Gazyvaro

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/0059	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	28/11/2024	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).

PSUSA/10279 /202310	Periodic Safety Update EU Single assessment - obinutuzumab	27/06/2024	06/09/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10279/202310.
II/0054/G	This was an application for a group of variations. Grouped application comprising two variations as follows: C.I.4 - Update of section 4.8 of the SmPC in order to add cytokine release syndrome (CRS) to the list of adverse drug reactions (ADRs) with frequency rare, based on the cumulative review of the MAH safety database, clinical trials and literature. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.3. A.6 - To change the ATC Code of Obinutuzumab from L01XC15 to L01FA03. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/09/2024		SmPC and PL	Not applicable.
IB/0055	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/12/2023	n/a		
IA/0057/G	This was an application for a group of variations.	06/12/2023	n/a		

	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.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
IA/0056	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	06/12/2023	n/a		
II/0053/G	This was an application for a group of variations. 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.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.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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/09/2023	06/09/2024	Annex II	
II/0051	Update of section 4.8 of the SmPC in line with the SmPC Guideline following the recommendation by PRAC in the outcome for the signal assessment of	01/09/2022	05/05/2023	SmPC and PL	SmPC new text The tabulated list of ADRs is updated to reflect: Infections and infestations Hepatitis B reactivation

	non-overt disseminated intravascular coagulation (DIC) (EPITT no: 19711). The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				frequency Uncommon Nervous system disorders: Progressive multifocal leukoencephalopathy frequency Not known Gastrointestinal disorders: gastrointestinal perforation frequency Common For more information, please refer to the Summary of Product Characteristics.
II/0050	B.I.e.1.a - Introduction of a new design space or extension of an approved design space for the AS - One unit operation in the manufacturing process of the AS including the resulting IPCs and/or test procedures	01/09/2022	n/a		
II/0047	Submission of the final report from study BO21223/GALLIUM listed as a category 3 study in the RMP. This is an open-label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of obinutuzumab administration at standard infusion rate plus chemotherapy followed by obinutuzumab maintenance therapy for responders (G-chemo arm) compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for responders (R-chemo arm) in patients with previously untreated advanced indolent non-Hodgkin's lymphoma (iNHL). The RMP version 9.0 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	21/07/2022	05/05/2023	SmPC	Please refer to Scientific Discussion 'Gazyvaro-H-C-2799-II-0047. For more information, please refer to the Summary of Product Characteristics.

IAIN/0049	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/05/2022	05/05/2023	SmPC and PL	
IB/0048	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	19/04/2022	n/a		
IB/0046/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.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.g.3 - Deletion of an approved change management protocol related to the finished product B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/02/2022	n/a		

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.e.3 - Deletion of an approved change management protocol related to the AS 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.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.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.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.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
II/0044/G	This was an application for a group of variations. C.I.4 Update of sections 4.2, 4.8 and 5.1 of the SmPC in	16/09/2021	19/10/2021	SmPC and PL	In patients with Follicular Lymphoma, obinutuzumab may be administered as a short (approximately 90 minutes) duration infusion after the first cycle of treatment, provided the patient did not experience Grade ≥3 infusion related reactions (IRRs) during the first cycle of treatment.

	order to include the administration of obinutuzumab as a short duration infusion (SDI) of approximately 90 minutes in patients with Follicular Lymphoma (FL), based on the end of induction safety and efficacy data from the ongoing Phase IV study MO40597 (GAZELLE); the Package Leaflet is updated accordingly. The RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.11.z Update of RMP version 8.0 to: - change the due date for the submission of the final CSR for Category 3 study BO21223 (GALLIUM), from Q4 2021 to Q1 2022; - remove important identified risks as per the PRAC Assessment Report for the PSUR covering period 01Nov2018 to 30Oct2019 (Procedure no.EMEA/H/C/PSUSA/00010279/201910); - correction of clinical cut-off dates and trial exposure data from previously conducted studies C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				For more information, please refer to the Summary of Product Characteristics.

IA/0045	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)	03/08/2021	n/a		
PSUSA/10279 /202010	Periodic Safety Update EU Single assessment - obinutuzumab	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/01/2021		SmPC, Annex II, Labelling and PL	
PSUSA/10279 /201910	Periodic Safety Update EU Single assessment - obinutuzumab	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0038	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/04/2020	n/a		
IB/0041/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/04/2020	n/a		
II/0036	Update of sections 4.8 and 5.1 of the SmPC based on data from the final CSR of the pivotal study GA04753g/GO01297/GADOLIN to fulfill a Category 3	13/02/2020		SmPC and PL	In the pivotal clinical study in patients with indolent Non-Hodgkin's lymphoma (GAO4753/GADOLIN), 97% (171 out of 176) of evaluable patients treated with Gazyvaro were

	PAM (MEA 006). The PL and RMP are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				B-cell depleted at the end of the treatment period, and 97% (61 out of 63) remained depleted for more than 6 months from the last dose. Recovery of B-cells was observed within 12-18 months of follow-up in 11% (5 out of 46) of evaluable patients. At final analysis, the median observation time was 45.9 months (range: 0-100.9 months) for follicular lymphoma patients in the bendamustine arm and 57.3 months (range: 0.4-97.6 months) for patients in the Gazyvaro+bendamustine arm, representing an additional 25.6 months and 35.2 months of median follow-up in the two arms, respectively, since the primary analysis. Overall, the investigator assessed efficacy results were consistent with what was observed in the primary analysis. For more information please refer to the Summary of Product Characteristics.
IA/0040	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	07/02/2020	n/a		
II/0037	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	16/01/2020	n/a		
IA/0035/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	02/10/2019	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release) B.I.a.z - Change in manufacture of the AS - Other variation				
II/0034	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	11/07/2019	n/a		
PSUSA/10279 /201810	Periodic Safety Update EU Single assessment - obinutuzumab	16/05/2019	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	31/01/2019	02/04/2019	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Gazyvaro in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/1070	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	04/03/2019	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	02/04/2019	PL	
IB/0029	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished	25/07/2018	n/a		

	product - Other variation				
II/0028	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	19/07/2018	n/a		
IB/0027	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/05/2018	n/a		
II/0023	Update of section 4.8 and 5.1 of the SmPC in order to update the overall survival data based on final results from study BO21004/CLL11 listed as a category 3 study in the RMP; this is the pivotal study that evaluated the efficacy and safety of obinutuzumab as therapy for patients with previously untreated CLL with comorbidities; The RMP version 4.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity format the listing of "other side effects" and correct the term heart attack to heart failure in section 4 of the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/05/2018	02/04/2019	SmPC and PL	Section 4.8 and 5.1 of the SmPC were updated to amend the overall survival data based the final results from a study that evaluated the efficacy and safety of obinutuzumab as therapy for patients with previously untreated CLL with comorbidities.
PSUSA/10279 /201710	Periodic Safety Update EU Single assessment - obinutuzumab	17/05/2018	n/a		PRAC Recommendation - maintenance

IB/0026/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/04/2018	n/a		
IB/0025	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	14/04/2018	n/a		
T/0024	Transfer of Marketing Authorisation	15/03/2018	06/04/2018	SmPC, Labelling and PL	
IB/0021	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	20/12/2017	n/a		
PSUSA/10279 /201704	Periodic Safety Update EU Single assessment - obinutuzumab	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0020	Update of section 4.4 of the SmPC to revise the safety information on delayed hypersensitivity reactions based on a review of relevant cases by the Marketing authorisation holder (MAH). In addition, the MAH took the opportunity to introduce editorial changes to the SmPC and package leaflet.	26/10/2017	06/04/2018	SmPC and PL	Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to clinically distinguish from infusion related reactions. Hypersensitivity symptoms can occur after previous exposure and very rarely with the first infusion. If a hypersensitivity reaction is suspected

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated.
II/0016	Extension of Indication to include a new indication for Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance. In addition, the due date for provision of the final clinical study report of study BO21223/GALLIUM listed in the Gazyvaro RMP as Category 3 has been updated. Furthermore, the Annex II is brought in line with the latest QRD template (version 10). In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/07/2017	18/09/2017	SmPC, Annex II and PL	Please refer to the published Assessment Report Gazyvaro H-2799-II-016.
PSUSA/10279 /201610	Periodic Safety Update EU Single assessment - obinutuzumab	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0013/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a	15/12/2016	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.g.1.a - Introduction of a new design space or extension of an approved design space for the finished product - One or more unit operations in the manuf. process of the FP including the resulting IPCs and/or test procedures				
PSUSA/10279 /201604	Periodic Safety Update EU Single assessment - obinutuzumab	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0015/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	17/11/2016	n/a		
IB/0017	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2016	n/a		

IB/0014	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/10/2016	n/a		
IB/0012	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/08/2016	n/a		
II/0007	Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the MAH took the opportunity to make editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/04/2016	13/06/2016	SmPC and PL	Please refer to the scientific discussion for Gazyvaro EMEA/H/C/002799/II/0007
II/0010	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	26/05/2016	n/a		
PSUSA/10279 /201510	Periodic Safety Update EU Single assessment - obinutuzumab	13/05/2016	n/a		PRAC Recommendation - maintenance
II/0009	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	01/04/2016	20/05/2016	Annex II and	

	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			Labelling	
PSUSA/10279 /201504	Periodic Safety Update EU Single assessment - obinutuzumab	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0005	B.I.b.z - Change in control of the AS - Other variation	22/07/2015	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		
II/0003	Update of the SmPC sections 4.2 and 4.4 to revise the wording related to tumour lysis syndrome (TLS) in order to emphasize the importance of pre-medication and careful monitoring of patients at risk of TLS. In addition, text relating to batch number has been included in section 4.4 of the SmPC to improve the traceability of biological medicinal products. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	20/05/2016	SmPC and PL	
PSUSA/10279 /201410	Periodic Safety Update EU Single assessment - obinutuzumab	07/05/2015	n/a		PRAC Recommendation - maintenance

IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		