Increlex

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/0067	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	11/11/2021		Annex II and PL	
IB/0071	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	09/11/2021		SmPC and PL	To update the shelf-life from '36 months' to '60 months' in section 6.3 of the Summary of Product Characteristics

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	(supported by real time data)				(SmPC); To update the visual description of the appearance of the product in section 3 of the SmPC and in section 6 of the Patient Information Leaflet (PIL) to comply with section 3.2.P.5.1 Specification(s); To update section 4.4 of the SmPC and section 2 of the PIL with regards to sodium content according to the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668).
IB/0072/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	27/10/2021	n/a		
IAIN/0073/G	This was an application for a group of variations. 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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/10/2021		Annex II and PL	
IB/0069/G	This was an application for a group of variations.	06/10/2021	n/a		

	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.z - Change in control of excipients in the Finished Product - Other variation 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.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0068/G	This was an application for a group of variations. B.II.e.z - Change in container closure system of the Finished Product - Other variation 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.e.z - Change in container closure system of the	22/07/2021		SmPC	

	Finished Product - Other variation 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.e.z - Change in container closure system of the Finished Product - Other variation B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
S/0064	13th annual re-assessment	25/02/2021	21/04/2021	Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Increlex should be maintained. The description of the non-interventional PASS has been reworded and the timeline for completion of the final study report was extended to 2030.
PSUSA/1942/ 202008	Periodic Safety Update EU Single assessment - mecasermin	09/04/2021	n/a		PRAC Recommendation - maintenance
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	n/a		

PSUSA/1942/ 201908	Periodic Safety Update EU Single assessment - mecasermin	12/03/2020	n/a		PRAC Recommendation - maintenance
S/0061	12th annual re-assessment	30/01/2020	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Increlex should be maintained.
IA/0063	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	16/01/2020	n/a		
II/0060	Update of sections 4.1, 4.2, 4.3, 4.4, 4.8 and 4.9 of the SmPC in order to update the safety information on benign or malignant neoplasia based on the EU Registry Study, the Ipsen global safety database and literature review. The Package Leaflet is updated accordingly. The MAH also submitted the updated RMP version 11.3. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	16/12/2019	SmPC, Annex II and PL	Mecasermin should only be used in the treatment of confirmed severe primary IGF-1 deficiency and the maximum dose of 0.12 mg/kg given twice daily should not be exceeded. Increlex is contraindicated in children and adolescents with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia. There have been post-marketing reports of both benign and malignant neoplasms in children and adolescents who have received treatment with Increlex. These cases represented a variety of different malignancies and included rare malignancies usually not seen in children. Current knowledge of IGF-1 biology suggests that IGF-1 plays a role in malignancies in all organs and tissues. Physicians should therefore be vigilant of any symptoms of potential malignancy. If benign or malignant neoplasia develops, Increlex

					treatment should be discontinued and appropriate expert medical care sought. "Benign and malignant neoplasms" have been introduced in section 4.8 of the SmPC, with frequency "not known". In case of an acute or a chronic overdose, Increlex must be discontinued immediately. If Increlex is restarted, the dose should not exceed the recommended daily dosage.
II/0059	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/10/2019	n/a		
S/0055	11th annual re-assessment	26/04/2019	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Increlex should be maintained.
IB/0057	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	28/03/2019	n/a		
PSUSA/1942/ 201808	Periodic Safety Update EU Single assessment - mecasermin	14/03/2019	n/a		PRAC Recommendation - maintenance
IB/0058	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	12/03/2019	n/a		

IB/0053	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	09/10/2018	n/a		
IB/0054/G	This was an application for a group of variations. 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 B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	30/08/2018	n/a		
PSUSA/1942/ 201708	Periodic Safety Update EU Single assessment - mecasermin	12/04/2018	n/a		PRAC Recommendation - maintenance
S/0050	Annual re-assessment.	22/02/2018	n/a		
IB/0052	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	07/02/2018	n/a		
IB/0048	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/11/2017	n/a		
IB/0049	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	08/11/2017	n/a		

	of the AS				
IB/0047	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	16/10/2017	n/a		
II/0044/G	This was an application for a group of variations. C.I.4 - Update of section 4.4 of the SmPC in order to update the warning regarding antibody response to injected IGF-1. C.I.11.b - Submission of an updated RMP version 9.3. As part of this update, the risks of cardiomegaly and scoliosis were changed from important potential risks to important identified risks. In addition, wording regarding antibody testing was amended in Physician educational brochure as per update of the SmPC linked to antibody response to injected IGF-1. In addition, the marketing authorisation holder took the opportunity to introduce editorial changes in the SmPC and Annex IIIA. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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	14/09/2017	20/09/2018	SmPC	Update of section 4.4 of the SmPC to indicate that patients that have high blood values of IGF-1 after injection, or who fail to show a growth response without any identified cause may be linked the production of anti-IGF-1 IgEs, sustaining antibodies or neutralizing antibodies respectively. An updated RMP has been submitted as part of this application.

	by new additional data to be submitted by the MAH where significant assessment is required				
R/0042	Renewal of the marketing authorisation.	21/04/2017	16/06/2017	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 Increlex in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0040	Update of section of 4.1 of the SmPC in order to re-word the recommendation to confirm diagnosis with an IGF-1 generation test used for diagnosis of Severe Primary IGFD. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	02/06/2017	SmPC	The current indication reflected in section 4.1 for Increlex states that it is recommended to confirm the diagnosis of severe primary IGF-1 deficiency (SPIGFD) by conducting an IGF-1 generation test. Section 4.1 of the SmPC is being updated as part of this procedure in relation to the diagnosis to "In some cases, when deemed necessary, the physician may decide to assist in the diagnosis by performing an IGF-I generation test". Following a literature review, IGFGT test did not prove to be a strong predictor of growth response in GH deficiency. However, the test may be used to assist the diagnosis. Therefore, the clinician decides whether there is a need to use the IGF-1 generation test to confirm the diagnosis of severe primary IGFD.
II/0046/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	30/03/2017	02/06/2017	Annex II	

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for 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.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.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
PSUSA/1942/ 201608	Periodic Safety Update EU Single assessment - mecasermin	09/03/2017	n/a		PRAC Recommendation - maintenance
S/0041	Annual re-assessment.	23/02/2017	n/a		
IA/0045/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	16/12/2016	n/a		

	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.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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				
IB/0039/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.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.7 - Administrative change - Deletion of manufacturing sites 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	06/10/2016	n/a		
II/0037/G	This was an application for a group of variations.	26/05/2016	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.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
S/0035	Annual re-assessment.	25/02/2016	08/04/2016	Annex II	The CHMP considered that the benefit/risk profile of the medicinal product remains positive in the approved indication and concluded that Marketing Authorisation of Increlex should be varied. The specific obligation S0 001 is considered fulfilled and the Annex II is amended accordingly. In addition updated information related to S0 002 is introduced. The remaining Specific obligation (SO 002) needs to be fulfilled and the Marketing Authorisation will continue to be reviewed annually.
PSUSA/1942/ 201508	Periodic Safety Update EU Single assessment - mecasermin	17/03/2016	n/a		PRAC Recommendation - maintenance
IB/0038	C.I.11.z - Introduction of, or change(s) to, the	29/01/2016	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/1942/ 201408	Periodic Safety Update EU Single assessment - mecasermin	26/03/2015	27/05/2015	SmPC	Please refer to Increlex PSUSA-1942-201408 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
S/0032	7th Annual Re-assessment	26/02/2015	05/05/2015	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, remains favourable and concluded that Marketing Authorisation of Increlex should be varied. Minor changes are implemented to bring the annex II in line with the QRD template, introducing dues date for the specific obligations.
II/0028	Update of section 4.8 of the SmPC in line with the updated Company Core Safety Information, and upon request by PRAC following the assessment of PSUV/0026, and section 5.1 of the SmPC with the results from the integrated Clinical Study Report of study 1419. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	08/04/2016	SmPC, Annex II and PL	

IAIN/0034	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	02/02/2015	n/a		
II/0031	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	22/01/2015	n/a		
IAIN/0030	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	15/08/2014	05/05/2015	SmPC and PL	
IAIN/0029	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	01/07/2014	n/a		
S/0024	Annual re-assessment.	25/04/2014	n/a		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/04/2014	05/05/2015	PL	
PSUV/0026	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IAIN/0025	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	10/12/2013	n/a		

N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/11/2013	05/05/2015	PL	
IB/0023/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/10/2013	n/a		
S/0021	5th Annual Re-assessment	21/02/2013	22/04/2013	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0020	Update of SmPC section 4.8, upon request by the CHMP following assessment of PSUR 7, to include the ADR 'alopecia'. The Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to update the contact details of the local representatives in the 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 -	19/07/2012	30/08/2012	SmPC and PL	A total of 43 cases have been received involving 'alopecia' and/or 'hair texture changes' (all non-serious events). A very small number of these cases reported confounding factors. However, in these cases, a causal relationship with mecasermin could not be excluded. In three cases reporting 'alopecia', mecasermin treatment was discontinued due to the event. Two cases involving 'alopecia' reported that the patient recovered after the mecasermin dose was reduced, demonstrating a dose-response relationship. One case involving 'alopecia' reported that the patient recovered despite no action being

	Change(s) with new additional data submitted by the MAH				taken with mecasermin treatment. In addition, the reporting rate meets the Company's internal threshold for disproportionate reporting. Although very little can be found in the literature regarding IGF-1 and adverse events relating to hair, it is possible that IGF-1 treatment may have an impact on hair growth.
R/0019	Renewal of the marketing authorisation.	24/05/2012	03/08/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers that the benefit-risk balance of Increlex in the treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) remains favourable and therefore recommends the renewal of the marketing authorisation under exceptional circumstances. The CHMP recommended the renewal of the Marketing Authorisation for Increlex, subject to the conditions as laid down in Annex II to the Opinion. The CHMP considers that the benefit-risk balance of Increlex remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Increlex was granted a MA under exceptional circumstances and at the time the available safety data was limited to 76 subjects with severe primary IGFD. Although more clinical safety data has been gathered during the period since the granting of the initial MA, the number of patients for whom long-term data are available is still limited. For example, it was not yet possible to enrol any patients into the registry substudy that aims to enrol 100 patients who have reached near-adult height and who will be followed for 5 years. Thus, the long-term safety of Increlex, including a potential

					effect on the incidence of neoplasia, has not yet been fully established. The CHMP decided that the PSUR cycle for the product will follow the yearly cycle until otherwise agreed by the CHMP. Therefore, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time. In view of new data submitted as part of the renewal application, the CHMP recommends amendments to the Annexes I, II, IIIA and IIIB. These changes do not affect the benefit-risk balance of the product, which remains positive.
S/0018	4th Annual Re-assessment	24/05/2012	03/08/2012	Annex II	The CHMP, having reviewed the level of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0017/G	This was an application for a group of variations. - Change in test procedure - Addition of a specification parameter - Addition of a bioassay working cell bank - Changes to in-process controls - Change of name of a QC site B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	23/06/2011	23/06/2011		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS 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				
II/0016/G	This was an application for a group of variations. - Change in the manufacturing site of the active substance - Changes to manufacturing process - Addition of five raw material QC testing sites and one release testing site - Change in the specifications of raw materials and reagents - Change in analytical procedures - Deletion of a manufacturing site B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	19/05/2011	17/06/2011	Annex II	

	change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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 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 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 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.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change				

	(replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS A.7 - Administrative change - Deletion of manufacturing sites				
S/0015	Annual re-assessment.	17/03/2011	16/06/2011	SmPC, Labelling and PL	
II/0014	Update of Annex II and Package Leaflet C.I.8.a - Introduction of a new Pharmacovigilance system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH	16/12/2010	01/02/2011	Annex II and PL	
II/0013	Update of sections 4.4 and 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 4, with further information regarding local allergic reactions at the injection site and cases of systemic hypersensitivity. The Package Leaflet has been updated accordingly. Consequently, annex IIB - conditions or restrictions with regard to the safe and effective use of the medicinal product - has been updated to specify that the existing paragraph providing information on treatment interruption and need of medical attention refers to systemic allergic reactions. In addition, the MAH takes the opportunity to implement minor editorial changes in the annexes and to update the name of the Czech local representative in the Package Leaflet.	24/06/2010	28/07/2010	SmPC, Annex II and PL	

	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				
S/0012	Annual re-assessment.	21/01/2010	30/03/2010	Annex II	
II/0011	Change(s) to the manufacturing process for the finished product	19/11/2009	25/11/2009		
T/0010	Transfer of Marketing Authorisation	19/06/2009	14/07/2009	SmPC, Annex II, Labelling and PL	Transfer of Marketing Authorisation for Increlex from Tercica Europe Ltd. to Ipsen Pharma.
IA/0008	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/03/2009	n/a	Annex II	
IA/0009	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	23/03/2009	n/a		
IB/0006	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	17/03/2009	n/a	SmPC	
IA/0007	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	17/03/2009	n/a		

S/0003	Annual re-assessment.	25/09/2008	20/11/2008	Annex II	Based on the available data, the safety profile of Increlex has not changed from the time of the marketing authorisation and no new adverse events have been described during this first year. Furthermore, none of the additional information provided as part of the post-authorisation specific obligations or follow-up measures in clinical and quality data suggest any change to the safety profile of Increlex. Most of the post-authorisation commitments are still ongoing and the closely reporting will continue during this year. Overall, the CHMP considered that the MA for Increlex should remain under exceptional circumstances in view of the pending Specific Obligations.
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	15/09/2008	n/a		
IA/0004	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	15/09/2008	n/a	Annex II and PL	
II/0002	Update of Detailed Description of the Pharmacovigilance System (DDPS) Update of DDPS (Pharmacovigilance)	26/06/2008	29/07/2008	Annex II	In accordance with Article 8(3)(ia) of directive 2001/83/EC as amended, the MAH submitted a Detailed Description of the Pharmacovigilance System (DDPS) for Increlex, with their Marketing Authorisation Application. This is now being updated.
IA/0001	IA_01_Change in the name and/or address of the marketing authorisation holder	23/11/2007	n/a	SmPC, Labelling and PL	