Aranesp

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
N/0162	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2022		Labelling	
II/0161	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a	27/10/2022	n/a		

[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).

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	biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
IB/0160	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/05/2022	n/a		
II/0158	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	17/03/2022	n/a		
II/0157/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	13/01/2022	n/a		
N/0159	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2021	19/05/2022	PL	
II/0156	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	28/10/2021	n/a		

	Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method				
WS/2026	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.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	08/07/2021	n/a		
PSUSA/932/202010	Periodic Safety Update EU Single assessment - darbepoetin alfa	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0153	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/02/2021	19/05/2022	SmPC and PL	
IB/0152/G	This was an application for a group of variations. 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.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)	02/12/2020	n/a		

II/0150	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	06/02/2020	SmPC, Labelling and PL	
II/0151	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	27/06/2019	n/a		
II/0148	Update of Annex IID to implement information on education materials proposal to address the incorrect self-administration of Aranesp via the SureClick pre-filled pen and associated dosing errors. The RMP (version 9.2) is updated accordingly and aligned to the latest GVP Module revision 2. 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	14/02/2019	06/02/2020	Annex II	
IB/0149	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	20/12/2018	n/a		
PSUSA/932/201710	Periodic Safety Update EU Single assessment - darbepoetin alfa	14/06/2018	n/a		PRAC Recommendation - maintenance
IG/0946	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	04/06/2018	23/08/2018	PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IG/0853	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	10/11/2017	23/08/2018	Annex II and PL	
II/0143	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	23/08/2018	SmPC and PL	Update of section of section 4.2 and 4.8 of the SmPC in order to add information that Aranesp may be administered by the patient or carer after being trained by a doctor and a warning on injection site bruise and haemorrhage with frequency unknown. The package leaflet has been updated to provide additional instructions on the use of the device in the PL following signal procedure EMEA/H/C000332/SDA/090 on cases of incorrect device use / device malfunction
II/0141	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on severe cutaneous conditions including Erythema multiforme and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) following a request for cumulative review triggered by EMA signal adopted by PRAC on 09 February 2017. The Package Leaflet is updated accordingly. The RMP version 7.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	20/07/2017	24/08/2017	SmPC, Labelling and PL	Update of section 4.4 and section 4.8 of the SmPC following a cumulative review of the reported cases of a signal initiated by the Pharmacovigilance Risk Assessment Committee (PRAC) EPITT no: 18846. The update includes the introduction of a class warning that severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins. The SmPC and RMP have been updated accordingly. In addition, a direct healthcare professional communication (DHPC) letter

	data				is being distributed to inform about this risk.
IAIN/0140	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/03/2017	24/08/2017	Annex II and PL	
IB/0139	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	23/01/2017	n/a		
II/0137/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits 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 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 B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant	15/09/2016	n/a		

	effect on the overall quality of the AS B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP 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 B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
IA/0138	A.7 - Administrative change - Deletion of	07/09/2016	n/a		

	manufacturing sites				
IB/0136	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/02/2016	n/a		
II/0135/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	17/12/2015	n/a		
IB/0134	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2015		SmPC and PL	
II/0130	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to reflect the available data in the paediatric population. Additional changes are included to reflect the latest QRD template. The labelling and Package leaflet have been updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to	25/06/2015		SmPC, Annex II, Labelling and PL	This type II variation for Aranesp (darbepoetin alfa) is based on the availability of study 20050256 conducted in paediatric patients and submitted under an Article 46 procedure. The scope of this variation includes amendments to the Summary of Product Characteristics to incorporate dosing recommendations for paediatric patients from 1 to < 11 years of age in section 4.2 and include updates to section 4.8, 5.1 and 5.2 to reflect the available data in the paediatric population. Consequential changes in the PIL have also been proposed.

	new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/932/201410	Periodic Safety Update EU Single assessment - darbepoetin alfa	11/06/2015	n/a		PRAC Recommendation - maintenance
WS/0660	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	26/03/2015	n/a		
II/0129	to introduce a real time release testing parameter in the manufacture of the finished product B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	20/11/2014	n/a		to introduce a real time release testing parameter in the manufacture of the finished product
II/0128	to submit a post-approval change management protocol related to the finished product B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	20/11/2014	n/a		to submit a post-approval change management protocol related to the finished product
IB/0131/G	This was an application for a group of variations.	12/11/2014		SmPC	

	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0122/G	This was an application for a group of variations. To include an alternative primary container closure system and its supplier B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	25/09/2014	n/a		To include an alternative primary container closure system and its supplier
IB/0127	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	12/08/2014	n/a		
IA/0126	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	12/08/2014	n/a		
IB/0125	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/08/2014	n/a		

II/0123/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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 B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	24/07/2014	n/a		
N/0124	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/05/2014	16/09/2014	SmPC	
II/0121	to add a new manufacturing site for testing of the finished product 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	22/05/2014	n/a		
IB/0120	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a	04/02/2014	n/a		

	biological/immunological medicinal product				
II/0118	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	23/01/2014	n/a		
IA/0119	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2013	n/a		
II/0117	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/11/2013	n/a		
II/0116	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/11/2013	n/a		
IAIN/0115	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	13/09/2013	n/a		
IB/0114	B.IV.1.z - Change of a measuring or administration device - Other variation	12/09/2013	16/09/2014	Labelling and PL	
IA/0113	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	16/08/2013	n/a		

II/0112	Addition of new manufacturing site of Drug product testing. B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method	25/07/2013	n/a		
II/0108	Update of section 4.2 of the SmPC in relation to new data supporting a QM dosing schedule for darbepoetin alfa for the correction phase in patients not on dialysis with chronic renal failure (adults only) from Study 20060163. Additionally, section 5.1 of the SmPC has been updated with the study results from the trial supporting the new dosing schedule. The Package Leaflet was updated accordingly, with instructions to the SureClick pre-filled pen presentation. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version v.9 The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	27/06/2013	25/07/2013	SmPC, Annex II, Labelling and PL	

	clinical, clinical or pharmacovigilance data				
IB/0111	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	14/05/2013	n/a		
IAIN/0110	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/03/2013	n/a		
IG/0247	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2012	n/a		
IB/0107/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	07/11/2012	n/a		
IAIN/0106	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	15/08/2012	29/10/2012	Annex II and PL	
N/0103	Changes in the local representative details for Cyprus, Spain, Greece, Poland, Slovenia and Portugal in the package leaflet. Minor change in labelling or package leaflet not	07/08/2012	29/10/2012	PL	

	connected with the SPC (Art. 61.3 Notification)				
IA/0105	A.7 - Administrative change - Deletion of manufacturing sites	20/07/2012	n/a		
II/0100	To introduce a post-approval change management protocol to introduce a new manufacturing site for Aranesp finished product. B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	19/07/2012	19/07/2012		
IB/0101	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/06/2012	n/a		
IAIN/0104/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.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	16/05/2012	n/a		
IAIN/0102	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/04/2012	n/a		

IB/0099	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/03/2012	n/a		
IB/0098	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	27/01/2012	n/a		
N/0097	The MAH has updated the package leaflets to improve the instructions for use of Automatic Needle Guard (ANG) presentation. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2011	29/10/2012	PL	
II/0092/G	This was an application for a group of variations. Update of section 4.8 of the SmPC with adverse events concerning the TREAT study. Inclusion of a cross reference in section 4.1 to 4.2 of the SmPC , and alignment of this latter section regarding paediatric patients from birth to 18 years of age in the renal anaemia indication. Update of section 4.9 of the SmPC concerning information about overdose with darbepoetin alfa. Inclusion of a pregnancy surveillance programme in section 4.6 of the SmPC	20/10/2011	05/12/2011	SmPC, Labelling and PL	In the present variation, the MAH suggested an extensive amendment of the Product Information including an update of section 4.8 of the SmPC to include tabular listings and comments concerning safety results of the TREAT study. The MAH also wished to align the reference to the paediatric population "from birth to 18 years of age"in section 4.2 with section 4.1 of the SmPC. Other updates have been made to section 4.6 (pregnancy surveillance program), 4.9 (overdose) of the SmPC, sections 2, 3, 4 and 7 of the Package Leaflet as well as changes to the details of local representatives. The MAH has also updated the product information in line with latest QRD template and SmPC guidance.

	Minor changes to the instructions for use in the PL and administrative changes to formatting, consistency and details of local representatives (SmPC and PIL). In addition to this, the Marketing Authorisation Holder has taken the opportunity to update the product information in line with latest QRD template and SmPC guidance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IA/0096	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	12/08/2011	n/a		
IB/0093/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	28/07/2011	n/a		
IA/0095/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance	28/06/2011	n/a		

	system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0094/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	09/06/2011	n/a		
IB/0091/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/04/2011	n/a		
II/0090	To widen specification limits for Aranesp pre-filled pen drug product.	14/04/2011	15/04/2011		

	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
X/0084	To register vial presentations of 25, 40, 60 100, 200 and 300 µg/mL at 1.0 mL fill. Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(c) Change or addition of a new strength/potency	16/12/2010	28/02/2011	SmPC, Labelling and PL	
II/0087	Update of section 4.4 "Special Warnings and Precautions" of the Summary of Product Characteristics (SmPC) to add a warning to specify that cases of severe hypertension have been seen in chronic renal failure (CRF) patients treated with Aranesp, including cases of hypertensive crisis, hypertensive encephalopathy and seizure, following a review of post marketing safety data conducted at the request of the CHMP following the 10th Periodic Safety Update Report (PSUR) The Package Leaflet (PL) has been updated accordingly. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update section 7 of the PL of pre-filled syringes with automatic needle guard, with minor editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	18/11/2010	20/12/2010	SmPC and PL	Further to the request of the CHMP following the assessment of PSUR 10, the MAH has conducted a review of post-marketing data and concluded that there have been several cases of severe hypertension including hypertensive crisis, hypertensive encephalopathy and seizures in the chronic renal failure (CRF) indication for which a causative role for Aranesp could not be ruled out. Therefore, the MAH has included a warning in section 4.4 of the SmPC to specify that cases of severe hypertension, including hypertensive crisis, hypertensive encephalopathy, and seizures, have been observed in CRF patients treated with Aranesp. The MAH has also updated section 2. "Before you use Aranesp" of the PL to align it with the SmPC, reflecting concerns that chronic renal failure patients, treated with Aranesp and exhibiting symptoms of high blood pressure should contact their doctor. Minor editorial changes have been made to section 7 of the PL.

	clinical, clinical or pharmacovigilance data				
II/0086	Update of section 4.4 "Special Warnings and Precautions" and 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to include an additional warning related to the increased incidence of stroke in the TREAT population, and implementation of an additional description of the outcome of the TREAT study in section 5.1 "Pharmacodynamic Properties" of the SmPC. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update Section 2 "Before you use Aranesp" of the Package leaflet accordingly. Annex II B has been updated in line with the EC decision to delete the version number of the DDPS. Minor linguistic changes have been made to Section 4.2 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC, Annex II and PL	Further to the request of the CHMP regarding the assessment of outcome of Study 20010184 "Trial to Reduce Cardiovascular Events with Aranesp Therapy" (TREAT) in March 2010, the MAH has reflected additional warnings and the results of the TREAT study in the current product information for Aranesp. The MAH has also updated section 2. "Before you use Aranesp" of the PL to align it with the SmPC, reflecting the concern that elevated haemoglobin concentrations could increase the risk of myocardial infarction, stroke and death.
IB/0089	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	29/11/2010	n/a		
IA/0088/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance	09/11/2010	n/a	Annex II	

	system as described in the DDPS - Change in the safety database C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0085/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.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.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	25/08/2010	n/a	Annex II	
II/0082	Update of Section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to include hypertension as an adverse reaction identified in the post-marketing setting further to the request of the CHMP following assessment of a cumulative review submitted in response to the assessment of the 10th PSUR. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update Section 4. "Possible Side	24/06/2010	28/07/2010	SmPC and PL	Further to the request of the CHMP in the assessment of the 10th PSUR of Aranesp, the MAH conducted a review of cases of hypertension. All cases of this adverse reaction were "medically confirmed" (assumption of causality in post-marketing). Therefore, the MAH was requested to include "hypertension" as an adverse drug reaction to Aranesp reported during the post-marketing setting in section 4.8 of the SmPC. It has also been reflected that it is not possible to confirm the frequency of this ADR since the

	Effects" of the Package Leaflet to align it with the SmPC and describe adverse reactions from either clinical trial or post-marketing experience. The MAH also took the opportunity to make with minor editorial changes to the SmPC and 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 - Change(s) with new additional data submitted by the MAH				cases on which this addition is based were identified in the post-marketing setting. Furthermore, the MAH further clarified that frequency can not be estimated for other undesirable effects identified in the post-marketing setting including convulsions and allergic reactions. The MAH has also taken this opportunity to update section 4. "Possible Side Effects" of the PL to align it with the SmPC and describe adverse reactions from either clinical trial or post-marketing experience.
II/0081	Update of section 4.4 of the Summary of Product Characteristics (SmPC) in order to implement the CHMP/PhVWP 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 been updated accordingly. The list of local representatives in the Package Leaflet was also updated. 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	24/06/2010	28/07/2010	SmPC 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 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 (SmPC) and Package Leaflet (PL) of

					Aranesp, 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 Section 2. Before you use Aranesp: "Take special care with other products that stimulate red blood cell production": Aranesp is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional should always record the exact product you are using. "
IB/0083	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	01/06/2010	n/a		
IA/0080/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	31/03/2010	n/a	Annex II and PL	
II/0079	This variation concerns an update of the SPC following the completion of a class safety review by	21/01/2010	23/03/2010	SmPC, Labelling and	As a result of the discussion of the updated risk management plans (RMPs) and the results of the Cochrane

	the PhVWP 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 to update section 5.1 of the SPC to include additional data on the Cochrane meta-analysis and the effects of epoetins in cancer patients. The Package leaflet Section 2 has also been updated accordingly. Furthermore, the contact details for the local representatives in Bulgaria and Slovenia have been updated in the Package Leaflet, and Section 16 of the Labelling has been amended to reflect all strengths in Braille. Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	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 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. In addition, Section 2 of the Package leaflet has also been updated accordingly. Furthermore, the contact details for the local representatives in Bulgaria and Slovenia have been updated in the Package Leaflet and Section 16 of the Labelling was amended to reflect all strengths in Braille.
II/0078	To reduce the current overfill volume for Aranesp (darbepoetin alfa) 0,4 ml Pre-filled Syringe (PFS) presentation. Quality changes	21/01/2010	09/02/2010		
II/0076	Revision of the method for potency testing of Aranesp drug substance and drug product. Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	25/11/2009		

	Change(s) to the test method(s) and/or specifications for the finished product				
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2009	n/a	PL	
II/0075	Update of SPC sections 4.2 "Posology", 4.4 "Special Warnings and Precautions for Use", 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic properties" in accordance with amendments to the Company Core Data Sheet. The SPC is also being updated throughout to correct use of "erythropoetic protein" to "erythropoeisis-stimulating agent (ESA)". The Package Leaflet has been amended accordingly. Update of Package Leaflet section "If you use more Aranesp than you should". Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	Update of SPC sections 4.2, 4.4, 4.8 and 5.1. The amendment in section 4.2 (Posology and method of administration) is the conversion from r-HuEPO to Aranesp in Paediatric Chronic Renal Failure (CRF) Patients. The CHMP is the opinion that the addition of information about initial dosing for the once every other week schedule for paediatric patients is clearer. This is in line with the posology guidance for CRF adult patients and may avoid dosing errors when converting from r-HuEPO to a once every other week schedule. Amendment in section 4.4 (Special Warnings and Precautions for Use) is to remove redundant reference to Epilepsy. In section 4.8 (Undesirable effects) the amendment is to replace reference to "Dyspnoea" with "Allergic Bronchospasm.The MAH has carried out a safety assessment of allergic reactions responsible for dyspnoea in patients on darbepoetin alfa or epoetin alfa therapy in order to evaluate allergic reactions other than anaphylactic reactions or angioedema that can be responsible for dyspnoea and occur in association with darbepoetin alfa and epoetin alfa therapy. Based on these findings, the event "allergic bronchospasm" has been added to the list of allergic reactions associated with darbepoetin alfa or epoetin alfa therapy within the CDS for darbepoetin alfa.

					The SPC is also being updated throughout to correct use of "erythropoetic protein" to "erythropoeisis-stimulating agent (ESA)". The Package Leaflet has been amended accordingly. Update of Package Leaflet section "If you use more Aranesp than you should".
IA/0074	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	22/04/2009	SmPC, Labelling and PL	
IA/0073	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0072	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0071	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0070	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0069	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0068	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	

IA/0067	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0066	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0065	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0064	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0063	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0062	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0061	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0060	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0059	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	

IA/0058	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0057	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0056	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0055	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0054	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0053	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0052	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0051	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
IA/0050	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	

IA/0049	IA_28_Change in any part of primary packaging material not in contact with finished product	20/04/2009	20/04/2009	SmPC, Labelling and PL	
II/0045	Change(s) to the manufacturing process of the finished product. Change(s) to the manufacturing process for the finished product	20/11/2008	01/12/2008		
II/0048	Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	28/10/2008	SmPC and PL	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. 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
II/0046	Update of Detail Description of the Pharmacovigilance System (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	25/09/2008	28/10/2008	Annex II	The Marketing Authorisation Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS). There have been no significant changes made to the MAH's pharmacovigilance systems. Version 3.0 of the DDPS has been updated in line with the summary of pharmacovigilance systems submitted in May 2008. The changes are administrative and provide further clarity on the pharmacovigilance systems in place.
II/0044	Update of sections 4.4 and 4.8 of the SPC following an update of the Company Core Data Sheet. The	24/07/2008	01/09/2008	SmPC and PL	Update of sections 4.4 and 4.8 of the SPC following an update of the Company Core Data Sheet. The package

	package leaflet has also been amended accordingly. The MAH also introduced a Getting Started Guide (GSG) as additional information to the package leaflet. Update of Summary of Product Characteristics and Package Leaflet				leaflet has also been amended accordingly. The MAH also introduced a Getting Started Guide (GSG) as additional information to the package leaflet.
IA/0047	IA_47_c_Deletion of a pack size(s)	29/07/2008	n/a	SmPC, Labelling and PL	
X/0042	Annex I_1.(d) Modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source	24/04/2008	03/07/2008	Annex II	
II/0043	Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	26/02/2008	SmPC and PL	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. The package leaflet has also been updated accordingly. Additional sections 2, 4.9 and 5.2 have also been amended to correct minor inconsistencies. In addition, the MAH has taken this opportunity to re-format the approved package leaflet and take into account the results of user testing.
II/0035	The MAH has submitted an extension of indication to allow treatment to CRF paediatric subjects >/=11 years of age. As a result, sections 4.1, 4.2 and 5.2 of the SPC have been updated. New data from efficacy and safety based study 20000100 supports removing this restriction, and allow treatment of all ages of CRF paediatric subjects, in addition to adults. As a result of this, section 4.2 of the SPC has also been updated to provide clarity over dosing paediatric subjects. The data from pharmacokinetic (PK) study 20000126 investigated in paediatric subjects with nonmyeloid malignancies who were receiving chemotherapy supports an additional statement in section 5.2 of the SPC. The limited PK data in paediatric subjects receiving chemotherapy is only supportive of a statement in section 5.2 of the SPC, with regards to the study findings. The package leaflet was updated accordingly. Extension of Indication	19/07/2007	30/08/2007	SmPC and PL	Please refer to the Scientific Discussion: Aranesp-H-332-II-35-AR.

N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/07/2007	n/a	PL	
II/0039	New presentation(s)	22/03/2007	02/05/2007	SmPC, Labelling and PL	
II/0040	Change(s) to the manufacturing process for the finished product	22/03/2007	26/03/2007		
II/0038	Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	29/11/2006	SmPC and PL	To amend sections 4.2 and 5.1 of the SPC in response to CHMP request (FUM 056) requiring the MAH to remove the recommendation for dose increase in patients receiving darbepoetin alfa once weekly with an inadequate response. The Package Leaflet has been amended accordingly.
II/0037	Update of Summary of Product Characteristics	21/09/2006	30/10/2006	SmPC	The MAH has applied to amend section 5.1 of the SPC to modify the language relating to influence of darbepoetin alfa on tumour progression and survival for lymphoproliferative subjects treated with darbepoetin alfa.
II/0034	Change(s) to the manufacturing process for the active substance	27/07/2006	03/08/2006		
IB/0036	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	31/07/2006	31/07/2006	SmPC, Labelling and PL	
R/0033	Renewal of the marketing authorisation.	23/03/2006	19/05/2006	SmPC, Labelling and	

				PL	
II/0032	Update of or change(s) to the pharmaceutical documentation	23/02/2006	28/02/2006		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	The MAH has applied to amend sections 4.2 and 5.2 to modify the posology for patients with chronic renal failure switching from recombinant human erythropoietin to darbepoetin alfa during the maintenance phase of treatment. The Package Leaflet has also been amended accordingly.
II/0030	Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	08/09/2005	SmPC and PL	The MAH has applied to update sections 4.4 and 4.8 of the SPC in relation to Pure Red Cell Aplasia. The Package Leaflet has also been updated accordingly.
II/0029	Change(s) to the manufacturing process for the active substance	27/07/2005	03/08/2005		
II/0028	Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	08/07/2005	SmPC and PL	Please refer to the Scientific Discussion: Aranesp-H-332-II-28
II/0027	The Marketing Authorisation Holder applied to change the product specifications. Quality changes	16/03/2005	23/03/2005		
II/0026	The Marketing Authorisation Holder applied to add a new pre-filled pen injection device to the product range. New presentation(s)	20/01/2005	28/02/2005	SmPC, Labelling and PL	

II/0024	Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	09/09/2004	SmPC and PL	The marketing authorisation holder applied to support the extension of the dosing intervals in the treatment of anaemia associated with chronic renal failure in adults and paediatric subjects 3 11 years of age (once monthly) and in adults with chemotherapy-induced anaemia (once every three week). The SPC and Package Leaflet have been updated accordingly.
IA/0025	IA_28_Change in any part of primary packaging material not in contact with finished product IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	26/05/2004	26/05/2004	SmPC, Labelling and PL	
II/0022	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	14/04/2004	SmPC and PL	The marketing authorisation holder applied to introduce additional text to Section 4.4 "Special Warnings and Special Precautions for Use" and Section 4.8 "Undesirable Effects" of the SPC. The package leaflet has been updated accordingly.
II/0021	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	21/01/2004	21/01/2004		
II/0015	Extension of Indication	22/05/2003	11/08/2003	SmPC and PL	
II/0019	Update of or change(s) to the pharmaceutical documentation Change(s) to the test method(s) and/or specifications for the finished product	24/07/2003	28/07/2003		
I/0017	01_Change in or addition of manufacturing site(s) for	10/04/2003	23/04/2003		

	part or all of the manufacturing process				
I/0018	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	03/04/2003	08/04/2003		
I/0016	16_Change in the batch size of finished product	19/03/2003	02/04/2003		
II/0013	Update of Summary of Product Characteristics and Package Leaflet	21/11/2002	27/02/2003	SmPC and PL	
II/0003	New presentation(s) Extension of Indication	30/05/2002	22/08/2002	SmPC, Labelling and PL	
I/0008	11_Change in or addition of manufacturer(s) of active substance 12_Minor change of manufacturing process of the active substance	27/06/2002	30/07/2002	Annex II	
I/0010	13_Batch size of active substance	27/06/2002	10/07/2002		
I/0009	12_Minor change of manufacturing process of the active substance	27/06/2002	10/07/2002		
I/0011	25_Change in test procedures of the medicinal product	21/06/2002	03/07/2002		
I/0007	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	29/05/2002	31/05/2002		

I/0006	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	11/04/2002	16/05/2002		
I/0005	24_Change in test procedure of active substance	11/04/2002	16/05/2002		
I/0004	01_Change in the name of a manufacturer of the medicinal product	11/04/2002	16/05/2002		
I/0002	20a_Extension of shelf-life or retest period of the active substance	13/07/2001	23/10/2001		
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	13/07/2001	n/a	SmPC	