Zevalin

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/0053	Update of the RMP in line with the new GVP module V revision 2. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	10/06/2021	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).

	where significant assessment is required				
PSUSA/1704/ 202002	Periodic Safety Update EU Single assessment - ibritumomab tiuxetan	01/10/2020	n/a		PRAC Recommendation - maintenance
II/0051/G	This was an application for a group of variations. 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.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.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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	03/09/2020	n/a		
T/0050	Transfer of Marketing Authorisation	09/01/2020	11/02/2020	SmPC, Labelling and PL	

PSUSA/1704/201702	Periodic Safety Update EU Single assessment - ibritumomab tiuxetan	12/10/2017	08/12/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1704/201702.
II/0046/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing 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.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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	18/05/2017	n/a		

IB/0048	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)	27/02/2017	n/a		
IB/0047	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)	10/02/2017	08/12/2017	SmPC	
IAIN/0045	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	16/11/2015	n/a		
IB/0044	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)	14/09/2015	n/a		
II/0043	Submission of an updated RMP in order to comply with the format specified in GVP Module V as well as updating information on the Study SAG 307722. The requested variation leads to amendments to the Risk Management Plan (RMP). 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	26/03/2015	n/a		
II/0042	B.II.b.2.b - Change to importer, batch release	20/11/2014	n/a		

	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				
PSUV/0040	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IAIN/0041	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	09/09/2014	n/a		
II/0039	Update of sections 4.4 and 4.8 of the SmPC to add a warning on the risk of secondary malignancies and reflect data from study SAG 307722 on the incidence of secondary malignancies during the five year extended observation period. The MAH took the opportunity to correct minor typographical errors. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	15/04/2015	SmPC, Annex II and PL	Study SAG 304820 evaluated Zevalin in patients with follicular non-Hodgkin's lymphoma (NHL) who achieved partial or complete remission after first line chemotherapy. At the end of study SAG 304820, the surviving patients entered study SAG 307722 for five years. Of the 204 patients receiving Y-90 Zevalin following first line chemotherapy, 26 (12.7%) patients in the Zevalin arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving Zevalin, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the Zevalin arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the Zevalin arm compared to no patients in the control arm.

IB/0037	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)	08/05/2013	14/03/2014	SmPC	
IA/0038	A.7 - Administrative change - Deletion of manufacturing sites	30/04/2013	14/03/2014	Annex II and PL	
IAIN/0036	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/04/2013	n/a		
IAIN/0035/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	03/04/2013	14/03/2014	Annex II and PL	
IAIN/0034	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/01/2013	n/a		
T/0033	Transfer of Marketing Authorization from Bayer Pharma AG to Spectrum Pharmaceuticals B.V. Transfer of Marketing Authorisation	26/10/2012	30/11/2012	SmPC, Labelling and PL	
IAIN/0032/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	14/05/2012	n/a		

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0031/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/08/2011	n/a	SmPC, Annex II, Labelling and PL	
II/0026	Change to batch release arrangements and quality control testing of the finished product. B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of	17/03/2011	13/04/2011		

	the test methods is a biol/immunol/immunochemical method				
IB/0029/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	19/01/2011	n/a		
IB/0028	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/01/2011	n/a	SmPC	
IA/0030/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	10/01/2011	n/a		

N/0027	The MAH applied to update the contact details of the local representative for Czech Republic and Iceland in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2010	n/a	PL	
IA/0025/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/07/2010	n/a		
II/0024	Update of SPC as requested by the CHMP during the Renewal procedure R-22 to replace the adverse events mentioned in the section 4.8 under post marketing experiences, as well as adverse reactions observed in the study (Fatigue, Petechia, Hypertension, Hypotension and amenorrhoea) to the table of adverse events and revision of the Product Information in accordance with the proposal from the Quality Review of Documents group. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	04/09/2009	SmPC and PL	The MAH was requested by the CHMP to replace the adverse events mentioned in the section 4.8 under post marketing experiences, as well as adverse reactions observed in the study (Fatigue, Petechia, Hypertension, Hypotension and amenorrhoea) to the table of adverse events in accordance with current guidelines. Moreover, adverse events mentioned in the Section 4.4 are now included in the table of adverse events (section 4.8). The Product Information was revised in accordance with the proposal from the Quality Review of Documents group during the Renewal procedure.
II/0023	Change in the finished product manufacturing process	19/02/2009	27/02/2009		

	Change(s) to the manufacturing process for the finished product				
R/0022	Renewal of the marketing authorisation.	20/11/2008	07/01/2009		Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Zevalin continues to be favourable.
S/0021	4th Annual Reassessment	19/03/2008	22/05/2008	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that amendments of Annexes I and III to the Community Marketing Authorisation are necessary. Annex II has been amended according to the conclusions reached during the CHMP discussion.
II/0020	Change of manufacturing process facility for the Active substance. Minor changes in manufacturing process, IPC, r-h-insulin and test method. Change(s) to the manufacturing process for the active substance	24/04/2008	05/05/2008		
II/0018	Extension of Indication to include: The [90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been	19/03/2008	18/04/2008	SmPC, Annex II and PL	Please refer to the Scientific Discussion (H-547-II-18-AR)

	established. Extension of Indication				
IB/0019	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	11/01/2008	n/a	SmPC	
II/0017	Update of sections 4.4 and 4.8 of the SPC regarding extravasation and tissue damage. The Package Leaflet has been updated accordingly. Additionally, section 4 of the Package Leaflet "Possible Side Effects" has been restructured to present side-effects according to frequency. Editorial changes to SPC section 6.6 and to the Package Leaflet have been introduced. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	22/10/2007	SmPC and PL	The Summary of Product Characteristics has been updated to include under section 4.4 a warning that close monitoring for evidence of extravasation during the injection of Zevalin is required in order to avoid radiation-associated tissue damage. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Section 4.8 has beed updated to include that isolated reports of extravasation with subsequent infusion site dermatitis, infusion site desquamation and infusion site ulcer and also isolated reports showing that Zevalin-associated radiation might cause damage to lymphoma-surrounding tissue and complications due to lymphoma swelling.have been received. The Package Leaflet section 4 has been updated to describe extravasation and damage to the lymphoma- surrounding tissue. Additionally, section 4 of the Package Leaflet "Possible Side Effects" has been restructured to present side-effects according to frequency. Editorial changes to SPC section 6.6 and to the Package Leaflet have been introduced.
II/0016	Change(s) to the test method(s) and/or specifications for the finished product Quality changes	24/05/2007	31/05/2007		

S/0014	3rd Annual Reassessment	22/03/2007	26/03/2007		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of the Annexes of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.
IA/0015	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	15/03/2007	n/a	SmPC, Annex II, Labelling and PL	
II/0011	Change(s) to the manufacturing process for the active substance	18/10/2006	14/11/2006	SmPC, Annex II and PL	
II/0012	Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/09/2006	19/10/2006	SmPC, Annex II, Labelling and PL	Update of section 4.3 to add hypersensitivity to rituximab as a contraindication, section 4.4; to add statement on severe and prolonged cytopenia, and a warning regarding cytopenia, neutropenia and thrombocytopenia after prior therapy with fludarabine and to add information on time to onset of mucocutaneous reactions, section 4.8, to update the frequency of Myelodysplastic syndrome / Acute Myeloid Leukaemia, and to convert terminology in MedDRA and section 5.3: to add an introductory statement. References to rituximab prescribing information in sections 4.4 and 4.8 were added. Changes were made for text compliance with the SPC guideline and QRD templates. The Package Leaflet has been revised accordingly.
II/0010	Quality changes	28/06/2006	03/07/2006		

S/0009	Annual re-assessment.	23/03/2006	27/03/2006		
II/0008	Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/10/2005	15/11/2005	SmPC, Labelling and PL	Inclusion of "mucocutaneous reaction" in section 4.4 and 4.8 of the SPC, to revise some of the values of radiation absorbed doses under section 5.4, to update the ATC code and to add some editorial changes. The PL was updated accordingly. Editorial changes have been implemented in the Labeling and PL.
II/0006	Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	27/07/2005	SmPC and PL	Update of the SPC to include in section 4.2 drug administration alternatively on days 7, 8 and 9, and to express radioactivity values in exact figures to add a warning on infusion reactions under section 4.4 and to change the presentation of ADRs in section 4.8. The PL was updated accordingly.
S/0007	Annual re-assessment.	21/04/2005	08/07/2005	Annex II	
IB/0005	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	04/02/2005	n/a	SmPC	
II/0004	Quality changes	15/12/2004	20/12/2004		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/09/2004	n/a	PL	
II/0001	Quality changes	16/09/2004	22/09/2004		
II/0002	Quality changes	16/09/2004	21/09/2004		