Mircera

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0096	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/12/2023		SmPC, Annex II and PL	
II/0092	Extension of indication to include treatment of paediatric patients from 3 months to less than 18 years of age who are converting from another	22/06/2023	26/07/2023	SmPC, Labelling and	Please refer to Scientific Discussion 'Mircera-H-C-000739-II-0092.

[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).

	erythropoiesis stimulating agent (ESA) after their haemoglobin level was stabilised with the previous ESA. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the Instruction for Use in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			PL	
WS/2414/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	14/04/2023	n/a		
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2023	26/07/2023	PL	
IA/0091/G	This was an application for a group of variations.	10/06/2022	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/2242	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/06/2022	n/a		
IB/0089	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/03/2022	n/a		
IG/1462/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/02/2022	n/a		

IB/0087	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/12/2021	28/11/2022	SmPC, Annex II, Labelling and PL	
WS/2161	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	02/12/2021	n/a		
IA/0086/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	03/11/2021	n/a		
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2021	28/11/2022	PL	
PSUSA/2017/202007	Periodic Safety Update EU Single assessment - methoxy polyethylene glycol-epoetin beta	11/03/2021	n/a		PRAC Recommendation - maintenance
WS/1935	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.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial	28/01/2021	n/a		

	change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
WS/1914/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.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	19/11/2020	n/a		
IA/0082/G	This was an application for a group of variations. 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 B.II.e.6.b - Change in any part of the (primary)	10/11/2020	n/a		

	packaging material not in contact with the finished product formulation - Change that does not affect the product information				
II/0078/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.z - Change in control of the AS - Other variation	05/06/2020	n/a		
IB/0079	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	14/05/2020	n/a		
IB/0077	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	30/03/2020	n/a		

II/0068	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	22/10/2020	SmPC, Annex II and Labelling	
IA/0076	A.7 - Administrative change - Deletion of manufacturing sites	19/08/2019	n/a		
IB/0075	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	07/03/2019	n/a		
IG/1070	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	04/03/2019	n/a		
IG/1049/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change	17/01/2019	n/a		

	to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IG/0997/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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/11/2018	n/a		
WS/1481	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/11/2018	n/a		
II/0067	Submission of the final study results from Study NH 19707(Dolphin): an open-label, multi-center, multiple dose study to determine the optimum starting dose of intravenous Mircera for maintenance treatment of anemia in paediatric patients with chronic kidney disease on hemodialysis; listed in the paediatric investigation plan (PIP).	15/11/2018	n/a		Please refer to Scientific Discussion Mircera-H-C-00739-II-0067.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0070	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	25/10/2018	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	22/10/2020	PL	
T/0066	Transfer of Marketing Authorisation	20/02/2018	16/03/2018	SmPC, Labelling and PL	
PSUSA/2017/ 201707	Periodic Safety Update EU Single assessment - methoxy polyethylene glycol-epoetin beta	08/03/2018	n/a		PRAC Recommendation - maintenance
IA/0065	B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits	15/12/2017	n/a		
II/0062/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for	28/09/2017	n/a		

	biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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				
IAIN/0063	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/09/2017	16/03/2018	SmPC and PL	
IA/0061/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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	28/06/2017	n/a		
IG/0736	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	19/10/2016	n/a		
N/0059	Update of Annex IIIA to add the 2D barcode unique identifier according to QRD template vs 10. Minor change in labelling or package leaflet not	18/08/2016	16/03/2018	Labelling	

	connected with the SPC (Art. 61.3 Notification)				
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2015	06/07/2016	PL	
IA/0058	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	30/10/2015	n/a		
II/0055/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to include the ADR 'Stevens Johnson syndrome / toxic epidermal necrolysis' under post-marketing experience, following the assessment of LEG 037. Further, section 4.8 has been revised in accordance with the current EU SmPC guidance to include a single table with adverse events from clinical studies and adverse reactions reported post-marketing. Furthermore, sections 4.2, 4.4 and 5.1 of the SmPC have been updated, upon request by PRAC following the assessment of LEG 032, to include an agreed class wording related to the risk of high cumulative doses in patients not responding to the treatment. The Package Leaflet has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/07/2015	06/07/2016	SmPC and PL	Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed. Patients should be monitored closely to ensure that the lowest approved effective dose of MIRCERA is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dl (7.45 mmol/l). Caution should be exercised with escalation of MIRCERA doses in patients with chronic renal failure. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered.

	data				
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
IA/0054/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	24/04/2015	n/a		
PSUSA/2017/ 201407	Periodic Safety Update EU Single assessment - methoxy polyethylene glycol-epoetin beta	12/02/2015	n/a		PRAC Recommendation - maintenance
IG/0497	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	18/11/2014	n/a		
IA/0051/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or	29/10/2014	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0050/G	This was an application for a group of variations. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/09/2014	15/12/2014	Annex II	
IB/0049/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits	12/06/2014	n/a		

IAIN/0048	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	13/05/2014	15/12/2014	SmPC, Labelling and PL	
PSUV/0046	Periodic Safety Update	05/02/2014	n/a		PRAC Recommendation - maintenance
IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2013	15/12/2014	SmPC, Annex II and PL	
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
WS/0299	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. minor changes to the manufacturing process of the active substance. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/09/2012	n/a		
II/0041/G	This was an application for a group of variations. To add changes to the specifications and test procedure for the active substance. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change	20/09/2012	n/a		

	(replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological 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.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.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.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting				

	material/intermediate B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
A20/0039	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 December 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the manufacturing site Roche Carolina Inc. (RCI), Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of Mircera and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	19/07/2012	20/09/2012		Please refer to the assessment report : EMEA/H/C/739/A-20/0039
R/0037	Renewal of the marketing authorisation.	16/02/2012	15/05/2012	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 Mircera 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 Mircera, 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/0161	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	14/03/2012	n/a		
IG/0125	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	06/12/2011	n/a		
II/0035	Update of section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to include "thrombocytopenia" as an adverse reaction following a review of spontaneous reports and uncontrolled post-marketing studies with Mircera. 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	22/09/2011	20/10/2011	SmPC	Although the analysis of platelet counts in placebo-controlled studies showed that there was no difference between Mircera and placebo treatment, and that there was a lack of first-dose effect in patients in controlled clinical trials, an update of the ADVENT safety database showed 44 events of thrombocytopenia from spontaneous reports and uncontrolled post-marketing studies. Therefore the MAH proposed to amend section 4.8 of the SmPC to state that a clinically relevant reduction in platelet counts is attributable to Mircera administration, although the frequency of this adverse event is unknown.
II/0034	Update of sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to include "Pure Red Cell Aplasia" (PRCA) as an adverse reaction. Section 2 of the Package Leaflet (PL) has been updated accordingly.	22/09/2011	20/10/2011	SmPC and PL	The first case of PRCA related to the use of Mircera confirmed by an independent external assessor was documented on the 21st of December 2010. Following such report, the MAH sought to include "pure red cell aplasia" as undesirable effect in sections 4.4 and 4.8 of the SmPC and Section 2 of the PL, as a safety follow-up action.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0092/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in 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	08/08/2011	n/a		
II/0032	to revise specification limits for the active substance. 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	23/06/2011	23/06/2011		
IB/0033	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	20/06/2011	n/a	SmPC and PL	
II/0031	Update of sections 4.4 "Special Warnings and precautions for use, and 4.8 "Undesirable effects" of the SmPC to reflect the risk of thrombosis including	19/05/2011	17/06/2011	SmPC and PL	The cumulative review of thrombosis and embolism resulting from the evaluation of PSUR 5 identified 17 cases of thrombosis and 9 cases of pulmonary embolism (PE)

	pulmonary embolism as requested by CHMP following the evaluation of PSUR 5. The Package Leaflet has been updated accordingly. 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				with fatal outcome in four cases of PE. Based on the absence of ADRs of embolism and thrombosis in the Mircera clinical database and considering that frequencies based on reporting rates from a spontaneous reporting system should not be used to assign frequency categories, the MAH has reported "frequency unknown" for embolism and thrombosis in Section 4.8 of the SmPC, and included thrombosis as a serious cardiovascular event in section 4.4 when haemoglobin concentrations are increased beyond 12g/dl. The Package Leaflet has been updated accordingly.
IB/0030/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.7.b - Deletion of - a strength	11/02/2011	n/a	SmPC, Annex II, Labelling and PL	The MAH has applied to split and amend the wording in the annexes for multipack presentations as well as to delete all vials and some pre-filled syringe presentations. Annex II.B has also been updated to delete the DDPS version number as per the latest QRD template.
II/0027	Update of section 4.2 of the SmPC to introduce a new dosing schedule of once-monthly subcutaneous administration of Mircera in patients who are not on dialysis and not currently treated with an erythropoiesis stimulating agent, based on the results of study NH20052. Sections 4.8 and 5.1 of the SmPC were also updated to reflect the new data. The Package Leaflet has been updated accordingly. Minor editorial changes to Annex II were also introduced. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	26/08/2010	SmPC, Annex II and PL	Following the results of study NH20052 comparing Mircera administered subcutaneously (sc) once every 4 weeks (153 patients) to darbepoetin alfa treatment administered either once per week or once every 2 weeks (154 patients) during a 20-week correction period and an 8-week evaluation period, the MAH submitted a type II variation to updated section 4.2 of the SmPC to include a new dosing schedule of once monthly sc administration of Mircera. Sections 4.8 and 5.1 were also updated to reflect the data from study NH20052.

IB/0029	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	23/08/2010	n/a	SmPC and PL	Inclusion of "anaphylactic reactions" as an adverse reaction in section 4.8 of the SmPC and in the Package Leaflet as a follow-up action to the assessment concerning Mircera PSUR 4 (Period 20.1.09 - 19.07.09).
IB/0028	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	22/07/2010	n/a	SmPC and PL	Inclusion in the SmPC and PL of all ESAs agents of a statement agreed in December 2009 by the PhVWP and the CHMP to allow identification and traceability of all epoetin products.
II/0022	This variation concerns an update of the SmPC following the completion of a class safety review by the PhVWP and the CHMP. As a result, CHMP requested to update SmPC section 4.4 to include more information on pure red cell aplasia (PRCA) in patients with hepatitis C treated with Interferon, Ribavirin and Epoetin, as well as SmPC section 5.1 to include additional data on the Cochrane meta-analysis and the effects of epoetins in cancer patients. Additionally, following the class label text describing the Cochrane analysis in section 5.1 the following product-specific wording has been implemented: " Mircera is not approved for treatment of patients with chemotherapy induced anaemia (see section 4.1), no patiens treated with Mircera were part of	22/04/2010	04/06/2010	SmPC and PL	As a result of the discussion of the updated risk management plans (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 summary of product characteristics (SmPC). 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 SmPC. The amendments of Sections 4.4 and 5.1 of the SmPC have been implemented as recommended by the PhVWP / CHMP. Additional product specific wording has been implemented to section 5.1.

	this data analysis". The Patient Leaflet has been amended to reflect the increased risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin and the risk of anaemia worsening in patients treated with interferon and ribavirin (e.g. patient with hepatitis C). Update of Summary of Product Characteristics and Package Leaflet				The Patient Leaflet has also been amended to reflect the increased risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin and the risk of anaemia worsening in patients treated with interferon and ribavirin (e.g. patient with hepatitis C).
II/0026	Roche - Update of the detailed description of the pharmacovigilance system (version 4.1). Annex II has been updated accordingly. In addition, Annex II has been updated in line with the latest QRD templates. Update of DDPS (Pharmacovigilance)	18/03/2010	29/04/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 4.1) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed core DDPS. In addition, Annex II has been updated in line with the latest QRD templates.
II/0024	To implement changes to the analytical methods and release specifications. Quality changes	21/01/2010	04/02/2010		
II/0023	To implement changes to the cultivation process for the drug substance and related changes. Quality changes	21/01/2010	04/02/2010		

IB/0025	To change the storage condition of the Mircera active substance. IB_17_b_Change in the storage conditions for the active substance	22/12/2009	n/a		
IB/0021	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/09/2009	25/09/2009	SmPC, Labelling and PL	
IB/0020	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/09/2009	25/09/2009	SmPC, Labelling and PL	
IB/0019	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/09/2009	25/09/2009	SmPC, Labelling and PL	
II/0013	The MAH applied for a reduction of the shelf life for the vials and reduced time for room temperature storage for the vials. Quality changes	19/02/2009	07/04/2009	SmPC and PL	
II/0012	to extend the shelf life for the prefilled syringes and patient convenience room temperature storage for pre-filled syringes. Quality changes	19/02/2009	07/04/2009		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/01/2009	n/a	PL	

IA/0015	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	08/01/2009	n/a	Annex II and PL	
IA/0014	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	06/01/2009	n/a		
X/0001	Annex I_2.(c) Change or addition of a new strength/potency	26/06/2008	05/09/2008	SmPC, Labelling and PL	The new presentations consists in 5 new Mircera pre-filled syringe strengths (30 micrograms/0.3 ml, 40 micrograms/0.3 ml, 60 micrograms/0.3 ml, 120 micrograms/0.3 ml and 360 micrograms/0.6 methoxy polyethylene glycol-epoetin beta, solution for injection). The active substance and the finished product are identical to the authorised strengths except for the 5 new strengths. The available data supported this new strengths application satisfactorily. The product will be continuously followed in the future through the PSURs and the Follow-up measures agreed by the CHMP.
II/0018	Change to one of the sites responsible for the testing of the biological activity for the drug product Change(s) to the test method(s) and/or specifications for the finished product	23/07/2009	30/07/2008		
II/0017	To provide supporting information on the reprocessing of the active substance. To update analytical methods for the control of the active substance. Change(s) to the manufacturing process for the active substance	23/07/2009	30/07/2008		

II/0010	Scale-up the drug substance manufacturing process. Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0009	Addition of analytical method to the release specification of the active substance. Change(s) to the test method(s) and/or specifications for the active substance	24/07/2008	29/07/2008		
II/0008	scale up of manufacturing process for epoetin beta Change(s) to the manufacturing process for the active substance	30/05/2008	11/06/2008		
II/0007	change of a storage eluent for chromatographic column Change(s) to the manufacturing process for the active substance	30/05/2008	11/06/2008		
II/0005	The MAH has applied to amend section 4.2 and 5.2 of the SPC to include the results of a clinical study report on the effect of severe hepatic impairment on the pharmacokinetics of Mircera (RO0503821). Update of Summary of Product Characteristics	19/03/2008	23/04/2008	SmPC	SPC sections 4.2 has been amended to include the statement: "No adjustments of the starting dose nor of the dose modification rules are required in hepatic impaired patients" following the results of a clinical study report on the effect of severe hepatic impairment on the pharmacokinetics of Mircera (RO0503821). In section 5.2, the following statement has also been added "In a single dose study, after IV administration, the pharmacokinetics of MIRCERA are similar in patients with severe hepatic

					impairment as compared to healthy subject".
II/0002	Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	05/03/2008	SmPC, Labelling 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 been updated accordingly. In addition, minor details in the labelling have been updated.
II/0003	Change(s) to the manufacturing process for the active substance	21/02/2008	25/02/2008		
IB/0004	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/02/2008	n/a		