C/000899/II/0034/G.

	symptomatic treatment of acute attacks of hereditary angioedema; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The possibility of caregiver/self-administration has also been introduced. In addition, the Marketing authorisation holder (MAH) took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3. Update section 5.2 of the SmPC to update the effect of age (elderly), gender and race on the pharmacokinetics of icatibant. The Package Leaflet is updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10. The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (version 6.2). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0038	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	30/05/2017	n/a		

IA/0037/G	This was an application for a group of variations. 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	05/04/2017	n/a		
II/0036/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 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 importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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 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	23/03/2017	19/10/2017	SmPC	

	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 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 B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.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				
PSUSA/1714/ 201607	Periodic Safety Update EU Single assessment - icatibant	09/02/2017	n/a		PRAC Recommendation - maintenance
PSUSA/1714/ 201507	Periodic Safety Update EU Single assessment - icatibant	11/02/2016	n/a		PRAC Recommendation - maintenance
IG/0621	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/10/2015	n/a		
IB/0031/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a	20/08/2015	n/a		

	non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
IA/0030/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)	22/07/2015	n/a		
IAIN/0029/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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	17/06/2015	26/05/2016	Annex II and PL	

	specification limits 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				
II/0028	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/04/2015	n/a		
PSUV/0027	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0024/G	This was an application for a group of variations. Update to section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054). In addition the MAH has taken the opportunity to make minor editorial changes throughout the PI and to amend the Package Leaflet based on the results of user testing submitted and assessed as part of FUM 028. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/02/2014	06/02/2015	SmPC, Annex II and PL	For further information please refer to the scientific conclusion: Firazyr H-899-II-24-G-AR
PSUV/0026	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance

IA/0025/G	This was an application for a group of variations. 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.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	16/04/2013	n/a		
R/0022	Renewal of the marketing authorisation.	17/01/2013	13/03/2013	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is 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 Firazyr continues to be favorable. The CHMP was of the opinion that the renewal could be granted with unlimited validity.
IA/0023	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	06/12/2012	n/a		
II/0020	Update of section 5.3 of the SmPC in order to include information on the results of study JE049-0162, a two-year carcinogenicity study in rats, following the assessment of RMP 023 (RMP version 4.0) by the CHMP.	15/11/2012	13/03/2013	SmPC	This type II variation concerns an update of section 5.3 of the SmPC to include information on the results of study JE049-0162, a two-year carcinogenicity study in rats. This study showed that subcutaneous administration of icatibant to rats at dose levels of 1, 3 or 6 mg/kg/day for at least

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				104 weeks, was well tolerated, but associated with a slight reduction in body weight gain among males given 6 mg/kg/day and with non-neoplastic microscopic changes in the adrenal glands, brown fat and bone marrow of females and in the injection sites and the feet of both sexes. There was no effect of treatment on the incidence or morphology of tumours to indicate any carcinogenic potential of icatibant at those dose levels. To conclude, this study did not indicate a carcinogenic potential for icatibant.
II/0017/G	This was an application for a group of variations. This submission concerns grouping of two type II variations to include additional information on the impact of icatibant on fertility-related parameters: - Update of SmPC section 4.6 with information on results of a phase I randomised double-blind, placebo controlled single centre study to assess the effects of icatibant on serum reproductive hormone levels and semen analysis in male and premenopausal female healthy adult subjects. - Update of SmPC section 5.3 with information on results of a 7-week toxicity study in the juvenile rat with the assessment of fertility. 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	20/09/2012	25/10/2012	SmPC	Results from the double-blind, randomised, placebo-controlled phase I study HGT-FIR-062 in male and premenopausal female healthy adult subjects showed some statistically significant changes in the levels of reproductive hormones at some time points after icatibant administration, but those were assessed as unlikely to have unfavourable reproductive effects and therefore as not being clinically significant. There were no significant effects of icatibant on semen parameters in males. In the 7-week GLP toxicity study, in male juvenile rats microscopic findings in testes and epididymides, which were partially reversible, were seen at doses of 3, 9 or 25 mg/kg/day subcutaneously. However, the effects seen in the present study at 3 and 9 mg/kg/day did not result in any functional deficit in terms of mating performance and fertility of the male rat, which also is in line with previous fertility studies where no effect was seen in rats at a top dose of 10 mg/kg/day. Impaired fertility in male juvenile rats was seen at 25 mg/kg/day, but In view of the results from the clinical study it is agreed that the effects seen on male fertility at 25 mg/kg/day is not relevant to the prescriber. A no-observed-adverse-effect-level for female

					rats of 9 mg/kg/day was established. The findings from these two studies were deemed not to affect the positive benefit-risk balance of icatibant and information about important findings has been added to the SmPC.
IG/0216	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2012	n/a		
IA/0019/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.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) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	10/09/2012	n/a		

	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.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
IB/0016/G	This was an application for a group of variations. 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.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	30/08/2012	n/a		

	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.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
II/0015	Update of SmPC sections 4.7, 4.8 and 5.1 based on results of a phase III randomised double-blind, placebo controlled multicenter study of icatibant in patients with acute attacks of hereditary angioedema and related update to the Company Core Data Sheet. The Package Leaflet is updated in accordance. In addition, the ATC code has been updated in the SmPC. Furthermore, Annex II is being brought in line with the latest QRD template version. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	23/08/2012	SmPC, Annex II and PL	SmPC section 5.1 has been updated with results from a phase III randomised double-blind, placebo controlled multicenter study of icatibant in patients with acute attacks of hereditary angioedema (FAST 3). The MAH had also conducted a comprehensive analysis of adverse events in the increased safety database. The list of adverse reactions has been updated accordingly. Due to lack of evidence to support a likely causal relationship, the following AEs have been removed: blood creatinine phosphokinase increased, prothrombin time prolonged, vomiting, asthenia, fatigue, contusion, weight increased, blood glucose increased, hyperuricaemia, hyperglycaemia, muscle spasm, proteinuria, asthma, cough, nasal congestion, generalised urticaria, and hot flush. SmPC section 4.7 has been revised according to the updated list and frequencies of adverse reactions that may have an effect on ability to drive or use machines.

IA/0018	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	10/08/2012	n/a		
IA/0014	A.1 - Administrative change - Change in the name and/or address of the MAH	27/10/2011	08/03/2012	SmPC, Labelling and PL	
II/0013	Change in the specification limit of the finished product at shelf-life. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	20/10/2011	20/10/2011		
IA/0012/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.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites	19/08/2011	n/a	Annex II and PL	
II/0011	Introduction of a new DDPS after integration of pharmacovigilance departments of Jerini AG and Shire Pharmaceuticals. C.I.8.a - Introduction of a new Pharmacovigilance	23/06/2011	23/06/2011		The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the

	system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH				notification of any adverse reaction suspected of occurring either in the Community or in a third country.
II/0010	Update of sections 4.6 and 5.3 of the SmPC to reflect the non-clinical findings from the chronic toxicology studies in rats (JE049-0163) and dogs (JE049-0164). The DDPS version number is being deleted from Annex II. 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	17/03/2011	18/04/2011	SmPC and Annex II	The MAH has conducted a 6-months chronic toxicity study in rats and a 9-months study in dogs, which have been assessed as follow-up measures. As an outcome of the assessment, the MAH was requested to submit a type II variation to include relevant information from these studies in sections 4.6 and 5.3 of the SmPC. Effects of icatibant treatment observed in both rats and dogs included a dose related reduction in circulating sex hormone levels, and the repeated use of icatibant reversibly delayed sexual maturation. Furthermore, adrenal gland hypertrophy was seen in rats, the clinical relevance of which is unknown.
II/0009	Update of SPC and package leaflet C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	28/02/2011	SmPC and PL	Update of sections 4.2, 4.4, 4.8 of the SPC based on the safety and efficacy data from Study JE049-3101A to include information for self-administration of icatibant (Firazyr®) during acute attacks of Hereditary Angioedema (HAE). The corresponding changes have been introduced in the Package Leaflet. In addition, minor changes are introduced in the product information to bring it in accordance with the latest SPC/QRD guideline.
IB/0006	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	23/07/2010	n/a	SmPC	

IB/0007	To add a new presentation comprising three pre-filled syringes. 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	19/07/2010	19/07/2010	SmPC, Labelling and PL	
IA/0005	IA_06_a_Change in ATC code: Medicinal products for human use	26/06/2009	n/a	SmPC	
II/0004	Change to the specification of the finished product, to remove the impurity (specified) from the specification. Change(s) to the test method(s) and/or specifications for the finished product	23/04/2009	28/04/2009		
II/0002	The Marketing Authorisation Holder applied to add an alternative manufacturing site for testing of bacterial endotoxins and microbial limit in the active substance. Quality changes	22/01/2009	27/01/2009		
IB/0003	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	19/12/2008	n/a	SmPC	
II/0001	The Marketing Authorisation Holder Applied to add an alternative manufacturing site for the terminal sterilization of the finished product.	20/11/2008	27/11/2008		

	Change(s) to the manufacturing process for the finished product				