Epoetin alfa Hexal

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
WS/1688	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	19/09/2019	n/a		
WS/1675	This was an application for a variation following a worksharing procedure according to Article 20 of	12/09/2019		SmPC, Labelling and	

[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).

	Commission Regulation (EC) No 1234/2008. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH			PL	
PSUSA/1237/ 201808	Periodic Safety Update EU Single assessment - epoetin alpha	16/05/2019	n/a		PRAC Recommendation - maintenance
WS/1548	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	07/03/2019	n/a		
N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2019		PL	
WS/1546/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	31/01/2019	n/a		

	specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation				
IG/1058	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	29/01/2019	n/a		
WS/1507	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	06/12/2018		SmPC, Labelling and PL	
WS/1470	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/10/2018	n/a		
WS/1465/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	04/10/2018	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.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				
WS/1463	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	20/09/2018	n/a		
WS/1419	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.z - Quality change - Finished product - Other variation	13/09/2018	n/a		
WS/1406	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of	26/07/2018	31/08/2018	SmPC, Labelling and PL	Please refer to Scientific Discussion Abseamed-H-C-WS-1406, Binocrit-H-C-WS-1406, Epoetin alpha Hexal-H-C-WS-1406

	≤ 10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml) for Binocrit, Epoetin alfa Hexal and Abseamed; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The Package Leaflet and the risk management plan (finally agreed version 17.1) are updated in accordance. In addition, the worksharing applicant (WSA) took the opportunity to align information with the reference medicinal product and with the EC guideline on Excipients, to improve the quality and readability of the translations in the product information and to update the Annex A in line with EMA guideline. C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH				
IG/0970/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.7 - Administrative change - Deletion of manufacturing sites	17/08/2018	n/a		

IB/0070	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	09/07/2018	n/a		
IA/0071	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	29/06/2018	n/a		
WS/1367	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	19/04/2018	n/a		
IG/0882	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	21/12/2017	n/a		
WS/1290	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	14/12/2017	n/a		

WS/1287	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	14/12/2017	n/a		
IG/0847/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/10/2017	31/08/2018	SmPC, Annex II and PL	
WS/1175	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	22/06/2017	n/a		
WS/1155	This was an application for a variation following a worksharing procedure according to Article 20 of	05/05/2017	n/a		

	Commission Regulation (EC) No 1234/2008. 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				
IB/0061/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.z - Changes in the manufacturing process of the AS - Other variation	15/03/2017	n/a		
IG/0752	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)	12/12/2016	n/a		
IG/0746	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/12/2016	n/a		
N/0060	Update of the package leaflets with revised contact details of the local representatives for all the member	06/12/2016	07/09/2017	PL	

	states. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
WS/1032	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	13/10/2016	07/09/2017	SmPC, Labelling and PL	
WS/1011	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/10/2016	n/a		
WS/0981	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/09/2016	n/a		

PSUSA/1237/ 201508	Periodic Safety Update EU Single assessment - epoetin alpha	14/04/2016	n/a		PRAC Recommendation - maintenance
WS/0877	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 4.4 of the SmPC in order to add administration by subcutaneous (s.c.) route in addition to the intravenous (i.v.) route in treatment of anaemia in patients with chronic renal failure based on clinical study HX575-308 (SENSE) to address MEA 024.1. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to make minor editorial changes in the SmPC and to update the list of local representatives in the Package Leaflet for Abseamed and Binocrit and to bring the PI in line with the latest QRD template version 9.1. Moreover, the updated RMP version 15 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	31/03/2016	SmPC, Annex II, Labelling and PL	In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of Abseamed/Binocrit/ Epoetin alfa Hexal by the intravenous route is preferable. Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) Abseamed/Binocrit/ Epoetin alfa Hexal may be administered as a subcutaneous injection. During the maintenance phase, Abseamed/Binocrit/ Epoetin alfa Hexal can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks. The maximum dosage should not exceed 150 IU/kg, 3 times per week, 240 IU/kg (up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks. Chronic renal failure patients treated with epoetin alfa by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin alfa treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in epoetin alfa dosage.
WS/0866	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an	14/01/2016	n/a		

	approved test procedure				
WS/0811/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.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	17/09/2015	n/a		
WS/0783	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	06/08/2015	n/a		
WS/0780/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.z - Change in control of the AS - Other variation B.III.1.z - Submission of a new/updated or deletion of	06/08/2015	n/a		

	Ph. Eur. TSE Certificate of Suitability - 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.z - Quality change - Active substance - Other variation				
WS/0764	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	25/06/2015	31/07/2015	SmPC, Labelling and PL	
WS/0717	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.f.1.e - Stability of FP - Change to an approved stability protocol	23/04/2015	n/a		
IG/0529	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	05/02/2015	n/a		

IG/0480	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/09/2014	n/a		
IB/0044/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	23/05/2014	n/a		
IG/0373	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	12/11/2013	n/a		
WS/0442	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Relocation of a quality control testing site for the active substance. 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	24/10/2013	n/a		

WS/0423	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Move of a quality control testing site for the active substance. 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	19/09/2013	n/a		
IB/0041	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/09/2013	n/a		
IB/0039	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH	17/07/2013		SmPC, Annex II and PL	
IG/0287/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of	11/03/2013	21/03/2014	SmPC, Labelling and PL	

	the currently approved pack sizes				
IG/0281	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	11/03/2013	21/03/2014	SmPC, Labelling and PL	
IB/0036	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	20/02/2013	n/a		
WS/0307	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to replace the quality control testing site for the active substance. 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	18/10/2012	n/a		
WS/0265	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to add an alternative storage site in the manufacture of the drug substance.	21/06/2012	21/06/2012		

	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
R/0031	Renewal of the marketing authorisation.	19/04/2012	18/06/2012	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 Epoetin alfa Hexal continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Epoetin alfa Hexal, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted with unlimited validity The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP.
IG/0183	A.7 - Administrative change - Deletion of manufacturing sites	25/05/2012	n/a		
WS/0233	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to introduce changes to the manufacturing process of HX575 drug substance (DS) 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 medicinal product and is not related to a protocol	24/05/2012	n/a		

WS/0184	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change the batch size of the active substance production. B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	15/12/2011	15/12/2011		
WS/0093	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change shelf life specifications for the finished product B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	19/05/2011	19/05/2011		
IG/0063	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	20/04/2011	n/a		
WS/0084	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/01/2011	14/03/2011	Annex II	The requirement of distributing cool boxes with epoetin alfa has been questioned with the main arguments that stability of the product is granted by the label for 3 days out of fridge

	This was an application for a type IB variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Deletion of the requirement for distribution of cool boxes with the marketed products from Annex II and Annex 127a of the conditions of the Marketing Authorisation. Annex II.B has also been updated to delete the version number of the detailed description of the pharmacovigilance system (DDPS). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				and that no other MAH of an erythropoiesis-stimulating agent (ESA) bears a similar requirement. The current wording of the cool box requirement can also be misinterpreted as obligation to provide one cool box with each box of epoetin alfa. The requirement has been in place for Abseamed/Binocrit/Epoetin Alfa only as it was suggested by the applicants themselves at the time of marketing authorization.
IG/0050	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	23/02/2011	n/a		
WS/0078	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change the active substance specifications. 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	20/01/2011	20/01/2011		
WS/0051	This was an application for a variation following a worksharing procedure according to Article 20 of	20/01/2011	20/01/2011		

	Commission Regulation (EC) No 1234/2008. Change in the immediate packaging of the finished product. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
IA/0021/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	08/10/2010	08/10/2010	SmPC, Labelling and PL	

	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information				

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	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information				
WS/0013	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a type IB variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the Summary of Product Characteristics (SmPC) and Section 2 of the Package Leaflet (PL) in order to implement the CHMP/PhVWP	22/07/2010	18/08/2010	SmPC, Annex II and PL	Two cases of pure red cell aplasia (PRCA) occurred during a clinical study investigating erythropoiesis stimulating agents (ESAs), where anti-epoetin antibodies were detected. While investigations on the cause of PRCA in these cases are still ongoing, the CHMP and Pharmacovigilance Working Party (PhVWP) considered it important that accurate medication histories are maintained for patients treated with epoetins, recording the trade name or the scientific name with the name of the manufacturer. It is recommended that the product information of all ESAs includes a request to

	agreed wording for all erythropoiesis stimulating agents (ESA) regarding the need to maintain patient medication records and the information concerning any modification to the ESA prescribed. The Package Leaflet has also been aligned with the SmPC with regards to wording on pure red cell aplasia in patients with hepatitis C. Minor linguistic changes were introduced to the Dutch, Greek and German annexes. The list of local representatives in the Package Leaflet was also updated. Additionally, minor changes to the product information were introduced. 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				maintain patient medication records. The scope of this variation is to implement the CHMP/PhVWP agreed wording for all erythropoiesis stimulating agents (class labelling) to the Summary of Product Characteristics and Package Leaflet of Abseamed/Binocrit/Epoetin Hexal, as requested by the CHMP. SmPC Section 4.4: Special warnings and precautions for use ."In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file." PL: Take special care with other products that stimulate red blood cell production: Binocrit/Epoetin alfa Hexal/Abseamed is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional will always record the exact product you are using. The Package Leaflet has also been updated with regards to wording on PRCA in patients with hepatitis receiving a combination of ESAs with interferon and ribavirin. Additionally, minor changes to the annexes were introduced. Furthermore minor linguistic changes were introduced to the Dutch, Greek and German annexes. Also the contact details of local representatives were

					updated.
IG/0013/G	This was an application for a group of variations. 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 or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	28/07/2010	n/a	Annex II	
IB/0020	To add the already approved Lek Pharmaceutical d.d site (menges, Slovenia) as an additional manufacturing site regarding release and stability testing for the finished product. 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	28/04/2010	n/a		
II/0017	Establishment of an additional filing suite in combination with the upscale of the btach size for drug product Quality changes	18/03/2010	24/03/2010		
II/0018	This variation concerns an update of the SPC following the completion of a class safety review by the PhVWP	17/12/2009	20/01/2010	SmPC	As a result of the discussion of the updated risk management plans (RMPs) and the results of the Cochrane meta-analysis

	and the CHMP. As a result, CHMP requested to update section 4.4 of the SPC to include more information on pure red cell aplasia (PRCA) in patients with hepatitis C treated with Interferon, Ribavirin and Epoetin and section 5.1 to include additional data on the Cochrane meta-analysis and the effects of epoetins in cancer patients. Minor linguistic and formatting changes have also been introduced. Update of Summary of Product Characteristics				it was agreed at the PhVWP/CHMP meeting in September 2009 that all MAHs for epoetins should submit a type II variation to amend the summary of product characteristics (SPC). Information with respect to the results of the Cochrane meta-analysis on the effects of epoetins in cancer patients and to the occurrence of PRCA in patients with Hepatitis C treated with Interferon, Ribavirin and Epoetin should be included into the SPC. The amendments of Sections 4.4 and 5.1 of the SPC have been implemented as recommended by the PhVWP / CHMP. Minor linguistic and formatting changes have also been implemented.
II/0015	To add an additional manufacturing site for the drug substance. Quality changes	19/11/2009	16/12/2009	Annex II	
IA/0019	To replace the manufacturer responsible for batch release IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	19/11/2009	n/a	Annex II and PL	
X/0010	The Marketing Authorisation Holder applied to add three presentations to the existing range, comprising the new strengths 20,000, 30,000, and 40,000 IU in pre-filled syringes.	25/06/2009	01/10/2009	SmPC, Labelling and PL	

	Annex I_2.(c) Change or addition of a new strength/potency				
IA/0016	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	09/09/2009	n/a		
II/0014	The MAH applied for changes in the label of the syringe label. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	25/08/2009	SmPC and PL	
II/0012	The MAH applied for the introduction of additional process lines for the drug substance. Quality changes	23/04/2009	07/05/2009		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/05/2009	n/a	Labelling	
II/0006	Extension of indication to increase the yield of autologous blood from patients in a predonation program. Update of sections 4.1, 4.2, 4.3, 4.4, 4.6 and 4.8 of the SPC. Labelling and Package Leaflet have been updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/10/2008	21/11/2008	SmPC, Labelling and PL	Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with chronic renal failure (CRF), including those on dialysis and those who do not require regular dialysis. In addition, severe anaemia caused by non-renal disease can be corrected or alleviated following treatment with epoetin alfa, e.g. in cancer patients on chemotherapy. Response to epoetin alfa in these patients is manifested by increased haematocrit, haemoglobin, reduced transfusion requirements and increase in quality of life. In patients with moderate anaemia undergoing major elective surgery accompanied by considerable blood loss, epoetin alfa can be used to increase the yield of autologous blood in a

					predonation program. Epoetin alfa treatment was shown to reduce the exposure to allogeneic blood transfusion in patients undergoing major elective orthopaedic surgery. An application for a "Similar Biological Medicinal Product" via the centralised procedure under Article 10(4) of Directive 2001/83/EC as amended, also making reference to its Annex 1 was submitted to get marketing approval. The application was based on a comparability concept against the reference medicinal product Erypo® (Janssen-Cilag), as authorized in Germany which has been registered in Europe for more than 10 years.
IA/0011	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	13/11/2008	n/a	SmPC, Annex II, Labelling and PL	
II/0009	This variation concerns an update of the SPC following the completion of a class safety review by the PhVWP and the CHMP. The safety review was initiated because recent data show a consistent unexplained excess mortality in cancer patients with anaemia treated with epoetins. As a result, CHMP requested to update section 4.4 of the SPC to include an additional ESA class warning in the epoetins with cancer indication. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	29/10/2008	SmPC and PL	This variation concerns an update of the SPC following the completion of a class safety review by the PhVWP and the CHMP. The safety review was initiated because recent new available data from studies that showed an increased risk of tumour progression, venous thromboembolism and shorter overall survival in cancer patients who received epoetins compared to patients who did not receive them. Following this review, the CHMP concluded, at its June 2008 meeting, that the benefits of epoetins continue to outweigh their risks in the approved indications. However, in cancer patients with a reasonably long life-expectancy, the benefit of using epoetins does not outweigh the risk of tumour progression and shorter overall survival and therefore the Committee concluded that in these patients anaemia should be corrected

					with blood transfusions. The decision to administer epoetin-containing medicines should be based on an informed assessment of the benefits against the risks on individual basis, taking into account the type and stage of tumour, the degree of anaemia, the patient's life-expectancy, the environment in which the patient is being treated and patient preference. As a result, Section 4.4 of the SPC and section 2 of the Package Leaflet are being updated to reflect these conclusions by incorporating wording requested by CHMP for inclusion for all epoetins for which a cancer indication is licensed.
II/0008	The Marketing Authorisation Holder applied for revised storage conditions for sterile formulated bulk. Change(s) to the manufacturing process for the finished product	25/09/2008	03/10/2008		
IA/0007	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/07/2008	n/a		
II/0001	New presentation(s)	30/05/2008	08/07/2008	SmPC, Labelling and PL	
II/0004	The Marketing Authorisation Holder applied to change the method and specification for the analysis of sialic acids per mol epoetin. Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	30/06/2008		

II/0003	Change(s) to the manufacturing process for the active substance	30/05/2008	05/06/2008		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/05/2008	n/a	PL	
II/0002	Update of Summary of Product Characteristics and Labelling	24/01/2008	29/02/2008	SmPC and Labelling	This variation primarily concerns an update of the SPC following the completion of a class safety review by the PhVWP and the CHMP. The safety review was initiated because recent data show a consistent unexplained excess mortality in cancer patients with anaemia treated with epoetins, and that treatment of anaemia with epoetins in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with an increase in the risk of mortality and cardiovascular morbidity. As a result, the main changes being implemented are: i) in section 4.1, to highlight that epoetins should be used only if associated with symptoms, ii) in Section 4.2 to establish a uniform target haemoglobin range for all epoetins, iii) in Section 4.4 to mention the observed negative benefit risk balance in patients treated with high target haemoglobin concentrations, and iv) in section 5.1 to include the relevant results of the trials triggering the safety review. In addition, minor details in the labelling have been amended.