Venclyxto

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0044/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.1.e - Replacement or addition of a	04/01/2023	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).

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
II/0042	Update of section 5.1 of the SmPC in order to update data supporting the efficacy of the combined regimen of obinutuzumab and venetoclax (VEN+G; also known as GDC-0199 or ABT-199) versus obinutuzumab plus chlorambucil (GClb) in previously untreated CLL patients based on final results from study BO25323/CLL14; this is a prospective, open-label, multicenter randomized phase 3 trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax (GDC-0199/ABT-199) versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/10/2022		SmPC	For more information, please refer to the Summary of Product Characteristics.
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2022		PL	
PSUSA/10556 /202112	Periodic Safety Update EU Single assessment - venetoclax	07/07/2022	n/a		PRAC Recommendation - maintenance

IB/0041	To change the milestones due dates for some category 3 studies. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/05/2022	n/a		To change the milestones due dates for some category 3 studies.
IB/0039	A.z - Administrative change - Other variation	22/03/2022		SmPC and PL	
IA/0038	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	06/12/2021	n/a		
II/0036	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/09/2021	n/a		
II/0035	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/09/2021	n/a		
PSUSA/10556 /202012	Periodic Safety Update EU Single assessment - venetoclax	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0037	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	22/06/2021	n/a		
II/0031	to update venetoclax SmPC wording regarding Tumor lysis syndrome (TLS) prophylaxis and management	20/05/2021	21/06/2021	SmPC, Annex II and PL	This procedure concerns an application to update of product information for venetoclax related to TLS (tumor lysis

	following an update to the Company Core Data Sheet (CCDS), as well as amendment of the annex II.D to propose additional risk minimisation measures in the form of Patient Card implementation and Direct Healthcare Professional Communication (DHPC) distribution as result of a medical safety assessment conducted on TLS post-marketing reports. The Package leaflet and RMP (version 8) have also been updated, accordingly. The proposed changes to the SmPC include section 4.2 and 4.4: • Section 4.2: A more prescriptive table which replaces the text around the risk assessment, prophylaxis and monitoring measures based on the level of tumor burden. In addition, the text on the recommended dose modifications for toxicities is replaced by a table format for clarity. • Section 4.4: the text is revised to emphasize the fact that TLS occur in all patients and requires adequate risk assessment that considers comorbidities, particularly renal impairment, and other risk factors such as splenomegaly. The Annex A has also been updated at EMA request. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				syndrome) prophylaxis and management following a medical safety assessment conducted by MAH on post-marketing reports of TLS. The EMA scientific committees CHMP and PRAC included a request for additional minimisation measures and educational material for which a Direct Healthcare Professional Communication (DHPC) with the purpose of informing EU prescribers of the product changes which encompass the totality of CLL patients treated with Venclyxto as well as to emphasize that adherence to TLS mitigation measures as per SmPC is essential in these patients. A patient card has also been included since the Package leaflet as the routine risk minimisation measure is not considered a sufficient tool for such serious risk and the available evidence of its background. The proposed key elements are the following: contact details on the prescriber and the patient, signs and symptoms of TLS, the need to seek immediate medical attention in case of their occurrence, a warning message for healthcare professionals treating the patient at any time that this treatment is associated with the risk of TLS and the need to carry the card at any time. The SmPC section 4.2 and 4.4, Annex II, and PL has been updated accordingly.
II/0030	Extension of indication for Venclyxto (venetoclax) in combination with Hypomethylating Agents (HMAs) for the treatment of adult patients with newly-	22/04/2021	19/05/2021	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Venclyxto-H-C-Product Number-II-30

	diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. As a consequence, Sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0032	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2021	19/05/2021	SmPC	
PSUSA/10556 /201912	Periodic Safety Update EU Single assessment - venetoclax	09/07/2020	n/a		PRAC Recommendation - maintenance
IB/0028	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	04/06/2020	n/a		
IA/0029/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	29/05/2020	n/a		

	changes to an approved test procedure				
PSUSA/10556 /201906	Periodic Safety Update EU Single assessment - venetoclax	30/01/2020	08/04/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10556/201906.
II/0023/G	This was an application for a group of variations. Extension of indication to include, in combination with an anti-CD20 antibody (obinutuzumab), treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Venclyxto based on the results of the pivotal CLL14/BO25323 phase 3 study; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC and corresponding sections of the PL have been revised. The updated RMP version 5.4 has been agreed. Additionally, the SmPC section 5.3 has been updated based on the results of a 4-week dose ranging study, a 6-month carcinogenicity study and two embryo-foetal development (EFD) studies in mice. Minor editorial changes have been introduced throughout the Product Information. The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	30/01/2020	09/03/2020	SmPC and PL	Please refer to Scientific Discussion Venclyxto-H-C-4106-II-23-G.

	data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0026/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	10/10/2019	n/a		
II/0020	Update of sections 4.2 and 5.2 of the SmPC in order to modify posology recommendations in patients with severe hepatic impairment and to reflect the final results of study M15-342 (A Study to Evaluate the	29/05/2019	28/06/2019	SmPC and PL	In a dedicated hepatic impairment study, venetoclax Cmax and AUC in subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment were similar to subjects with normal hepatic function, after

	Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment) listed as a category 3 study in the RMP; the Package Leaflet is updated accordingly. The RMP version 3.4 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				receiving a 50 mg single dose of venetoclax. In subjects with severe (Child-Pugh C; n=5) hepatic impairment, the mean venetoclax Cmax was similar to subjects with normal hepatic function but venetoclax AUCinf was on average 2.7-fold higher (range: no change to 5-fold higher) than venetoclax AUCinf in the subjects with normal hepatic function. In conclusion, a dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment. These patients should be monitored more closely for signs of toxicity.
PSUSA/10556 /201812	Periodic Safety Update EU Single assessment - venetoclax	14/06/2019	n/a		PRAC Recommendation - maintenance
IB/0021/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/02/2019	n/a		

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size				
PSUSA/10556 /201806	Periodic Safety Update EU Single assessment - venetoclax	17/01/2019	n/a		PRAC Recommendation - maintenance
II/0016	Submission of the report from study M13-982 listed as a category 3 study in the RMP. This is a Phase 2 Open-Label Study of the Efficacy of ABT199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion. Following the CHMP request, the MAH has updated SmPC section 4.8 with updated safety data from M13-982 and M14-032 studies. Frequency of following adverse reactions has been upgraded from common to very common: Pneumonia, Lymphopenia, Hyperkalaemia, Hypocalcaemia. The package leaflet has been updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/12/2018	28/06/2019	SmPC and PL	The interim analysis of study M13-982, which is listed as additional activity category 3 study in the risk management plan (RMP), was submitted by MAH as required. The aim of the study was to better characterise the Safety in long-term exposure (> 12 months) of venetoclax and second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy. Study M13-982 is now fully enrolled and exposure time is longer compared to previously submitted data; the efficacy endpoints do not differ from previously reported data; the safety profile is consistent with previous data. Approximately 14% of patients experienced Richter’s transformation and 15% reported a second primary malignancy. No clear pattern has been detected regarding the different types of second primary malignancies reported. A causal association between venetoclax administration and Richter transformation / other second primary malignancies cannot be ruled out based on the available data and the MAH is required to submit a final study report for M13-982. In addition, following the CHMP request, the MAH has

					updated SmPC section 4.8 with updated safety data from M13-982 and M14-032 studies. Frequency of following adverse reactions has been upgraded from common to very common: Pneumonia, Lymphopenia, Hyperkalaemia, Hypocalcaemia. The package leaflet has been updated accordingly.
II/0011	The Annex II is being updated following the fulfilment of Specific Obligation, which was requested to confirm the efficacy and safety of venetoclax in monotherapy, based on the assessment of interim study report of M14-032. In addition, section 5.1 of SmPC is being updated to reflect the updated results of Study M14-032. The Package Leaflet is updated accordingly. Study M14-032 is: a phase II open-label study investigating efficacy and safety of venetoclax in patients with CLL with relapse or refractory to B-cell receptor signalling pathway inhibitor therapy, listed as a category 2 study in the RMP. The CHMP recommends granting of a marketing authorisation no longer subject to specific obligations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/09/2018	20/11/2018	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Venclyxto-H-C-4106-II-11'.
II/0008	Extension of Indication to include Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	20/09/2018	29/10/2018	SmPC, Annex II and PL	Please refer to the Scientific Discussion – Venclyxto II-08.

	As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. This submission also fulfils the Annex II condition to submit the results of the MURANO study comparing venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL. In addition, RMP version 3.3 (in version 2 of the RMP template) is being approved. The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0019	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)	05/10/2018	28/06/2019	SmPC	
R/0013	Renewal of the marketing authorisation.	26/07/2018	06/09/2018		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Venclyxto, subject to the

					Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10556 /201712	Periodic Safety Update EU Single assessment - venetoclax	28/06/2018	23/08/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10556/201712.
IA/0017	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	07/08/2018	n/a		
IB/0015	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/07/2018	n/a		
IAIN/0014	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	13/07/2018	n/a		
T/0012	Transfer of Marketing Authorisation	30/05/2018	31/05/2018	SmPC, Labelling and PL	
II/0007/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to update the drug-drug interaction between venetoclax and digoxin based on final results from study M16-042; this is study to assess the effect of venetoclax on the pharmacokinetics of digoxin in healthy female subjects. Update of section 4.5 of the SmPC in order to update	22/03/2018	31/05/2018	SmPC, Labelling and PL	Section 4.5 of SmPC has been updated to include additional information on interactions between venetoclax and ritonavir, which is a strong CYP3A and P-gp inhibitor, in healthy subjects co-administration resulted in increased venetoclax Cmax and AUC. Information on co-administration of azithromycin with venetoclax has been included in section 4.5 of SmPC, in healthy subjects a decrease in venetoclax Cmax and AUC∞ were observed. However, no dose adjustment is considered

	the drug-drug interaction between venetoclax and ritonavir, based on final results from study M15-719; this is study to assess the effect of ritonavir on the pharmacokinetics of venetoclax in healthy female subjects of non-childbearing potential. Update of section 4.5 of the SmPC in order to update the drug-drug interaction between venetoclax and azithomycin, based on final results from study M16-068; this is study to assess effect of azithromycin on the pharmacokinetics of venetoclax in healthy female subjects. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				necessary during short-term use of azithromycin when administered concomitantly with venetoclax. In addition, the information is included on interaction between venetoclax with digoxin, a P-gp substrate, which resulted in an increase in digoxin Cmax and a AUC. The SmPC already includes warning that co administration of narrow therapeutic index P gp, or BCRP substrates with venetoclax should be avoided.
IB/0009	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/02/2018	n/a		
PSUSA/10556 /201706	Periodic Safety Update EU Single assessment - venetoclax	11/01/2018	n/a		PRAC Recommendation - maintenance
R/0005	Renewal of the marketing authorisation.	14/09/2017	30/10/2017		

II/0003	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	n/a		
IA/0004	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	28/04/2017	30/10/2017	SmPC	
IB/0001/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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.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.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	10/03/2017	n/a		

IAIN/0002/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/02/2017	n/a		