MabThera

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
WS/2572/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.II.c.z - Change in control of excipients in the	18/01/2024	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).

	Finished Product - Other variation 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				
II/0199	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2023	n/a		
WS/2514	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation	31/08/2023	n/a		
PSUSA/2652/202211	Periodic Safety Update EU Single assessment - rituximab	22/06/2023	16/08/2023		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2652/202211.
IB/0196	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/05/2023	n/a		
N/0197	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2023	16/08/2023	PL	
WS/2364/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	15/12/2022	n/a		

	1234/2008. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product				
WS/2243/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.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	10/11/2022	n/a		
WS/2277	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation	01/09/2022	n/a		
PSUSA/2652/202111	Periodic Safety Update EU Single assessment - rituximab	23/06/2022	17/08/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s) for PSUSA/2652/202111.

II/0189/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol A.7 - Administrative change - Deletion of manufacturing sites 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.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 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.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	07/04/2022	n/a		
II/0188	Submission of the final report from study MA28150 (RITAZAREM) entitled Rituximab versus azathioprine as therapy for maintenance of remission for anti-	24/03/2022	n/a		

	neutrophilcytoplasm antibody-associated vasculitis listed as an interventional category 3 study in the RMP. The RMP version 23.0 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				
IG/1496	A.7 - Administrative change - Deletion of manufacturing sites	18/03/2022	n/a		
IA/0187	B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	22/11/2021	n/a		
II/0186	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	28/10/2021	n/a		
WS/2044	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.4.c - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient excipient - The excipient is a biological/immunological substance	23/09/2021	n/a		
PSUSA/2652/ 202011	Periodic Safety Update EU Single assessment - rituximab	24/06/2021	26/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2652/202011.
II/0185/G	This was an application for a group of variations.	08/07/2021	08/07/2022	SmPC and PL	As a consequence of this grouping of variations the SmPC

	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.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) 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.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 B.II.f.1.e - Stability of FP - Change to an approved stability protocol 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.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an				section 6.3 Shelf-life has been updated to 3 years.

	approved protocol 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.z - Change in the specification parameters and/or limits of the finished product - 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)				
IG/1365	B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test procedure is already authorised	03/03/2021	n/a		
IB/0181	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/02/2021	26/08/2021	SmPC and PL	
II/0179	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	14/01/2021	n/a		
IB/0180/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	13/01/2021	n/a		

IA/0178	A.7 - Administrative change - Deletion of manufacturing sites	28/09/2020	n/a		
II/0177	Submission of the final Clinical Study Report for study WA29330 (Pemphix) in order to fulfill the Post Authorization Measure in the Annex IID of the MabThera PI following 48 week safety follow up period of the study. In addition, the marketing authorisation holder took the opportunity to update the statement on sodium in the package leaflet and to introduce minor editorial corrections in the labelling and package leaflet. 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	03/09/2020	18/02/2021	Annex II, Labelling and PL	The obligation to conduct the PEMPHIX trial has now been fulfilled and is therefore deleted from the Annex II of the product information. The statement on the content of sodium in the Package Leaflet is updated to include reference to "cooking / table salt" as per the QRD recommendations. Minor editorial changes have been implemented in the Package Leaflet. For more information, please refer to the Product Information.
II/0176	B.I.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol	03/09/2020	n/a		
II/0173/G	This was an application for a group of variations. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	03/09/2020	n/a		

	specification parameter which may have a significant effect on the overall quality of the AS and/or the FP 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0175	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	01/07/2020	n/a		
PSUSA/2652/ 201911	Periodic Safety Update EU Single assessment - rituximab	11/06/2020	n/a		PRAC Recommendation - maintenance
IA/0174/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	10/06/2020	n/a		

II/0168	Extension of indication to include treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL) in combination with chemotherapy for MabThera; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/01/2020	03/03/2020	SmPC and PL	Please refer to Scientific Discussion 'MabThera-H-C-165-II-0168'
II/0162	Extension of indication to include the induction of remission in paediatric patients (aged ≥ 2 to <18 years old) with severe, active granulomatosis with polyangiitis (GPA) (Wegener's) and microscopic polyangiitis (MPA); as a consequence sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.5, 8 of the SmPC are updated for MabThera 100 mg and 500mg concentrate for solution for infusion. The PL was updated accordingly. In addition, the product information for the MabThera 100 mg and 500mg concentrate for solution for infusion have been combined. The RMP has been updated to version 21.1. C.I.6.a - Change(s) to therapeutic indication(s) -	30/01/2020	03/03/2020	SmPC and PL	Please refer to Scientific Discussion 'Mabthera-H-C-165-II-162'.

	Addition of a new therapeutic indication or modification of an approved one				
IB/0172	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	27/02/2020	n/a		
II/0169	Update of the SmPC sections 4.8, 5.1 and 5.2. with the results of the Post-authorisation efficacy study (PAES) randomised phase 3 study (PEMPHIX WA29330) which further investigated the efficacy of Mabthera in the subgroup of patients with established PV as well as characterised its long term efficacy and safety on disease progression. Annex II and PL are updated accordingly. In addition, outstanding QRD comments from EMEA/H/C/00165/II/162 are being implemented. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/02/2020	18/02/2021	SmPC, Annex II, Labelling and PL	
IB/0170/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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion	10/12/2019	n/a		

	of a non-significant in-process test 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.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 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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.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.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.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue				

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - 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.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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol 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)				
IB/0167	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	30/07/2019	03/03/2020	SmPC	
PSUSA/2652/ 201811	Periodic Safety Update EU Single assessment - rituximab	14/06/2019	n/a		PRAC Recommendation - maintenance

IB/0163/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.z - Change in control of excipients in the Finished Product - Other variation	29/04/2019	n/a		
IA/0164/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/03/2019	n/a		
II/0150	Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV) for MabThera; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The MAH provided data from a phase III, randomized, controlled, multicenter, open-label study (Study ML22196) evaluating rituximab treatment plus short-term, low dose prednisone treatment compared to long-term, standard dose prednisone treatment as first-line treatment in	31/01/2019	11/03/2019	SmPC, Annex II and PL	Please refer to Scientific Discussion MabThera-H-C-165-II-150.

	patients with moderate to severe pemphigus. The Package leaflet is updated accordingly. Minor corrections are also proposed for the sake of accuracy and clarity. An updated RMP (v19.1) was agreed. The annex II is updated to include submission of results of the ongoing PEMPHIX clinical study. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0152	Submission of the final study report of the non-interventional drug utilisation study (DUS) BA28478 (MabThera drug utilisation study and patient alert card evaluation in non-oncology patients in Europe: an infusion centre-based approach); as a consequence, the RMP is also updated (version 19.1) to revise the text with the deletion of the safety concern 'off label use in autoimmune disease'. 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	n/a		
WS/1508/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	07/02/2019	n/a		

	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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0158	Update of Annex II section D of the product information with removal of an obligation following the submission of the final clinical study report for study BO25341 (SAWYER, a Phase Ib adaptive, comparative, randomized, parallel-group, multi-center study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL). This includes reports on long-term safety in relation to body surface area (BSA) (as a measure for exposure variation) and to gender. Furthermore, the RMP version 19.1 has been agreed. 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	31/01/2019	11/03/2019	Annex II	Following the submission of the final clinical study report Study BO25341 (SAWYER), the risk management plan (RMP) has been updated to remove the following safety concerns: - Immunogenicity associated with the subcutaneous formulation (NHL/CLL) - Prolonged B-cell depletion The study formed the basis for demonstrating that rituximab SC results in Ctrough levels was non inferior to rituximab IV for the dose and dosing interval used in the treatment of CLL and no new safety concerns have been identified with the long-term follow-up.
II/0157	Update of SmPC, section 5.1 and Annex II section D	31/01/2019	11/03/2019	Annex II	The study has demonstrated that the rituximab SC

	of the product information with removal of an obligation following the submission of the final clinical study report for study BO22334 (SABRINA, a two-stage Phase III, international, multi-centre, randomized, controlled, open-label study investigating the pharmacokinetics (PK), efficacy and safety of rituximab SC in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy or cyclophosphamide, vincristine, prednisolone (CVP) chemotherapy versus rituximab IV in combination with CHOP or CVP chemotherapy followed by maintenance treatment with either rituximab SC or rituximab IV). This includes reports on long-term safety in relation to body surface area (BSA) (as a measure for exposure variation) and to gender. Minor editorial changes were also made in sections 4.5 and 5.1 of the SmPC. Furthermore, the version 19.1 was agreed. 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				formulation is comparable to the IV formulation with respect to response rate (CR, CRu and PR), PFS, EFS and OS. Also, with the exception of the increased incidence of anticipated administration events, the rituximab SC formulation does not present any new or additional safety concerns. The safety profile of rituximab remains unchanged. For more information please refer to the Summary of Product Characteristics.
II/0149	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/11/2018	18/12/2018	SmPC, Annex II and PL	Please refer to Scientific Discussion MabThera-H-C-165-II-0149

IB/0159	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/11/2018	n/a		
II/0144	Update the RMP to remove the additional risk minimisation measure of Educational Outreaches for the important identified risk of Infusion Related Reactions and Acute Infusion Related Reactions (IRR). In addition, the RMP has been updated in line with the GVP module V guideline (rev 2). The finally agreed RMP version is 16.1. 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	31/10/2018	n/a		
IB/0156	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	24/09/2018	n/a		
IB/0154	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	24/09/2018	18/12/2018	SmPC	
IB/0153	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	15/08/2018	n/a		

N/0155	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	18/12/2018	PL	
II/0151	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	21/06/2018	n/a		
PSUSA/2652/ 201711	Periodic Safety Update EU Single assessment - rituximab	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0143	Update of section 5.1 of the SmPC to reflect the final results of the PRIMA study (MO18264), a study in Patients with Advanced Follicular Lymphoma Evaluating the Benefit of Maintenance Therapy with Rituximab after Induction of Response with Chemotherapy plus Rituximab in Comparison with No Maintenance Therapy. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/04/2018	18/12/2018	SmPC	Data from extended follow-up of patients in the PRIMA study (MO18264, median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT. For more information, please refer to the Summary of Product Characteristics.
T/0148	Transfer of Marketing Authorisation	20/02/2018	16/03/2018	SmPC, Labelling and PL	
IA/0147	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	20/02/2018	n/a		

IB/0145	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	07/02/2018	n/a		
IB/0142	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	13/01/2018	16/03/2018	SmPC	
IB/0141	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	09/11/2017	n/a		
IB/0139	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	10/08/2017	n/a		
IB/0140	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/08/2017	16/03/2018	SmPC, Annex II, Labelling and PL	
IAIN/0138	B.II.g.3 - Deletion of an approved change management protocol related to the finished product	14/07/2017	n/a		
PSUSA/2652/ 201611	Periodic Safety Update EU Single assessment - rituximab	09/06/2017	n/a		PRAC Recommendation - maintenance
IA/0136	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	06/06/2017	16/03/2018	Annex II	

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0132	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	17/05/2017	n/a		
IA/0135	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	04/05/2017	n/a		
IA/0134/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	03/05/2017	n/a		
II/0130/G	This was an application for a group of variations.	27/04/2017	n/a		

	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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
II/0129/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.2.c - Change in test procedure for an excipient - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent	27/04/2017	n/a		
IB/0133	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	26/04/2017	n/a		

IB/0128	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	04/01/2017	n/a		
IB/0124	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/12/2016	n/a		
IB/0127	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	12/12/2016	n/a		
IB/0125	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	09/12/2016	n/a		
IA/0126	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	07/12/2016	n/a		
IB/0123	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	30/11/2016	n/a		
IB/0121	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	10/11/2016	n/a		
IB/0122	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	07/11/2016	n/a		
II/0111	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	23/06/2016	16/05/2017	Annex II and Labelling	

	biological/immunological product				
IB/0120	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/06/2016	n/a		
IB/0119/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.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	21/06/2016	n/a		
PSUSA/2652/ 201511	Periodic Safety Update EU Single assessment - rituximab	09/06/2016	n/a		PRAC Recommendation - maintenance
IB/0118	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/05/2016	n/a		
X/0101/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	01/04/2016	26/05/2016	SmPC, Labelling and PL	

	data 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				
IB/0117	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	21/04/2016	n/a		
IB/0115	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	11/03/2016	n/a		
IB/0113	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	19/02/2016	n/a		
IA/0114	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	17/02/2016	n/a		
IB/0110/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/02/2016	26/05/2016	Annex II	

II/0108	B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method	04/02/2016	n/a		
WS/0833	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	03/12/2015	n/a		
IB/0107	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	04/09/2015	n/a		
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		
PSUSA/2652/ 201411	Periodic Safety Update EU Single assessment - rituximab	11/06/2015	n/a		PRAC Recommendation - maintenance
IB/0104/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	04/05/2015	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				
II/0098	Update of sections 4.4, 4.8, 4.9 and 5.1 of the SmPC of the 1400 mg solution for subcutaneous injection based on the study BO22334 ("SABRINA") in fulfilment of EU post-authorisation measures. Consequently, annex II has also been revised to remove the obligation: submission of the updated CSR of study BO22334. Minor editorial changes have been introduced throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/01/2015	15/10/2015	SmPC and Annex II	The MAH presented analysis of pharmacokinetic, efficacy and safety data from additional patients and from longer follow-up in study BO22334 (SABRINA). Consequently, sections 4.4, 4.8, 4.9 and 5.1 of the SmPC of the 1400 mg solution for subcutaneous injection have been updated.
IB/0102/G	This was an application for a group of variations. 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 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	06/01/2015	n/a		

II/0099/G	This was an application for a group of variations. 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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 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.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.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	20/11/2014	n/a		

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		
II/0097	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	25/09/2014	15/10/2015	Annex II	
II/0095	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	24/07/2014	n/a		
IB/0096/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/07/2014	n/a		
PSUV/0093	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance

II/0089	Update of sections 4.2 and 4.8 of the SmPC in order to revise the infusion rate for RA patients and update the information on infusion reactions. The Package Leaflet was updated accordingly. Amendments to the text of the patient alert card in the PL following completion of readability tests assessed as part of the follow up measure MEA071 were implemented. The updated RMP version 9.4 was also submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	23/05/2014	SmPC, Annex II, Labelling and PL	Study ML25641 demonstrated the safety of a 120 minute infusion schedule is adequate and have not demonstrated any unexpected events. The risks of administering rituximab are well characterized and the risk associated with administering faster infusions of rituximab were similar to or lower than the corresponding incidence rates from the weighted historical controls (8.1%, 11.5%, and 5.0%), respectively. The MAH has proposed changes to the SmPC section 4.2 and 4.8; section 4.2 to provide specific guidance on the administration of rituximab according to the faster infusion schedule that was followed in Study ML25641, and section 4.8 to state that nothing new was observed in relation to IRRs from this study. The MAH is also asked to confirm that the stated concentration of the solution to be used for the faster infusion time is identical to what is normally used for first infusion. The proposed changes were further revised by the CHMP and are now acceptable. SmPC section 4.2 was amended accordingly, the SmPC was also harmonised with the already approved strengths for IV use, with the recently approved strength for SC use. The updated RMP was acceptable.
IB/0094	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/05/2014	n/a		
II/0092	Update of section 4.8 of the SmPC in order to update the safety information on posterior reversible encephalopathy syndrome (PERS). C.I.4 - Change(s) in the SPC, Labelling or PL due to	25/04/2014	23/05/2014	SmPC	A previous drug safety report presented for the oncology approved indications (non-Hodgkin's lymphoma, NHL, and chronic lymphocytic leukaemia, CLL) concluded that due to the unclear nature of the pathogenesis of PRES and the temporal association in the oncology populations, a

	new quality, preclinical, clinical or pharmacovigilance data				contribution of rituximab could not be excluded. This is already reflected in the SmPC in section 4.8. At that time, no evidence of rituximab association in PRES in the autoimmune indications was found, therefore for rheumatoid arthritis PRES was not considered as an adverse drug reaction. In this variation an updated drug safety report concludes that no causal relationship with rituximab has been established for the autoimmune indications. PRES is reported very rarely with rituximab. The data and information do not confirm a clear causality but a contributive role of rituximab is possible due to the temporal relationship, although all cases with sufficient information reported notable additional risk factors for PRES. The proposed update to section 4.8 is considered to adequately reflect the data submitted, and the variation is recommended for a positive opinion. The newly submitted data do not change the overall benefit/risk which remains positive.
II/0090	Update of section 5.1 of the SmPC in order to reflect the 5 year follow up results from study PRIMA in maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy, following a request from the CHMP in the context of MEA 072. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	23/05/2014	SmPC	The MAH for Mabthera has presented the five year update based on a median observation time of 73 months from the PRIMA trial. The benefit of rituximab maintenance therapy over observation both in terms of the primary endpoint PFS and in terms of the secondary endpoints event-free survival, overall response, time to next anti-lymphoma treatment, and time to next chemotherapy is considered clinically significant. Still, no difference in overall survival is observed. The number of deaths in the study remains too low to make definitive conclusions on OS at this time (stratified HR 1.02, p □ 0.8960, log-rank test). Longer

					follow-up would be needed in order to evaluate the effects of rituximab maintenance on OS in this study. At the time of reporting, the study protocol is being amended to extend the duration of survival follow-up until the end of 2016 in order to collect additional longer-term data on survival. This data should be submitted for assessment.
X/0083	Annex I_2.(e) Change or addition of a new route of administration	23/01/2014	21/03/2014	SmPC, Annex II, Labelling and PL	
II/0088/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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.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.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	20/03/2014	n/a		

	product and any of the test methods at the site is a biol/immunol method 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				
IB/0091	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/02/2014	n/a		
II/0087	Update of section 4.4 of the SmPC in order to strengthen the warning regarding prevention of Hepatitis B reactivation. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	20/11/2013	SmPC, Annex II and PL	The Summary of Product Characteristics for MabThera is updated in section 4.4 with further information on the cases of hepatitis B reactivation and recommending hepatitis B virus screening to be performed in all patients before initiation of treatment, as per local guidelines. This information is to be communicated directly to the treating physicians and relevant Healthcare professionals via a "Dear Healthcare Professional Communication".
IA/0086	A.7 - Administrative change - Deletion of manufacturing sites	10/07/2013	20/11/2013	Annex II	
II/0085	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	27/06/2013	20/11/2013	SmPC and PL	

II/0084	Update of sections 4.4 and 4.8 of the SmPC in order to revise the safety information related to Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in patients receiving MabThera. The Package Leaflet was proposed to be updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	22/04/2013	SmPC and PL	Cases of severe skin reactions such as toxic epidermal necrolysis (TEN) and Stevens- Johnson Syndrome (SJS) have been very rarely reported in patients with autoimmune diseases with both first-time use and with later infusions. Some of the cases occurred on the day of dosing or within a few days of dosing. In other cases, the event occurred weeks or up to four months after the dose. Four of the cases in autoimmune patients had a close association in time to MabThera dosing (starting on the day of dosing or the next day), of which one case of TEN had a fatal outcome. In several of the cases in autoimmune patients, treatments known to be possibly associated with Toxic Epidermal Necrolysis and Stevens- Johnson Syndrome were given concomitantly with MabThera therapy. The mechanism of these reactions remains unknown. Severe bullous skin reactions, including fatal cases, of TEN have been reported very rarely in patients with haematological malignancies. This information was already included in the MabThera product information, which is now being updated to reflect the new safety information and to advise that if severe skin reactions occur, MabThera treatment should be discontinued.
II/0079	Update of section 4.1 of the SmPC in order to extend the indication of Mabthera to include the use of Mabthera in combination with glucocorticoids for the induction of remission in adult patients with severely active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA). SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 are also updated to reflect the efficacy and safety data for	21/03/2013	22/04/2013	SmPC and PL	Please refer to Scientific discussion Mabthera H-C-165-II-79.

	this indication. The Package Leaflet is updated in accordance. Furthermore, the Annex II is being brought in line with the latest QRD template version 9 to state the deadline for the next RMP update (v9.3) and has also been updated to reflect the additional risk minimisation measures following the assessment of a previous RMP version (v7.0) and a related follow-up measure FUM070.1. Annex IIIA has been updated to reflect that the patient alert card is addressed to all patients with non-oncology indications (not restricted to Rheumatoid Arthritis patients). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0080/G	This was an application for a group of variations. Update of sections 4.4, 4.8 and 5.1 of the SmPC with the addition of hypogammaglobulinaemia in paediatrics, addition of pneumocystis jirovecii at the request of CHMP further to the assessment of PSUR 020, inclusion of information on the duration of B-cell depletion in RA patients, amendment of a value given for the response to vaccination, rewording of the sentence referring to the occurrence of progressive multifocal leukoencephalopathy and addition of PML as "very rare". The Package Leaflet has been updated accordingly. Furthermore, the PI has been brought in line with the	21/02/2013	22/04/2013	SmPC, Annex II, Labelling and PL	Sections 4.4, and 5.1 of the SmPC have been updated to reflect that a small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of MabThera. Based on the mechanism of action of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following MabThera therapy. A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown. This information was

	latest QRD template version 8.3. 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 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.3.z - 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 - Other variation				added in section 4.8 of the SmPC. In addition, a numerical value given for response to vaccination was corrected and the statement referring to the occurrence of progressive multifocal leukoencephalopathy, under section 4.4 was reworded. Pneumocystis jirovecii infection was added in section 4.8. as "rare" and PML was added as very rare. The Package Leaflet was proposed to be updated accordingly. In addition editorial changes were made to the product information to comply with QRD template version 8 (revision 3) among these was the addition of a 'Fertility' sub-section and a statement under 4.6 on the lack of data on fertility. The MAH took this opportunity to make some minor typographical amendments to the SmPC and PL text.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
IB/0081	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	21/08/2012	n/a		
A20/0078	Art 20 review: In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP to	24/05/2012	03/08/2012		Please refer to the CHMP Assessment report for the Art 20 procedure on Mabthera EMEA/H/C/165/A20/0078

	assess the above concerns and its impact on the benefit/risk for Mabthera, and to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.				
II/0077/G	This was an application for a group of variations. Update of section 4.4 and 4.8 of the SmPC with regard to neutropenia further to the request of the CHMP during the assessment of the last PSUR and of section 4.8 of the SmPC in order to add adverse reactions regarding hypogammaglobulinaemia. In addition, a warning in section 4.4 of the SmPC has been included in relation to traceability of the medicinal product. The Package Leaflet has been updated accordingly. Furthermore, the MAH has taken this opportunity to bring the PI in line with the latest QRD template version 8 and to update the list of local representatives in the PL. 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.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation 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	19/04/2012	25/05/2012	SmPC, Annex II, Labelling and PL	The MAH submitted safety reviews on neutropenia and hypogammaglobulinaemia following treatment with MabThera in RA patients. While neutropenia was observed, the majority of events were transient and mild or moderate in severity. Neutropenic events, including severe late onset and persistent neutropenia, were rarely reported in the post-marketing setting; however some were associated with fatal infections. The data from placebo controlled trials revealed that 0.94% (13/1382) of rituximab treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia. Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) was observed in RA patients. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM. A warning in relation to traceability of the medicinal product was added to the SmPC.

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
II/0076/G	This was an application for a group of variations. Update of sections 4. 4, 4.8, 5.1 of the SmPC in order to provide a reanalysis of the ADRs frequency, information on the risk of prolonged B-cell depletion, information on hepatitis screening, the risk of prolonged neutropenia, warnings on cardiac events further to requests from the CHMP. The Package Leaflet has been updated accordingly. Editorial amendments were also included. 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 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 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 -	17/11/2011	14/12/2011	SmPC, Annex II and PL	The MAH has submitted a group of type II variations to update the Mabthera SmPC section 4.4, 4.8 and 5.1 with safety data further to several requests from the CHMP. Section 4 of the PL is also amended as a consequence. The changes are as follows; 1. Reassignement of the frequency of several adverse drug reactions (ADRs) listed as "unknown" to very rare or rare, as applicacle, in Table 1 of the SmPC (Section 4.8 Undesirable Effects) according to the current EC SmPC Guideline. 2. Update of the information regarding the risk of prolonged B-cell depletion further to a cumulative review. 3. Update of the warning related to hepatitis B, particularly with regard to the screening and surveillance. 4. Update of the information regarding the risk of prolonged neutropenia in the Chronic Lymphocytic Leukaemia (CLL) indication. 5. Addition of a warning on cardiac events in the rheumatoid arthritis (RA) indication further to the conduct of a cumulative review.

	Change(s) with new additional data submitted by the MAH 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 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				
IB/0075	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	19/09/2011	n/a	SmPC and PL	Updates to SmPC and Package Leaflet regarding fatal infusion reactions occurring in Rheumatoid Arthritics patients in the postmarketing setting agreed following assessment. Furthermore, linguistic amendments have been implemented in some languages.
IB/0074	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	19/08/2011	n/a		
II/0072	Update of section 5.1 of the SmPC with 3-year follow-up efficacy data from the phase III study ML17102 (also know as "CLL-8") in patients with previously untreated chronic lymphocytic leukaemia	19/05/2011	23/06/2011	SmPC, Annex II, Labelling and PL	Following the approval of the indication for the treatment of patients with CLL the MAH committed to submit the updated results from Study ML17102 (CLL-8) (FU2 061.1) which was the basis for the approval. The submitted data

	(CLL). These follow-up data were requested by the CHMP as a follow-up measure (FUM061). Annex II has been updated to reflect the latest Risk Management Plan (RMP) version number (v. 6.0) and other minor editorial amendments have also been made in the labelling and package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				now resulted in a variation to update section 5.1. The data presented in this dossier from an additional three years of follow-up beyond that for the primary analysis of study ML17102 continue to demonstrate clinically meaningful and statistically significant improvements in PFS and OS for patients with previously untreated CLL when treated with R-FC compared to FC alone. PFS was significantly improved in the R-FC arm compared to the FC arm (adjusted HR 0.55, $p < 0.0001$, Wald test), consistent with the results of the primary analysis. The median PFS in the R-FC arm increased from 39.8 months to 55.3 months with extended follow-up, while that in the FC arm was similar over time (32.2 months vs 32.8 months). OS was significantly improved in the R-FC arm compared to the FC arm (adjusted HR 0.73, $p = 0.0304$, Wald test). Although the hazard ratio has increased over time (from 0.64 to 0.73), which is most likely related to an increasing imbalance between treatment arms with respect to receiving non-protocol rituximab-containing regimens, the trend of improved survival in favor of the R-FC arm was confirmed with extended follow-up. The clinical benefits seen in PFS and OS in the overall population were also observed in most of the patient subgroups analyzed. In particular, the risk of disease progression/ relapse or death among patients with Binet stage C disease reached statistical significance with extended follow-up (HR 0.68, $p = 0.0224$, Wald test). There were no new or unexpected safety signals with extended follow-up, thus confirming the known safety profile of rituximab in combination with FC chemotherapy. Therefore, the benefit/risk ratio for rituximab in combination with FC chemotherapy for the first-line

					treatment of patients with CLL, as
IB/0073/G	This was an application for a group of variations. 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)	26/05/2011	n/a		
II/0070/G	This was an application for a group of variations. To add a drug substance manufacturing site and to introduce changes to the manufacturing process of the active substance for harmonization across all the registered sites 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.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	18/11/2010	20/12/2010	Annex II	
IB/0071/G	This was an application for a group of variations.	16/11/2010	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
II/0069	Extension of the non-Hodgkin's lymphoma indication to include treatment of follicular lymphoma patients responding to induction therapy. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, Annex II has been updated in order to include the new version number of the Risk Management Plan (version 5.1). Minor editorial changes have also been implemented. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/09/2010	25/10/2010	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Mabthera /H/C/000165/II/0069" for further information.
II/0065	Section 4.1 of the SmPC has been updated to include information on improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate. As a consequence, sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition to this, sections 5.1 and 5.2 of the SmPC have been updated with additional information from studies in patients with early arthritis. Furthermore changes were made to the SmPC,	23/09/2010	25/10/2010	SmPC, Annex II, Labelling and PL	In this application, the MAH submitted data from two pivotal studies IMAGE and SERENE as well as four supportive studies MIRROR, SUNRISE, REFLEX (2 years extension data from REFLEX study which has been submitted as part of the initial application for the rheumatoid arthritis (RA) indication) and DANCER, to support an extension of the current RA indication to earlier stages of RA, in methotrexate (MTX) naïve patients (1st line treatment) and in MTX inadequate response (MTX-IR) patients (2nd line treatment).

	labelling and Package Leaflet to bring them in line with the current QRD template. Finally Annex II has been updated in order to reflect the latest version of the RMP. Extension of Indication				Further to the assessment of the submitted data, the CHMP considered that efficacy data to support the 1st and 2nd line treatment was insufficient. However the CHMP considered acceptable to update section 4.1 with information on improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate and sections 4.2, 4.4, 4.5, 4.8 and 5.1 have been updated as a consequence. The Package Leaflet has been updated accordingly. In addition to this, sections 5.1 and 5.2 of the SmPC have been updated with additional information from studies in patients with early arthritis. Please refer to Scientific Discussion Mabthera -H-C-165-II-65.
II/0068	Update of sections 4.2, 4.4 and 4.8 of the Summary of Product Characteristics (SPC) following a review of data from post marketing experience. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	23/03/2010	SmPC and PL	This variation application was submitted in order to amend section 4.2 of the SPC to add reference to the MabThera Rheumatoid arthritis patient alert card. The PL has been updated accordingly. In addition to this, section 4.8 has been updated to add reference to the following adverse events: infusion related acute reversible thrombocytopenia, interstitial lung disease, Progressive Multifocal Leukoencephalopathy (PML) and serum sickness-like reaction. Furthermore, section 4.4 has been updated based on the experience gained from all of the reported cases of PML and in order to be consistent with information given in section 4.8. These sections have been updated to reflect the safety data from post marketing experience.
IA/0067	IA_28_Change in any part of primary packaging	11/11/2009	n/a		

	material not in contact with finished product				
IA/0066	IA_09_Deletion of manufacturing site	10/09/2009	n/a	Annex II	
II/0064	Extension of indication to include MabThera in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL). Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy. Annex II has been updated to reflect the new RMP version 3.1 and other editorial amendments have also been implemented in the SPC, Labelling and Package Leaflet. Extension of Indication	23/07/2009	21/08/2009	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion document (to be published shortly).
II/0063	Update of the information on immunization data for both Non-Hodgkin's lymphoma and rheumatoid arthritis, and of the information on concomitant/ sequential use of other DMARDs under section 4.4 of the SPC. As a consequence, section 4.5 of the SPC has also been updated to reflect the rate of infections in patients receiving subsequent therapy with other DMARDs. Postmarking information has also been included in section 4.8 of the SPC under rheumatoid arthritis. Update of Summary of Product Characteristics	19/02/2009	25/03/2009	SmPC	The information on immunization data for both Non-Hodgkin's lymphoma and rheumatoid arthritis, and of the information on concomitant/ sequential use of other DMARDs under section 4.4 of the SPC was updated following results from clinical trials. As a consequence, section 4.5 of the SPC has also been updated to reflect the rate of infections in patients receiving subsequent therapy with other DMARDs. Postmarking information has also been included in section 4.8 of the SPC under rheumatoid arthritis. Based on the limited data from clinical trials a statement has been added in section 4.4 in the SPC: The available

					data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with MabThera, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following MabThera therapy In addition, the overall safety profile of MabThera in rheumatoid arthritis under section 4.8 is now presented based on data from patients from clinical trials and from post-marketing surveillance. The safety information collected during post marketing experience reflects the expected adverse reaction profile as seen in clinical trials for MabThera.
II/0060	Extension of indication to include MabThera in combination with chemotherapy for the first-line treatment of patients with chronic lymphocytic leukaemia. Extension of Indication	22/01/2009	23/02/2009	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion (H-165-II-60-AR)
II/0062	Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	24/11/2008	SmPC and PL	
II/0059	The MAH applied to update the text regarding reactivation of Hepatitis B infections under Section 4.4 of the SPC; to delete non-relevant information from Section 4.5; to include safety observations from a limited number of pregnancies under section 4.6; and to include progression of Kaposi's sarcoma following treatment with MabThera + chemotherapy"under section 4.8 of the SPC. Revisions proposed by the QRD following the	30/05/2008	04/07/2008	SmPC, Annex II, Labelling and PL	The following sections of the Product Information have been amended: - Section 4.4: Opportunistic and reactivation infections: update of text regarding reactivation of Hepatitis B infections. - Section 4.5: Deletion of redundant information from the interactions section of the SmPC; interaction of MabThera with chemotherapy other than

	procedure for the 10-year Renewal have been introduced in the SPC, Labelling, Package Leaflet and are of editorial nature. Update of Summary of Product Characteristics, Labelling and Package Leaflet				cyclophosphamide, doxorubicin, vincristine, prednisolone [CHOP] or cyclophosphamide, vincristine, prednisolone [CVP]. - Section 4.6: Adverse events during pregnancy and lactation and the use of MabThera - to include safety observations from a limited number of pregnancies. - Section 4.8: Information in relation to "Progression of Kaposi's sarcoma" to include progression of Kaposi's sarcoma following treatment with MabThera + chemotherapy". In addition:, as committed during the license renewal procedure and in order to better comply with the current approved SPC guideline (2005) whilst considering the latest proposal for SPC guidance (revision released in December 2007 for consultation) the Marketing Authorisation Holder has overall revised section 4.8. Also the MAH has taken the opportunity to address comments received as a part of the recent 10-years renewal of the MA, including editorial revisions of the Labelling and the Package Leaflet.
R/0058	Renewal of the marketing authorisation.	19/03/2008	20/05/2008	SmPC, Annex II, Labelling and PL	The data submitted in the context of this second renewal of Mabthera confirm that the overall profile efficacy/safety of Mabthera is unchanged. As several indications have been recently approved and further new indications are expected the PSUR cycle should be continued at a once-yearly basis, after assessment of the next PSUR covering 8 October 2007- 31 May 2008. The renewal is granted with unlimited validity.

II/0057	Specification change in the column used for the purification of active substance. Change to the test procedure and/or specification of a raw material	21/02/2008	25/02/2008		
II/0056	Additional manufacturing site of bulk solution. Change(s) to the manufacturing process for the finished product	21/02/2008	25/02/2008		
II/0053	Extension of the first line follicular NHL indication to include all chemotherapy combinations options. Furthermore, the MAH has taken the opportunity to clarify posology and method of administration in section 4.2. Extension of Indication	13/12/2007	18/01/2008	SmPC and PL	Please refer to the Scientific Discussion (H-165-II-53-AR).
II/0055	Update of section 5.2 (Pharmacokinetic properties) of the SPC based on a population PK analysis in patients with non-Hodgkin lymphoma. Minor editorial changes are also included in sections 4.4 and 5.1 of the SPC. Update of Summary of Product Characteristics	18/10/2007	19/11/2007	SmPC	The median terminal elimination half-life of rituximab was 22.4 days (range, 6.14 to 51.9 days). Based on the subgroup dataset of Study IDEC 102-05, baseline CD19+ cell counts (CD19) and the sum of the product of perpendicular diameters (SPD) were the most significant covariates influencing CL2. The overall effects of covariates in the final model explained approximately 27% of the inter-individual variability in CL2. SPD was the most significant covariate influencing Kdes, but explained only approximately 6% of the inter-individual variability for Kdes in the final model. The large inter-individual variability on CL2 and Kdes remained after the inclusion of the CD19 and

					SPD covariates in the PK model. It is possible that the longitudinal SPD and CD19 data, which were not included in this analysis, might explain some of the remaining variability. Body surface area (BSA) was the most significant covariate influencing V1 and explained approximately 30% of the inter-individual variability in V1. The addition of covariate factors as predictors of variability in rituximab pharmacokinetics did not reduce unexplained inter-individual variability in CL1 and V1. It is possible that other covariate factors, not included in this analysis, might explain some of the remaining variability. The clinical relevance of this finding is that dose adjustment for known covariates (e.g, BSA) is not expected to result in a meaningful reduction in PK variability. Age, sex and WHO performance status had no statistically significant effect on the pharmacokinetics of rituximab. The section 5.2 "Pharmacokinetic Properties" is amended accordingly.
II/0054	Quality changes	18/10/2007	23/10/2007		
II/0052	Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	03/09/2007	SmPC and PL	In February 2007, the CHMP requested that the European Marketing Authorisation Holder, Roche, issue a DDL across the EU concerning the two reported cases of PML. Subsequently a new case of PML in a vasculitis patient was reported and the DDL was revised and issued as of 2 April 2007. The current variation is to update section 4.4. of the SPC and also section 4 of the PIL with appropriate wording covering PML in Non-Hodgkins Lymphoma and autoimmune diseases.

					Since then, the position on the interpretation of PML cases reported in NHL patients has not changed. However, considering the severity of the conditions and the proposal to update the "Warnings" Section of the SPC with a statement regarding the observed cases of PML with off-label use of rituximab in SLE/vasculits patients, it is appropriate to include a text on PML in the "Warnings" Section of the SPC, in addition to the text in the post-marketing experience of the "Undesirable Effects" section.
II/0050	Quality changes	24/05/2007	31/05/2007		
II/0048	The MAH applied to add efficacy information to section 5.1 Pharmacodynamic Properties in the SPC, as a result of the availability of radiographic data. A minor editorial change has been introduced in the Package Leaflet to bring it in line with the latest QRD template. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	27/03/2007	SmPC and PL	In Study 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score. Patients originally receiving rituximab/MTX demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81% received rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving the original rituximab/MTX treatment also had no erosive progression over 56 weeks (61% vs 52%). The present study has shown that rituximab has the ability to slow down the progression of structural damage in patients with active RA who had previously failed anti-TNF treatment. This effect is predominately seen in patients who possess RF or are anti-CCP positive. The study population comprised patients with high inflammatory activity as measured by DAS28 score

					and long disease duration. Various robustness analyses showed consistently that rituximab was significantly superior to placebo in total Sharp-Genant score, erosion score and joint space narrowing.
II/0051	Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	12/01/2007	SmPC and PL	The MAH has applied to update section 4.8 of the SPC to include information on gastrointestinal perforation and viral infections. The Package Leaflet was updated to include the addresses of local representatives in Bulgaria and Romania.
IA/0049	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/10/2006	n/a	Annex II and PL	
IA/0047	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	12/07/2006	n/a		
II/0044	Extension of Indication	01/06/2006	06/07/2006	SmPC and PL	The MAH applied to include maintenance therapy indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera. Please refer to the Scientific Discussion (H-165-II-44-AR) for more information.
II/0039	Extension of Indication	01/06/2006	06/07/2006	SmPC and PL	MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies. Please refer to the Scientific Discussion (H-165-II-39-AR) for more information.
II/0046	Change(s) to the test method(s) and/or	23/03/2006	29/03/2006		

	specifications for the finished product				
II/0043	Quality changes	23/02/2006	20/03/2006	Annex II	
IA/0045	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	24/01/2006	n/a		
II/0041	Quality changes	17/11/2005	22/11/2005		
II/0040	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	17/11/2005	22/11/2005		
IA/0042	IA_01_Change in the name and/or address of the marketing authorisation holder	14/10/2005	n/a	SmPC, Labelling and PL	
II/0035	Change(s) to the manufacturing process for the active substance	15/09/2005	29/09/2005		
II/0034	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	15/09/2005	29/09/2005		
IB/0037	IB_23_a_Change in source of excip./reagent to veg./synthetic material - biological act. subst.	06/07/2005	n/a		
IA/0038	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	29/06/2005	n/a		

IA/0036	IA_09_Deletion of manufacturing site	22/04/2005	n/a	Annex II	
II/0033	Update of Summary of Product Characteristics and Package Leaflet	20/01/2005	07/03/2005	SmPC and PL	The MAH applied to add information on Hepatitis B reactivation (section 4.4 and 4.8 of SPC) and information on Waldenström's macroglobulinemia (section 4.8 of SPC). The Package Leaflet is updated accordingly. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet.
II/0031	Extension of Indication	23/06/2004	02/08/2004	SmPC	
II/0030	Change(s) to the manufacturing process for the active substance	03/06/2004	11/06/2004		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/06/2004	n/a	Labelling and PL	
II/0029	Update of Summary of Product Characteristics	21/01/2004	19/03/2004	SmPC	
II/0028	Update of Summary of Product Characteristics	21/01/2004	19/03/2004	SmPC	
II/0027	Change(s) to the manufacturing process for the active substance	26/02/2004	05/03/2004		
II/0025	Quality changes	25/09/2003	14/01/2004	Annex II	
I/0026	04_Replacement of an excipient with a comparable excipient	21/08/2003	26/08/2003		
R/0017	Renewal of the marketing authorisation.	25/04/2003	28/07/2003	SmPC, Annex II, Labelling	

				and PL	
I/0023	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	25/06/2003	01/07/2003		
I/0022	Deletion of secondary packaging sites that are not in use (see background application) and to add QC-testing site. 01_Withdrawal of the manufacturing authorisation for a site of manufacture	20/06/2003	n/a		
I/0021	24_Change in test procedure of active substance	25/04/2003	02/05/2003		
I/0020	24_Change in test procedure of active substance	25/04/2003	02/05/2003		
I/0019	15_Minor changes in manufacture of the medicinal product	25/04/2003	02/05/2003		
I/0018	16_Change in the batch size of finished product	25/04/2003	02/05/2003		
II/0016	Update of Summary of Product Characteristics	25/04/2002	15/07/2002	SmPC	
II/0011	Update of or change(s) to the pharmaceutical documentation	30/05/2002	03/06/2002		
II/0014	Extension of Indication	18/10/2001	21/03/2002	SmPC and PL	
I/0015	20_Extension of shelf-life as foreseen at time of authorisation	22/10/2001	19/02/2002	SmPC	

N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2001	03/10/2001	Labelling	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	27/06/2001	SmPC and PL	
I/0010	15_Minor changes in manufacture of the medicinal product	28/06/2000	24/07/2000		
I/0009	12_Minor change of manufacturing process of the active substance	24/05/2000	24/07/2000		
I/0007	15_Minor changes in manufacture of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	12/04/2000	24/07/2000		
I/0006	08_Change in the qualitative composition of immediate packaging material	14/04/2000	24/07/2000		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/02/2000	03/05/2000	PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	22/09/1999	08/02/2000	SmPC and PL	
II/0004	Change(s) to the test method(s) and/or specifications for the finished product	17/11/1999	n/a		
II/0003	Update of Summary of Product Characteristics and Package Leaflet	20/05/1999	09/09/1999	SmPC and PL	

II/0002	Update of Summary of Product Characteristics and Package Leaflet	24/02/1999	18/06/1999	SmPC and PL	
I/0001	11_Change in or addition of manufacturer(s) of active substance 12_Minor change of manufacturing process of the active substance 13_Batch size of active substance 15_Minor changes in manufacture of the medicinal product	22/10/1998	n/a		