



## Silapo

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	Summary
IB/0061	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	05/11/2020		SmPC, Labelling and PL	

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



IB/0060	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/09/2020	n/a		
IA/0059	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)	20/04/2020	n/a		
IB/0057/G	This was an application for a group of variations.  B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	23/03/2020		SmPC and Labelling	
II/0056	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	19/03/2020	n/a		
IAIN/0058	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/03/2020	n/a		

IB/0055/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>	20/01/2020		SmPC, Annex II, Labelling and PL	
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IA/0054	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)	19/11/2019	n/a		

IA/0053	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	18/11/2019	n/a		
IB/0052/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p>	28/11/2018	18/01/2019	SmPC and PL	
PSUSA/1241/201712	Periodic Safety Update EU Single assessment - epoetin zeta	12/07/2018	n/a		PRAC Recommendation - maintenance
IB/0050	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	04/04/2018	n/a		

IB/0049	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)	10/01/2018	n/a		
IAIN/0048	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/09/2017	06/09/2018	SmPC, Annex II, Labelling and PL	
IA/0047	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)	10/08/2017	n/a		
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2017	06/09/2018	PL	
II/0045	<p>Submission of the final report from the registry based healthcare database study linked to PASCO (PMS-830-07-0043)) listed as a category 3 study in the RMP. This is an observational study on the incidence of thromboembolic events in patients with renal anaemia treated with erythropoietin-zeta as compared with erythropoietin-alpha and other erythropoiesis-stimulating agents. In addition, an updated RMP (version 11) is submitted to reflect the outcome of the study.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	06/07/2017	n/a		<p>The submitted study is a registry based health care database study (HDBS-study) linked to PASCO (Post-Authorisation Safety Cohort Observation of Epoetin zeta Administered Intravenously for the Treatment of Renal Anaemia). The study aimed to compare the crude incidence rate (with 95% CIs) of thromboembolic events in patients with renal anaemia treated with epoetin zeta vs. other epoetins (including epoetin alpha). Overall, no increased thromboembolic risk for epoetin zeta compared to the other epoetins in clinical practice can be derived from the data provided. No new safety concern associated with epoetin zeta was identified. The findings did not warrant changes to the product information.</p>

II/0044	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	23/02/2017	n/a		
IB/0043	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	11/11/2016	n/a		
IA/0042/G	This was an application for a group of variations.  A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	08/04/2016	n/a		
IB/0041	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	31/03/2016	n/a		
PSUSA/1241/201412	Periodic Safety Update EU Single assessment - epoetin zeta	10/09/2015	n/a		PRAC Recommendation - maintenance
IB/0039	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/08/2015	16/10/2015	SmPC and PL	
IA/0040	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/07/2015	n/a		
II/0037	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP -	25/06/2015	n/a		



	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				
II/0035	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	23/04/2015	n/a		
IAIN/0036	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	06/03/2015	n/a		
II/0034	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	18/12/2014	n/a		
IAIN/0033	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2014	16/10/2015	SmPC, Annex II and PL	
II/0031/G	This was an application for a group of variations.  C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority  C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		

IB/0032/G	<p>This was an application for a group of variations.</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p>	27/02/2014	n/a		
IB/0030/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p>	16/12/2013	n/a		
II/0029	<p>Upscaling of the manufacturing process of the drug substance.</p> <p>B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS</p>	19/09/2013	n/a		

IB/0028/G	<p>This was an application for a group of variations.</p> <p>B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product</p> <p>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</p>	08/04/2013	n/a		
IB/0027	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	09/10/2012	n/a		
R/0026	Renewal of the marketing authorisation.	24/05/2012	26/07/2012	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 Silapo 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 Silapo, 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 three-yearly PSURs unless otherwise specified by the CHMP.
II/0025	To register a new manufacturing site for the finished product	24/05/2012	24/05/2012		

	B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product				
IB/0024	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	26/05/2011	n/a	SmPC	
II/0020	To introduce changes to the Epoetin Reference Standard Material.  B.I.b.z - Change in control of the AS - Other variation	17/02/2011	28/02/2011		
IB/0023	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)	18/01/2011	n/a		
IB/0021	B.I.a.z - Change in manufacture of the AS - Other variation	18/01/2011	n/a		
IB/0022	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	17/01/2011	n/a	SmPC, Annex II and PL	
IB/0019	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	27/08/2010	n/a		

IB/0018	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	27/08/2010	n/a		
IB/0017	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	27/08/2010	n/a		
II/0014	<p>Addition of a subcutaneous route of administration in the indication of "anaemia associated with CRF on haemodialysis and patients on peritoneal dialysis" and "severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing analysis". SPC sections 4.2 and 4.4, and the Package Leaflet sections outlining the mode of administration of Epoetin zeta have been amended.</p> <p>Conditions or restrictions with regard to the safe and effective use of the medicinal product as detailed in Annex IIB have been lifted.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	18/02/2010	06/04/2010	SmPC, Annex II and PL	<p>The scope of this variation is to apply for the addition of the subcutaneous route of administration in the indication "Treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis" and "Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis".</p> <p>As a result of this variation, the respective SPC/PL-sections outlining the mode of administration of Epoetin zeta have been amended. Consequently the section "Conditions or restrictions with regard to the safe and effective use of the medicinal product" in Annex IIB has been removed as it currently refers to off-label SC use of Epoetin zeta.</p>
IB/0016	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	05/03/2010	n/a	SmPC and PL	

II/0015	<p>This variation concerns an update of the SPC following the completion of a class safety review by the PhVWP and the CHMP. As a result, CHMP requested to update section 4.4 of the SPC to include more information on 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.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	19/11/2009	16/12/2009	SmPC	<p>As a result of the discussion of the updated RMPs and the results of the Cochrane meta-analysis 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 SPC.</p> <p>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.</p>
II/0013	<p>The MAH applied to introduce changes to the premises of the manufacturing process of the active substance.</p> <p>11_Change in or addition of manufacturer(s) of active substance</p>	24/09/2009	05/10/2009		
II/0012	<p>This variation concerns an update of the SPC following the completion of a class safety review by the PhVWP and the CHMP. 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. In addition, the MAH has made some additional changes to Sections 4.2 and 5.1 of the current SPC The Package Leaflet has been updated accordingly.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	23/10/2008	24/11/2008	SmPC and PL	<p>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.</p> <p>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. In addition The MAH has made changes in section 4.2 and 5.1 of the SPC in order to clarify the posology and method of administration of the</p>

					product and align the text with CHMP recommendations.
II/0011	The Marketing Authorisation Holder applied for a modification of analytical methods used in the manufacturing process of the active substance.  Change(s) to the manufacturing process for the active substance	25/09/2008	03/10/2008		
II/0001	Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/06/2008	13/08/2008	SmPC, Labelling and PL	<p>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.</p> <p>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. The package leaflet has also been updated accordingly.</p> <p>The MAH also took this opportunity to perform some minor changes in section 6.4 of the SPC, in the Package Leaflet</p>

					and in the outer labelling and to amend the list of local representatives in the Package Leaflet.
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	08/08/2008	n/a	SmPC	
IB/0009	IB_37_a_Change in the specification of the finished product - tightening of specification limits	06/08/2008	n/a		
IB/0008	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	31/07/2008	n/a		
II/0002	Change(s) to shelf-life or storage conditions	30/05/2008	22/07/2008	SmPC and PL	
IA/0007	IA_05_Change in the name and/or address of a manufacturer of the finished product	18/07/2008	n/a		
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	13/05/2008	13/05/2008	SmPC, Labelling and PL	
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	13/05/2008	13/05/2008	SmPC, Labelling and PL	
IB/0004	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	13/05/2008	13/05/2008	SmPC, Labelling and PL	
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	24/04/2008	n/a		