EMA/511981/2020

Integrilin

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/0083	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/09/2020		SmPC, Annex II, Labelling and PL	
PSUSA/1246/ 202001	Periodic Safety Update EU Single assessment - eptifibatide	04/09/2020	n/a		PRAC Recommendation - maintenance

[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).

IA/0081	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	20/12/2019	n/a		
IAIN/0080	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	25/03/2019	09/03/2020	Annex II and PL	
T/0079	Transfer of Marketing Authorisation	12/10/2018	29/10/2018	SmPC, Labelling and PL	
IB/0078	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	25/07/2018	n/a		
IA/0077	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	14/11/2017	n/a		
PSUSA/1246/ 201701	Periodic Safety Update EU Single assessment - eptifibatide	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0075	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/04/2017	16/03/2018	Annex II, Labelling and PL	
IB/0073	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	21/12/2015	n/a		

N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/11/2015	12/05/2016	PL	
IA/0072	A.7 - Administrative change - Deletion of manufacturing sites	12/11/2015	n/a		
IB/0071	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/05/2015	12/05/2016	SmPC, Annex II, Labelling and PL	
PSUV/0070	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0069	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	20/12/2013	n/a		
IB/0068/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of	20/12/2013	n/a		

	the AS - Minor change to the restricted part of an ASMF				
IB/0067/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.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	16/12/2013	n/a		
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/11/2013	23/04/2014	PL	
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	23/04/2014	SmPC, Labelling and PL	
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/04/2012	23/04/2014	Labelling and PL	
IG/0150/G	This was an application for a group of variations.	05/04/2012	n/a		

	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0056	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	21/03/2012	SmPC and PL	
IB/0055/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.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	31/01/2012	n/a		

	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				
IB/0054/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 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	31/01/2012	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/01/2012	n/a		
IA/0060	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/01/2012	n/a		
IA/0059	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/01/2012	n/a		
IB/0053	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	06/01/2012	21/03/2012	SmPC and PL	
IA/0058	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	22/12/2011	n/a		
IA/0057	B.I.c.3.b - Change in test procedure for the immediate packaging of the AS - Other changes to a test procedure (including replacement or addition)	16/12/2011	n/a		
II/0051	Update of Summary of Product Characteristics	23/06/2011	27/07/2011	SmPC	Update of Summary of Product Characteristics to update the section 4.4 Special warnings and precautions for use

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				with regards to potential for immune related thrombocytopenia.
II/0049	C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	14/04/2011	SmPC, Annex II and PL	This variation seeks to update the Summary of Product Characteristics and Package Leaflet with data from the EARLY-ACS study. Sections 4.4 of the SmPC will be amended to include that early administration of eptifibatide may be associated with an increased risk of bleeding and Section 5.1 will include the EARLY-ACS data in support of this warning. In addition, the MAH took the opportunity to align the SmPC with the new QRD template version 7.3 (addition of headings in sections 4.2, 4.6 and 5.1); amend EMEA to EMA in website address and removal of EMEA acronym in Patient Information leaflet (PIL); update the contact phone number for Cyprus in the PIL; and in annex IIB delete the condition that "The MAH will continue to provide Periodic Safety Update Reports every 12 months".
IG/0034/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	06/01/2011	n/a	Annex II	

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0050	A.7 - Administrative change - Deletion of manufacturing sites	18/05/2010	n/a		
II/0047	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.

IA/0048	IA_09_Deletion of manufacturing site	05/11/2009	n/a	Annex II and PL	
II/0046	Update of Summary of Product Characteristics (sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 4.9, 5.1, 6.2, 6.4 and 6.6), Labelling and Package Leaflet following a revision to the Integrilin Product Information following QRD comments during the renewal procedure. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/09/2009	28/10/2009	SmPC, Labelling and PL	The MAH submit this variation to update the Summary of Product Characteristics, Labelling and Package Leaflet following a revision to the Integrilin Product Information following QRD comments during the renewal procedure.
R/0044	Renewal of the marketing authorisation.	23/04/2009	01/07/2009	SmPC and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Integrilin continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
II/0045	Update of the Detailed Description of the Pharmacovigilance System (DDPS) in order to include the change of the Qualified Person for Pharmacovigilance (QPPV). In addition, the Marketing Authorisation Holder (MAH) took the opportunity to notify other minor changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of	19/02/2009	07/04/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 6.2, November 2008) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.

	the agreed DDPS. Changes to QPPV Update of DDPS (Pharmacovigilance)				
IB/0043	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	16/12/2008	n/a		
II/0042	Quality changes	30/05/2008	25/06/2008		
IA/0041	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/11/2007	n/a		
IA/0040	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	31/07/2007	n/a		
II/0037	Change(s) to the manufacturing process for the active substance	21/06/2007	25/06/2007		
II/0039	Update of Summary of Product Characteristics, Labelling and Package Leaflet. Update of Summary of Product Characteristics and Labelling	24/01/2007	01/03/2007	SmPC, Labelling and PL	The MAH has applied to amend the posology for eptifibatide in patients with impaired renal function, based on the results of a controlled pharmacokinetic/pharmacodynamic study in patients with varying levels of renal function and post-hoc analyses of controlled clinical trials. By reducing the standard infusion dose of eptifibatide from 2.0 µg/kg/min to 1.0 µg/kg/min in patients with moderate renal impairment (i.e. CrCl 30-50 ml/min), appropriate therapeutic exposures to eptifibatide were achieved, while maintaining the efficacy as measured by inhibition of platelet aggregation. Review of clinical trial safety data related to bleeding showed that patients with moderate renal impairment who received reduced eptifibatide dose

					had a lower risk of bleeding. This recommendation and posology in patients with moderate renal impairment has been added in section 4.2 of the SPC and the current contraindication in patients with severe renal impairment in section 4.3 has been clarified accordingly. Further information on the pharmacokinetic properties of eptifibatide in patients with moderate to severe renal insufficiency has been added to section 5.2 of the SPC. A letter to inform healthcare professionals of the changes with the updated SPC has been sent following the adoption of this opinion by the CHMP.
II/0038	Change(s) to the test method(s) and/or specifications for the finished product	21/09/2006	27/09/2006		
IB/0036	IB_17_a_Change in re-test period of the active substance	26/04/2006	n/a		
II/0034	Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/10/2005	17/11/2005	SmPC, Labelling and PL	Inclusion of a new adverse event, pulmonary haemorrhage, in the post-marketing section of 4.8 "Undesirable effects" in the SPC.
IA/0035	IA_09_Deletion of manufacturing site	07/10/2005	n/a		
II/0033	Update of or change(s) to the pharmaceutical documentation	15/09/2005	23/09/2005		
II/0032	Update of or change(s) to the pharmaceutical documentation	27/07/2005	03/08/2005		

IA/0031	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	09/12/2004	n/a		
T/0030	Transfer of Marketing Authorisation	18/10/2004	06/12/2004	SmPC, Labelling and PL	Transfer of MAH from Schering-Plough Europe to Glaxo Group Ltd.
IA/0029	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	05/10/2004	n/a	Annex II and PL	
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/10/2004	n/a		
R/0025	Renewal of the marketing authorisation.	23/06/2004	02/09/2004	SmPC, Annex II, Labelling and PL	
II/0026	Quality changes	29/07/2004	29/07/2004		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2004	n/a	PL	
II/0024	Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	23/02/2004	SmPC and PL	
I/0023	20a_Extension of shelf-life or retest period of the active substance	10/09/2003	18/09/2003		
I/0022	12_Minor change of manufacturing process of the active substance	15/04/2003	28/04/2003		
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2003	24/03/2003	PL	

II/0018	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	03/10/2002	SmPC and PL	
I/0019	15_Minor changes in manufacture of the medicinal product	12/08/2002	05/09/2002		
II/0017	Update of Summary of Product Characteristics and Package Leaflet	13/12/2001	19/04/2002	SmPC, Labelling and PL	
II/0012	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	17/01/2002	07/02/2002		
II/0016	Change(s) to shelf-life or storage conditions	18/10/2001	17/12/2001		
I/0015	24_Change in test procedure of active substance	09/08/2001	n/a		
I/0014	24_Change in test procedure of active substance	09/08/2001	n/a		
I/0013	24_Change in test procedure of active substance	09/08/2001	n/a		
I/0007	15_Minor changes in manufacture of the medicinal product 16_Change in the batch size of finished product	27/07/2000	n/a		
I/0010	24_Change in test procedure of active substance	27/06/2000	06/07/2000		
I/0009	24_Change in test procedure of active substance	27/06/2000	06/07/2000		

I/0008	15_Minor changes in manufacture of the medicinal product	27/06/2000	06/07/2000		
I/0006	14_Change in specifications of active substance	07/09/1999	22/09/1999		
I/0005	14_Change in specifications of active substance	07/09/1999	22/09/1999		
I/0004	12_Minor change of manufacturing process of the active substance	07/09/1999	22/09/1999		
I/0003	12_Minor change of manufacturing process of the active substance	07/09/1999	22/09/1999		
I/0002	12_Minor change of manufacturing process of the active substance	07/09/1999	22/09/1999		
I/0001	13_Batch size of active substance	07/09/1999	22/09/1999		