Imbruvica

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
PSUSA/10301 /202311	Periodic Safety Update EU Single assessment - ibrutinib	27/06/2024	22/08/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/202311.
IAIN/0087	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	02/08/2024	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).

	pharmaceutical group as the currently approved manufacturer				
IA/0086/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	13/05/2024	n/a		
II/0083	Update of section 5.1 of the SmPC following the 24-month extended follow up from primary analysis data from Study CLL3011. This is a randomized, open-label, Phase 3 Study of the combination of Ibrutinib plus Venetoclax versus Chlorambucil plus Obinutuzumab for the First-line Treatment of Subjects with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). In addition, the MAH took the opportunity to add a footnote to the dose modifications table for non-cardiac events in section 4.2 to define the grading systems used for the adverse reactions. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2024	22/08/2024	SmPC	SmPC new text For more information, please refer to the Summary of Product Characteristics.
IB/0084	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	08/01/2024	n/a		

	authorisation, including the RMP - Other variation				
PSUSA/10301 /202211	Periodic Safety Update EU Single assessment - ibrutinib	22/06/2023	15/09/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/202211.
II/0082	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/08/2023	n/a		Submission of the final report from study PCI-32765CAN3001 in order to address the Post Authorization Measure (MEA017); this is a phase 3b, multicenter, open-label long-term extension study designed to collect long-term safety data.
IB/0079	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		
IA/0081	B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	12/05/2023	n/a		
IAIN/0080/G	This was an application for a group of variations. B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	03/04/2023	15/09/2023	Annex II and PL	

II/0075	Update of section 4.2 of the SmPC to incorporate information specific for dose modifications for non-cardiac events and events of cardiac failure or cardiac arrhythmias events based on data pool from clinical studies which included 4 Phase II (PCYC-1102-CA, PCYC-1104-CA, PCYC-1118E, PCYC-1142-CA) and 8 Phase III studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, CLL3011, and MCL3002). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2022	15/11/2022	SmPC	SmPC new text: please refer to the Summary of Product Characteristics.
II/0074	Update of section 4.2, 4.8, 5.1, and 5.2 of the SmPC in order to update the information related to Paediatrics following assessment done in procedure P46/035, based on results from the paediatric study LYM3003 "A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma". The Package Leaflet is updated accordingly. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	21/07/2022	24/08/2022	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.
II/0070	Extension of the existing CLL indication to include combination treatment with venetoclax for previously	23/06/2022	02/08/2022	SmPC and PL	Please refer to Scientific Discussion 'Imbruvica-H-C-3791-

	untreated patients based on efficacy and safety data from phase 3 study GLOW and phase 2 study CAPTIVATE; 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 is updated accordingly. The RMP was amended as version 19.3 in line with the extension of indication. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				II-0070’
II/0069	Update of the SmPC section 4.4. to include information on fatal and serious cardiac arrythmias and cardiac failure, relevant warnings and periodical monitoring of patients and update of the SmPC Section 4.8 to include cardiac arrest as an ADR following a safety assessment for increased risk of sudden death/cardiac death with the use of ibrutinib. Section 2 of the PL has been updated accordingly. Typographical errors have been corrected throughout the PI. The revised RMP version 19.4 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2022	24/08/2022	SmPC and PL	Update of SmPC new text For more information, please refer to the Summary of Product Characteristics.
IB/0077/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	20/07/2022	n/a		

	re-test period/storage period supported by real time data 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				
IB/0076/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.5.z - Change in pack size of the finished product - Other variation B.II.e.5.z - Change in pack size of the finished product - Other variation B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	12/07/2022	24/08/2022	SmPC and Labelling	
PSUSA/10301 /202111	Periodic Safety Update EU Single assessment - ibrutinib	10/06/2022	n/a		PRAC Recommendation - maintenance
IA/0071	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	17/01/2022	n/a		

II/0068	Update of section 4.4 of the SmPC in order to add baseline monitoring in addition to the current warnings for periodic monitoring of cardiac failure and cardiac arrhythmias in patients receiving ibrutinib. The Package Leaflet is updated accordingly. The RMP version 18.2 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/12/2021	02/08/2022	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.
PSUSA/10301 /202011	Periodic Safety Update EU Single assessment - ibrutinib	24/06/2021	20/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/202011.
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2021	20/08/2021	PL	
II/0064	Update of the SmPC section 5.1 to include PFS2 and data from the final analysis with long term follow-up relevant to the Waldenström's macroglobulinaemia (WM) indication and section 4.8, to include the long-term safety cumulative data - following the submission of the addendum to the final clinical study report from Study PCYC-1127-CA. In addition, an amendment to section 4.4 of the SmPC to add adequate language regarding excipients with known effect and an amendment to Table 1 of the SmPC to include a footnote by cardiac failure to reflect inclusion of events with fatal outcomes were implemented.	28/01/2021	20/08/2021	SmPC	For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0065/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/01/2021	20/08/2021	SmPC and PL	
II/0061	Update of the RMP introducing changes to safety concerns following the assessment of the renewal R/0049. The MAH is taking this opportunity to include additional changes related to two post-authorisation measures; postponement of the completion date of study cat3 study PCI-32765MCL3002 of ibrutinib in combination with BR versus BR alone and removal of Study 54179060CLL1017 on DDI as assessed in II/0058. 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	01/10/2020	n/a		
II/0059	Extension of indication in chronic lymphocytic leukaemia (CLL) to add combination with rituximab as follows: In combination with rituximab or	23/07/2020	28/08/2020	SmPC, Labelling and	Please refer to Scientific Discussion Imbruvica-H-C-3791-II-0059.

	obinutuzumab for the treatment of adult patients with previously untreated CLL. This extension of the approved CLL indication is based on results from the Phase 3 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG ACRIN) Study E1912 (also referred to as PCYC-1126e-CA). The SmPC is revised to include information related to the new indication. The PL has been revised accordingly. Minor editorial changes have been implemented in Annex IIIA. An updated RMP has been submitted. Furthermore, the MAH took the opportunity to update the list of local representatives for Hungary in Sweden in the PL. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			PL	
PSUSA/10301 /201911	Periodic Safety Update EU Single assessment - ibrutinib	25/06/2020	19/08/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/201911.
IA/0063/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 A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new/updated or	28/07/2020	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
IAIN/0062/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	12/06/2020	n/a		
II/0058	Update of Sections 4.5, 4.6 and 5.2 of the SmPC following the results from study CLL1017 (MEA 012.2). The PL is updated accordingly. In addition, the MAH took the opportunity to update the PI to the latest QRD template v10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/04/2020	17/07/2020	SmPC, Annex II and PL	
II/0053	Update of section 5.1 of the SmPC with final results on PFS by investigator assessment in Study PCYC-1112-CA, including PFS2 and overall survival data until study closure per protocol at 65-months follow-up. The Annex II is updated accordingly with deletion of ANX 003. The contact details of the local representatives have been updated in the Package Leaflet. Minor editorial revisions have been proposed throughout the PI.	05/12/2019	17/07/2020	SmPC, Annex II and PL	With a median follow-up time on study of 65 months in Study PCYC-1112-CA, the median investigator-assessed PFS2 (time from randomisation until PFS event after first subsequent anti-neoplastic therapy) according to IWCLL criteria was 65.4 months [95% CI (51.61, not estimable)] in the IMBRUVICA arm and 38.5 months [95% CI (19.98, 47.24)] in the ofatumumab arm, respectively; HR=0.54 [95% CI (0.41, 0.71)]. The median OS was 67.7 months

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				[95% CI (61.0, not estimable)] in the IMBRUVICA arm.
II/0052	Update of section 4.8 of the SmPC based on final results from study PAM 3038-1, which assessed long term safety data collected from predefined cohorts of subjects treated with ibrutinib for up to 5 years or until disease progression or unacceptable toxicity at the recommended daily doses of 420 mg/day for CLL/SLL and 560 mg/day for MCL (MEA 025). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/12/2019	17/07/2020	SmPC	The long-term safety data over 5 years from 1178 patients (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n = 646, and relapsed/refractory MCL n = 370) treated with IMBRUVICA were analysed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0 1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.
IAIN/0057	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	17/07/2020	SmPC and PL	
IA/0055/G	This was an application for a group of variations. 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	15/11/2019	n/a		

	manufacturer of a novel excipient B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IAIN/0056	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	08/11/2019	n/a		
PSUSA/10301 /201811	Periodic Safety Update EU Single assessment - ibrutinib	27/06/2019	06/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/201811.
IA/0054/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	13/08/2019	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place 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.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.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				
II/0047	Extension of indication to include combination use with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Imbruvica based on data from the phase 3 study PCYC-1130-CA; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) is agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2019	02/08/2019	SmPC and PL	Please refer to Scientific Discussion Imbruvica–H-C-3791-II-0047.

II/0046	Extension of Indication to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab; as a consequence, section 4.1 and 4.8 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2019	02/08/2019	SmPC and PL	Please refer to Scientific Discussion Imbruvica–H-C-3791-II-0046.
II/0048	Update of section 4.4 of the SmPC in order to amend the existing warning on bleeding-related events based on the final report of the non-interventional PASS PCYC-PMR-2060-4 aimed to evaluate the risks of major haemorrhage with the administration of Imbruvica; this is a category 3 study in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2019	17/07/2020	SmPC	Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding. Supplements such as fish oil and vitamin E preparations should be avoided.
R/0049	Renewal of the marketing authorisation.	26/04/2019	25/06/2019	SmPC and PL	
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/05/2019	02/08/2019	Labelling and PL	
IB/0045/G	This was an application for a group of variations.	27/03/2019	25/06/2019	SmPC, Annex II, Labelling	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing 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 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 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 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			and PL	

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.				

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)				
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	25/06/2019	PL	
PSUSA/10301 /201711	Periodic Safety Update EU Single assessment - ibrutinib	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/10301/201711.
X/0037	Annex I_2.(d) Change or addition of a new pharmaceutical form	26/04/2018	29/06/2018	SmPC, Labelling and PL	
IA/0043/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 B.III.1.b.2 - Submission of a new/updated or	14/06/2018	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
II/0042	Update of section 5.3 of the SmPC in order to update preclinical safety data information based on final results from a non-clinical carcinogenicity study in mouse (MEA011.1). In addition, the Marketing authorisation holder (MAH) took the opportunity to align the Package leaflet to information already included in the SmPC and to update the list of local representatives for Lithuania, Czech Republic, Netherlands, Slovenia and Portugal in the Package Leaflet.	31/05/2018	23/08/2018	SmPC and PL	Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day with an exposure margin of approximately 23 (males) to 37 (females) times the human AUC of ibrutinib at a dose of 560 mg daily.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0040/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/03/2018	n/a		
PSUSA/10301 /201705	Periodic Safety Update EU Single assessment - ibrutinib	14/12/2017	09/02/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/201705.
II/0039	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/01/2018	n/a		
IB/0038/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	17/11/2017	n/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.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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.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.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - 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) B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
II/0033/G	This was an application for a group of variations. C.I.4 (Type II) - Update of sections 4.4 and 5.1 of the SmPC in order to update the safety information related to bleeding related events based on final results from study PCYC-1132-NT listed as a	28/09/2017	09/02/2018	SmPC, Annex II and PL	The results of a new in vitro platelet aggregation study PCYC-PMR-2060-03 In Vitro Studies on the Effect of Ibrutinib on Platelet Function were submitted and sections 4.4 and 5.1 of the SmPC were updated to include a statement that the mechanism for the bleeding events is not understood. The results of a new DDI study LYM1003

	category 3 (MEA 004.1) study in the RMP; this is an in-vitro study to evaluate the effect of ibrutinib on platelet aggregation ;The Package Leaflet is updated accordingly. C.I.4 (Type II) - Update of section 4.4 and 4.5 of the SmPC in order to update the safety information based on final) results from study LYM1003 listed as a category 3 study in the RMP (MEA 009.1); this is a drug-drug interaction study to assess steady state PK of repeated oral doses of ibrutinib alone in patients with B-cell malignancies and when combined with a moderate and strong CYP3A inhibitor; The Package Leaflet is updated accordingly. C.I.4 (Type II) - Update of section 4.5 of the SmPC in order to update the safety information based on final results from study FK12024; this is a DDI study with CYP3A inhibitor posaconazole, in simulated subjects; The Package Leaflet is are updated accordingly. C.I.4 (Type II) - Update of section 4.4 of the SmPC in order to update the safety information on antimicrobial prophylaxis following routine pharmacovigilance activity. C.I.11.z (Type IB) - Submission of an updated RMP in order to extend the closure date of study PCYC-1112-CA (ANX 003.2) to Q2 2019. Yearly updates will be submitted in Q2 2017 and Q2 2018. Annex II has been updated accordingly.				confirm the previous recommendation for concomitant administration of a strong CYP3A4 inhibitor with ibrutinib. i.e. a dose reduction to 140 mg; sections 4.4 and 4.5 of the SmPC have been updated accordingly. A recommendation to use prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections and are treated with Imbruvica is added in section 4.4 of the SmPC.

	C.I.11.a (Type Iain) - To update the RMP to include an additional action for Study PCI-32765 CAN3001 (MEA017) to provide a ”further interim report in 5 years’ from time from the cut-off date of the current report (12 November 2015)”. This change has been agreed by the CHMP in the outcome of EMA/H/C/ 003791/MEA/017. The RMP version 6.8 has been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and Annex II 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 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 C.I.11.a - Introduction of, or change(s) to, the				

	obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/10301 /201611	Periodic Safety Update EU Single assessment - ibrutinib	22/06/2017	24/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/201611.
II/0034	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/06/2017	n/a		
IB/0035	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)	18/05/2017	24/08/2017	SmPC	
II/0029	Update of sections 4.5 of the SmPC to amend the statement on interaction between products increasing stomach pH and ibrutinib have not been studied and section 5.2 to include the findings from study CLL1005. The Package Leaflet is not impacted by these changes. In addition, the RMP is updated to version 6.3 to reflect this new safety information. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to	18/05/2017	24/08/2017	SmPC	4.5 Interaction with other medicinal products and other forms of interaction Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. A lower Cmax was observed in fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days (see section 5.2). There is no evidence that the lower Cmax would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical trials. 5.2 Pharmacokinetic properties

	new quality, preclinical, clinical or pharmacovigilance data				Absorption Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days, compared to ibrutinib alone, geometric mean ratios (90% CI) were 83% (68-102%), 92% (78-110%), and 38% (26-53%) for AUC0-24, AUClast, and Cmax, respectively.
II/0032/G	This was an application for a group of variations. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions 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.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.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	21/04/2017	n/a		

	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.z - Change in immediate packaging of the AS - Other variation				
II/0025	Update of the SmPC section 4.4 to remove the warning and precaution regarding the effect of Ibrutinib on the QT interval and section 5.1 to provide additional information regarding the pharmacodynamic effect of Ibrutinib on QT/QTc intervals and cardiac electrophysiology. No changes to the Annex III Package Leaflet are proposed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	24/08/2017	SmPC	4.4 Special warnings and precautions for use The below paragraph has been removed: Effects on the QT interval In a phase 2 study, ECG evaluations showed IMBRUVICA produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding are not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome). 5.1 Pharmacodynamic properties The below paragraph has been inserted:

					Effect on QT/QTc interval and cardiac electrophysiology The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomised, double blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2 sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (5.3 ms [90% CI: 9.4, 1.1] at a Cmax of 719 ng/mL following the supratherapeutic dose of 1680 mg).
PSUSA/10301 /201605	Periodic Safety Update EU Single assessment - ibrutinib	15/12/2016	17/02/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10301/201605.
II/0027/G	This was an application for a group of variations. C.I.4 - Update of sections 4.8 in order to include Stevens-Johnson Syndrome (SJS) and Onychoclasis as post-marketing adverse drug reactions (ADRs). In addition the applicant has taken the opportunity to make minor editorial amendments to the SmPC, including an editorial amendment to section 4.8 to mark the existing ADR terms of tumor lysis syndrome (added in variation EMEA/H/C/003791/II/0004), erythema, angioedema, and urticaria (added in variation EMEA/H/C/003791/0008/G) with an "a" referring to the existing ADR table footnote that indicates that they originated from spontaneous post-marketing reports.	15/12/2016	17/02/2017	SmPC and PL	4.4 Special warnings and precautions for use Atrial fibrillation/flutter Atrial fibrillation and atrial flutter have been reported in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms or new onset of dyspnoea should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed. 4.8 Undesirable effects Skin and subcutaneous tissue disorders: ☐ Onychoclasis: Common

	C.I.4 – Update of section 4.4 to include Hypertension as one of the risk factors for atrial fibrillation/flutter. 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				☐ Stevens Johnson syndrome: Not known
IA/0030/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.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	28/10/2016	n/a		

	Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/10/2016	n/a		
II/0017/G	This was an application for a group of variations. Extension of Indication for use of Imbruvica in combination with bendamustine and rituximab in patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Annex II are updated. The Package Leaflet is updated in accordance. In addition, a clarification is made that the indications in mantle cell lymphoma (MCL) and Waldenstroem's macroglobulinaemia (WM) refer to use of ibrutinib as single agent. In addition, the Marketing authorisation holder (MAH) introduced minor editorial changes throughout the product information. The RMP is updated accordingly (RMP version 6.1). 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	21/07/2016	25/08/2016	SmPC, Annex II and PL	Please refer to the scientific discussion Imbruvica EMEA/H/C/003791/II/0017/G

	new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0024	Update of sections 4.4 and 4.8 of the SmPC in order add a warning relating to Interstitial Lung Disease and to include it as a post-marketing adverse drug reaction with "common" frequency. The Package leaflet and RMP (version 6.1) are updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to updated the list of local representatives in the Package Leaflet Furthermore, the PI is brought in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	25/08/2016	SmPC, Labelling and PL	The MAH has reported six new cases of ILD, confirmed by bronchial biopsy, for which causality to ibrutinib could not be excluded from the available information. Based on these new cases from ibrutinib monotherapy studies and/or literature, section 4.4 of the SmPC for Imbruvica has been updated. Patients should be monitored for pulmonary symptoms indicative of ILD. If symptoms develop, Imbruvica should be interrupted and ILD managed appropriately. If symptoms persist, the risks and benefits of Imbruvica treatment should be considered and dose modification guidelines followed. Interstitial Lung Disease has also been added as an adverse reaction in section 4.8 of the SmPC. The incidence of ILD in clinical studies was 1.7%, considered a common (≥ 1/100 to < 1/10) adverse reaction.

PSUSA/10301 /201511	Periodic Safety Update EU Single assessment - ibrutinib	09/06/2016	n/a		PRAC Recommendation - maintenance
II/0016	Extension of indication to add the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) based on the results from the final CSR of study PCYC-1115-CA (MEA 021). As a consequence, sections 4.1, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC. A revised version of the RMP (version 5.0.3) has been approved as part of this application. 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	26/05/2016	SmPC and PL	Please refer to the Scientific Discussion Imbruvica-II-16.
IA/0023	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/05/2016	n/a		
II/0020	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
II/0018	Submission of final study reports in order to fulfil MEA 010: Non-clinical study reports for two studies undertaken in Transgenic (Tg) mice C.I.13 - Other variations not specifically covered	25/02/2016	n/a		Not applicable

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0013	Update of SmPC sections 4.8 and 4.9 with information on hepatic failure and hepatotoxicity. The PL and RMP are updated accordingly. Furthermore, the MAH took the opportunity to introduce editorial changes throughout the PI. The RMP version 4.5 was finally agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	26/05/2016	SmPC, Annex II and PL	
IA/0019/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 changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	22/12/2015	n/a		

	product - 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				
PSUSA/10301 /201504	Periodic Safety Update EU Single assessment - ibrutinib	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0007/G	This was an application for a group of variations. As agreed in the RMP and in order to address the post-authorisation measures: • Submission of final non-clinical study report FK10654. • Submission of final non-clinical study report FK10655. • Submission of final non-clinical study report FK10656. • Submission of final non clinical study report FK10806. • Following the submission of the non-clinical study report FK10657, update of section 4.5 of the SmPC regarding BRCP inhibition. • Following the submission of the non-clinical study reports FK10597, FK10598, FK10606, FK10650, FK10775 and FK10805, update of section 4.5 of the SmPC to delete the CYP3A4 inhibition statement. • Following the submission of the non-clinical study reports FK10804, FK10810, FK10811, FK10812 and FK10816, update of wording regarding the	22/10/2015	26/05/2016	SmPC and PL	

	coadministration with transport substrates/inhibitors in section 5.2 of the SmPC. • Following the submission of the non-clinical study reports FK10576, FK10577 and FK10643, update of wording regarding the coadministration with transport substrates/inhibitors in section 5.2 of the SmPC. The Package Leaflet has been updated accordingly and the updated RMP version 4.3 is agreed. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered				

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0015/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	14/10/2015	n/a		
IA/0014/G	This was an application for a group of variations. 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 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	24/09/2015	n/a		

	manufacturer of a novel excipient 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 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)				
II/0008/G	This was an application for a group of variations. 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	23/07/2015	26/05/2016	SmPC and PL	
IB/0012	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/07/2015	n/a		
IB/0010	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/07/2015	n/a		
II/0001	Extension of Indication to add treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for	21/05/2015	03/07/2015	SmPC and PL	Please refer to the Scientific Discussion Imbruvica-H-C-3791-II-01

	chemo-immunotherapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Furthermore, an updated RMP version 4.1 was approved as part of the application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0009/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.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 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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	02/07/2015	n/a		
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	05/03/2015	n/a		

	site				
II/0004	Update of section 4.4 and 4.8 of the SmPC in order to include a new warning regarding 'tumour lysis syndrome' (TLS). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	03/07/2015	SmPC and PL	Tumour lysis syndrome has been reported with IMBRUVICA therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Patients should be monitored closely and appropriate precautions taken. Tumour Lysis syndrome is also reported as new undesirable effect in the SmPC.
II/0003	Update of sections 4.2 and 5.2 of the SmPC with information related to patients with hepatic impairment, based on data from the final CSR for study PCI -32765CLL1006. The provision of study PCI-32765CLL1006 addresses MEA 014. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC, labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	03/07/2015	SmPC, Labelling and PL	Final results of study PCI -32765CLLl006 have been reflected in the product information for Imbruvica confirming the preliminary information regarding hepatic impaired patients. Dose recommendation have been maintained as already discussed at the time of authorisation and further pharmacology data have been added to the relevant section of the SmPC.
IA/0005/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	05/02/2015	n/a		

	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				
IB/0002/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	19/12/2014	n/a		