Ocrevus

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0041	Update of sections 4.6 and 5.3 of the SmPC in order to amend the recommendations for breast-feeding during ocrelizumab therapy, based on newly available clinical data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives	13/02/2025		SmPC and PL	Section 4.6 has been updated as follows: Human IgGs are known to be excreted in breastmilk the first few days after birth (colostrum period), which decreases to low concentrations soon afterwards. In a prospective, multicenter, open label study MN42989 (SOPRANINO), 13 lactating women received ocrelizumab at

[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).

	in the Package Leaflet. The RMP has been updated to version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				a median of 2.0 months postpartum (range 0.5 5.0 months). Low concentrations of ocrelizumab were detected in the breastmilk over 60 days following the mother's first postpartum infusion (median relative infant dose of 0.27% [range 0.0-1.8 %]), indicating minimal transfer of ocrelizumab to breastmilk. At 30 days after the mother's first postpartum infusion, ocrelizumab was undetectable in all available serum samples of breastfed infants (n=9), and infant B cell levels were within normal range in all available blood samples (n=10). No effects of ocrelizumab on health, growth and development were observed in breastfed infants over a follow-up period of 44.6 weeks (range 8.6-62.7 weeks). While no clinical data on infants potentially exposed to ocrelizumab via breastmilk receiving live or live-attenuated vaccines are available, no risks are expected due to normal B cell levels and undetectable serum ocrelizumab levels observed in those infants. In a separate prospective clinical study, low ocrelizumab concentrations in breastmilk (median relative infant dose of 0.1% [range 0.07-0.7%]) over 90 days after the mother's first postpartum infusion were observed in 29 lactating women who received ocrelizumab at a median of 4.3 months postpartum (range 0.1 36 months). Follow-up of 21 infants breastfed for at least 2 weeks showed normal growth and development up to 1 year. Ocrelizumab can be used during breastfeeding starting a few days after birth. Section 5.3 of the SmPC has been updated to remove the following statement: Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period

					For more information, please refer to the Summary of Product Characteristics.
PSUSA/10662 /202403	Periodic Safety Update EU Single assessment - ocrelizumab	14/11/2024	13/01/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10662/202403.
II/0040/G	This was an application for a group of variations. A grouped application comprised of three Type II Variations and one Type IA Variation, as follows: 3 Type II (C.I.4): Update of sections 4.4 and 4.8 of the SmPC in order to update clinical safety information based on final results from the three studies: study WA21092 (OPERA I), study WA21093 (OPERA II) and study WA25046 (ORATORIO). Study WA21092 (OPERA I) and study WA21093 (OPERA II) are randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis (RMS), while study WA25046 (ORATORIO) is a phase 3, multicentre, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis (PPMS). In addition, the MAH took the opportunity to introduce minor editorial change to the Product Information. Type IA (A.6): Change the ATC Code of ocrelizumab from L04AA36 to L04AG08.	31/10/2024	13/01/2025	SmPC	Section 4.4 is updated to inform that after approximately 10 years of continuous ocrelizumab treatment over the controlled period and Open Label Extension (OLE) phase of the pivotal clinical trials, the incidence of malignancies remained within the background rate expected for an MS population. Section 4.8 is updated to inform about the safety results from the above mentioned studies. In particular, subsection Infusion-related reactions, infections, immunoglobulins were updated. Section 5.1 is updated to reflect the change in the ATC code. For more information, please refer to the Summary of Product Characteristics.

	A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
X/0039	Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration	25/04/2024	20/06/2024	SmPC, Labelling and PL	
II/0036/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - 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.II.d.2.z - Change in test procedure for the finished product - Other variation A.7 - Administrative change - Deletion of manufacturing sites	20/04/2023	n/a		

	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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - 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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other				

	variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0035/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.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.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	30/03/2023	27/03/2024	SmPC and Annex II	SmPC section 9 has been updated with the date of the latest renewal. Annex II has been updated to include Roche Singapore Technical Operations, Pte. Ltd, 10 Tuas Bay Link, 637394 Singapore as alternative site responsible for manufacture of active substance.
II/0034/G	This was an application for a group of variations. Submission of the final report from study BN29739 (VELOCE) listed as a category 3 study in the RMP. This is a phase 3b, multicentre, randomized, parallel-group, open-label study to evaluate the effectiveness	16/03/2023	n/a		

	of vaccinations in patients with relapsing forms of multiple sclerosis (RMS) undergoing treatment with ocrelizumab. Submission of the final report from studies MA30005 (CASTING) and MN30035 (CHORDS). These are prospective, multicenter, international, interventional, open-label phase 3b studies to assess the efficacy and safety of ocrelizumab in patients with relapsing multiple sclerosis who have a suboptimal response to an adequate course of disease-modifying treatment. The RMP version 8.0 has also been submitted. 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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2023	27/03/2024	PL	
R/0033	Renewal of the marketing authorisation.	21/07/2022	21/09/2022	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Ocrevus in the approved indication remains favourable and therefore recommended the renewal of the marketing

					authorisation with unlimited validity.
IG/1496	A.7 - Administrative change - Deletion of manufacturing sites	18/03/2022	n/a		
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2022	21/09/2022	Labelling and PL	
PSUSA/10662 /202103	Periodic Safety Update EU Single assessment - ocrelizumab	28/10/2021	n/a		PRAC Recommendation - maintenance
IB/0029	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	05/10/2021	n/a		
IB/0028	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	13/08/2021	n/a		
IA/0026/G	This was an application for a group of variations. 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.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.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	10/06/2021	n/a		

IB/0025	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/04/2021	03/12/2021	SmPC and PL	
II/0024	Update of section 4.4 of the SmPC to amend the wording on progressive multifocal leukoencephalopathy (PML) as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010662/202003) adopted in November 2020. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/04/2021	03/12/2021	SmPC	The warning in section 4.4 of the SmPC on Progressive Multifocal Leukoencephalopathy (PML) is updated to include lymphopenia and advanced age as new risk factors for PML present in the ocrelizumab-treated patient who developed PML without prior disease-modifying therapy use. For more information, please refer to the Summary of Product Characteristics.
II/0023	Update of the SmPC Section 5.1 with the newly available post-hoc analysis results related to the time-to-wheelchair data performed on clinical study WA25046 (ORATORIO) in the PPMS population. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/03/2021	03/12/2021	SmPC	Given the established and observed clinical efficacy and safety profile for ocrelizumab, the exploratory analyses from controlled and open label extended periods of pivotal study for confirming efficacy and safety of ocrelizumab in early PPMS are considered as not statistically compelling. However, acknowledging the difficulties to demonstrate efficacy for disability long-term endpoints, even with the mentioned caveats, the CHMP agreed to include a brief and balanced summary of the 24W-CDP analysis in ECP in Section 5.1 of the SmPC. For more information, please refer to the Summary of Product Characteristics.
II/0021	Update of sections 4.4 and 4.8 in order to include the term ‘anaphylaxis’ among the possible symptoms of infusion-related reactions (IRRs), following an analysis of cases retrieved by anaphylactic reaction	11/02/2021	03/12/2021	SmPC and Annex II	

	MedDRA narrow SMQ. The MAH took the opportunity to update Annex II.C and D in line with the QRD template. The RMP version 7.0 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10662 /202003	Periodic Safety Update EU Single assessment - ocrelizumab	12/11/2020	11/01/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10662/202003.
II/0020	Update of section 5.3 of the SmPC in order to update information on embryo-fetal and pre- and postnatal development in cynomolgus monkeys based on final results from study 17-1133 listed as a Category 3 study in the RMP (MEA 006). The RMP v. 5.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/11/2020	03/12/2021	SmPC	SmPC new text Section 5.3 is updated to include results from study 17-1133 assessing embryo-fetal and pre- and postnatal development in cynomolgus monkeys. As a consequence of this variation, mortality and causes of mortality in this non-clinical study are included in the section 5.3 of the SmPC. The safety margin was revised because these events occurred at a lower dose as compared to the previous study (06-1260). For more information, please refer to the Summary of Product Characteristics.
IAIN/0022/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	18/11/2020	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0017	To update sections 4.2, 4.8 and 5.1 of the SmPC to add the option of a shorter infusion for second and subsequent doses of Ocrevus (2 hours, compared to the approved 3.5 hours infusion) based on the primary analysis of a therapeutic use substudy, MA30143 Shorter Infusion Substudy (Ensemble Plus). The Package Leaflet is updated accordingly. The RMP has been updated (ver. 4.0) with regards to the inclusion of shorter infusion duration (Part I Product Overview), the clinical trial exposure (Part II Module SIII) and the identified risk of infusion-related reactions (Part II Module SVII). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/04/2020	11/01/2021	SmPC and PL	With this variation the MAH proposes a 2 hour infusion duration, as an alternative to the 3.5 hour infusion duration, from the second dose and onwards, based on the primary analysis of a therapeutic use substudy, MA30143 Shorter Infusion Substudy (Ensemble Plus) designed to characterise the safety profile of shorter Ocrevus infusions in patients with Relapsing-Remitting Multiple Sclerosis. For more information, please refer to the Summary of Product Characteristics, sections 4.2, 4.8 and 5.1.
IB/0018	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	17/04/2020	11/01/2021	SmPC and PL	
PSUSA/10662 /201909	Periodic Safety Update EU Single assessment - ocrelizumab	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0016	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/02/2020	n/a		

PSUSA/10662 /201903	Periodic Safety Update EU Single assessment - ocrelizumab	17/10/2019	16/12/2019	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10662/201903.
II/0014/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.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	12/09/2019	n/a		

	or addition) for the AS or a starting material/intermediate B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
IB/0013	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	10/09/2019	n/a		
PSUSA/10662 /201809	Periodic Safety Update EU Single assessment - ocrelizumab	26/04/2019	20/06/2019	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10662/201809.
IB/0011	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/05/2019	n/a		
IA/0010/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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/02/2019	n/a		
II/0008	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	n/a		
II/0007	B.I.b.2.d - Change in test procedure for AS or	22/11/2018	n/a		

	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				
II/0002	Update of sections 4.4, 4.5, 4.6 and 5.1 of the SmPC in order to include information on vaccination based on interim results from study BN29739 listed as a category 3 study in the RMP; this is a phase IIIb, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of multiple sclerosis. The Package Leaflet is updated accordingly. The RMP version 2.3 has also been submitted. Furthermore, the MAH took the opportunity to implement a minor editorial change in section 6.6 of the SmPC with regards to instructions for dilution. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/10/2018	20/06/2019	SmPC and PL	In a randomized open-label study, patients with relapsing forms of multiple sclerosis (RMS) were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The percentage of patients with a positive response to tetanus vaccine at 8 weeks after vaccination was 23.9% in the ocrelizumab group compared to 54.5% in the control group (no disease-modifying therapy except interferon-beta). Geometric mean anti-tetanus toxoid specific antibody titers at 8 weeks were 3.74 and 9.81 IU/ml, respectively. Positive response to □5 serotypes in 23-PPV at 4 weeks after vaccination was 71.6% in the ocrelizumab group and 100% in the control group. In patients treated with ocrelizumab a booster vaccine (13-PCV) given 4 weeks after 23-PPV did not markedly enhance the response to 12 serotypes in common with 23-PPV. The percentage of patients with seroprotective titers against five influenza strains ranged from 20.0□60.0% and 16.7□43.8% pre-vaccination and at 4 weeks post vaccination from 55.6□80.0% in patients treated with ocrelizumab and 75.0□97.0% in the control group, respectively. It is recommended to vaccinate patients treated with Ocrevus with seasonal influenza vaccines that are inactivated. Due to the potential depletion of B cells in

					infants of mothers who have been exposed to Ocrevus during pregnancy, vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell levels, in neonates and infants, prior to vaccination is recommended. All vaccinations other than live or live-attenuated should follow the local immunisation schedule and measurement of vaccine-induced response titers should be considered to check whether individuals have mounted a protective immune response because the efficacy of the vaccination may be decreased. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to Ocrevus in utero.
PSUSA/10662 /201803	Periodic Safety Update EU Single assessment - ocrelizumab	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0004	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	20/09/2018	n/a		
IB/0005	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	23/08/2018	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	20/06/2019	PL	
T/0001	Transfer of Marketing Authorisation	20/02/2018	23/03/2018	SmPC, Labelling and PL	