Iclusig

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
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	20/10/2022		Annex II and PL	
IB/0065/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	16/08/2022	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).

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site				
II/0061	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from the OPTIC study (AP24534-14-203) listed as a specific obligation in the Annex II. This is a randomised, open-label, Phase 2 trial of ponatinib in patients with chronic myeloid leukemia to characterise the efficacy and safety of ponatinib over a range of doses; the Package Leaflet is	24/03/2022	08/07/2022	SmPC, Annex II and PL	SmPC new text For more information, please refer to the Summary of Product Characteristics.

	updated accordingly. The RMP version 21.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0063	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/11/2021	08/07/2022	SmPC and PL	
IB/0062	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)	23/11/2021	08/07/2022	SmPC	
II/0060/G	This was an application for a group of variations. 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.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 B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.2.e - Change in test procedure for AS or	16/09/2021	n/a		

	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				
PSUSA/10128 /202012	Periodic Safety Update EU Single assessment - ponatinib	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0059	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	17/06/2021	08/07/2022	SmPC	
IA/0057/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier 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	15/01/2021	n/a		

IA/0056	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/07/2020	n/a		
PSUSA/10128 /201912	Periodic Safety Update EU Single assessment - ponatinib	09/07/2020	n/a		PRAC Recommendation - maintenance
II/0053	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	12/03/2020	n/a		
IA/0054	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	27/02/2020	n/a		
II/0051	Update of the RMP to version 19.1, including deletion of previously agreed safety concerns; these deletions are proposed in line with the guideline on Good Pharmacovigilance Practices (GVP) Module V on RMP (revision 2 - dated on 31 March 2017). Other updates include: review of the categorisation of the posterior reversible encephalopathy syndrome (PRES) risk in the RMP in line with the request from PSUSA/00010128/201712; correction of the category (from Category 3 to 1) of the study AP24534-14-203, an imposed Annex II condition; revision of the due date for the submission of this study report to August 2021, as described in the Iclusig PI, and as	05/09/2019	27/07/2020	Annex II	

	agreed as part of procedure EMEA/H/C/002695/ANX/016. Additionally, The RMP and Annex II have been updated to remove the additional risk minimisation measures (Healthcare Professional Educational Brochure). 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				
IAIN/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2019	27/07/2020	SmPC and PL	
PSUSA/10128 /201812	Periodic Safety Update EU Single assessment - ponatinib	11/07/2019	n/a		PRAC Recommendation - maintenance
IA/0049	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	30/11/2018	n/a		
PSUSA/10128 /201712	Periodic Safety Update EU Single assessment - ponatinib	26/07/2018	20/09/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10128/201712.
IB/0048/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	28/06/2018	n/a		

	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 manufacturer of a novel excipient 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.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.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				
T/0047	Transfer of Marketing Authorisation	25/04/2018	04/06/2018	SmPC, Labelling and PL	
II/0045/G	This was an application for a group of variations. Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to reflect updated safety and efficacy information based on 64-month follow-up data from the completed study AP24534-10-201 (PACE) " A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia	31/05/2018	20/09/2018	SmPC and PL	Based on the efficacy and safety results from the completed pivotal phase 2 study AP24534-10-201, together with updated data from the final dose-finding phase 1 study AP24534-07-101, the product information is updated in sections 4.4, 4.8 and 5.1 of the SmPC with consequential changes to the Patient Leaflet to reflect the additional knowledge on ponatinib from longer term follow-up. The changes relate to the updated data cut off and include

	and Ph+ Acute Lymphoblastic Leukemia", as well as data from the final study AP24534-07-101 "A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukemia and other Hematologic Malignancies". 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				changes to length of follow up (64 months), revised frequencies for adverse reactions and revised efficacy data. For more information on the results from studies AP24534-07-101 and AP24534-10-201 (PACE) please refer to the Summary of Product Characteristics.
IAIN/0046	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	28/03/2018	04/06/2018	Annex II and PL	
R/0042	Renewal of the marketing authorisation.	14/12/2017	08/02/2018	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Iclusig in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0041	Update of section 4.8 of the SmPC in order to include a paragraph regarding severe cutaneous adverse reactions (SCARs) reported in the post-marketing setting. The Package Leaflet is updated accordingly.	07/12/2017	08/02/2018	SmPC and PL	Severe skin reactions (such as Stevens-Johnson Syndrome) have been reported with some BCR-abl Tyrosine Kinase Inhibitors. Patients should be warned to immediately report suspected skin reactions, especially if associated with

	In addition, discrepancies between the SmPC and the Package Leaflet are being corrected in order to align the safety information in the Package Leaflet with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				blistering, peeling, mucosal involvement or systemic symptoms.
IB/0043/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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 B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	14/11/2017	08/02/2018	Annex II and PL	

	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.2 - Change to importer, batch release arrangements and quality control testing of the FP - 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.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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 product - Minor changes to an approved test procedure				
II/0039/G	This was an application for a group of variations.	28/09/2017	n/a		

	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				
PSUSA/10128 /201612	Periodic Safety Update EU Single assessment - ponatinib	20/07/2017	21/09/2017	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10128/201612.
IB/0040	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)	04/08/2017	08/02/2018	SmPC	
II/0038	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	09/06/2017	n/a		
II/0032/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.8, 5.1 of the SmPC based on data from the ongoing Study AP24534-07-101 with a median duration of follow-up of approximately 48 months for the CP-CML patients and 3.6 months for the advanced phase Ph+ leukemia patients, as well as 48-month follow-up data from the ongoing Study AP24534-10-201 (PACE). The Package Leaflet has been updated	15/12/2016	26/01/2017	SmPC, Annex II, Labelling and PL	The risk of arterial occlusive events is likely to be dose-related. Consider reducing the dose of Iclusig to 15 mg for CP-CML patients who have achieved a major cytogenetic response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to cytogenetic response and BCR-ABL transcript levels. If dose reduction is undertaken, close monitoring of response is recommended. For more information on the results from studies AP24534-07-101 and AP24534-10-201 (PACE) please refer to the

	accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and to align the annexes with the latest QRD template v.10. An updated RMP version 15.3 was agreed during the procedure in order to include the 48-month follow up data from the phase 2 study (PACE), address the commitments made in the framework of the PSUR 4 assessment and update the educational materials in line with the changes to the SmPC. In addition, the MAH took the opportunity to update the RMP to include one additional potential risk identified in the post-marketing setting, i.e. posterior reversible encephalopathy syndrome (PRES), for which data were included in the PSUR 5 (PSUSA/00010128/201512). 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				Summary of Product Characteristics.
PSUSA/10128 /201606	Periodic Safety Update EU Single assessment - ponatinib	12/01/2017	n/a		PRAC Recommendation - maintenance
T/0036	Application for Transfer of Marketing Authorisation from ARIAD Pharma Ltd. to Incyte Biosciences UK Ltd. Transfer of Marketing Authorisation	13/10/2016	09/11/2016	SmPC, Labelling and PL	

II/0027	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include recommendations for dose modifications in case of hepatic toxicity during the treatment and to extend existing warnings and precautions for patients with severe hepatic impairment to patients with hepatic impairment of any severity. The Package Leaflet is updated accordingly. The updated RMP version 14.5 has been agreed. 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 and PL	Caution is recommended when administering Iclusig to patients with hepatic impairment. Dose interruption or discontinuation may be required in case of hepatic toxicity (for detailed recommendation please refer to the SmPC). Iclusig has not been studied at doses above 30 mg in patients with hepatic impairment (Childs-Pugh Classes A, B & C).
PSUSA/10128 /201512	Periodic Safety Update EU Single assessment - ponatinib	07/07/2016	n/a		PRAC Recommendation - maintenance
IAIN/0034/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.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	21/06/2016	25/08/2016	Annex II and PL	
IAIN/0033	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	03/06/2016	25/08/2016	Annex II and PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
II/0029/G	This was an application for a group of variations. Update of section 5.3 and 4.6 of the SmPC in order to add pre-clinical information on 'Fertility and Early Embryonic Development to Implantation' (study 2424-001) and of section 5.3 to add pre-clincial information on 'Carcinogenicity' (study 805826). In addition, the Marketing authorisation holder (MAH) has submitted final study results for preclinical studies ARP590, ARP591, ARP592, ARP593, ARP593 on vascular occlusion mechanism and study ARP598 on 'Effects of Ponatinib and its Metabolites on In Vitro Kinase Activity and Cellular Viability' following commitments taken during Article 20 referral procedure (EMEA/H/C/002695/A-20/0003; EC decision on 15 January 2015). The RMP has been updated accordingly (final version adopted: 14.3). 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	26/05/2016	25/08/2016	SmPC	In a fertility study in male and female rats, female fertility parameters were reduced at dose levels corresponding to human clinical exposures. Evidence for pre- and post-implantation loss of embryos was reported in female rats and ponatinib may therefore impair female fertility. There were no effects on male rat fertility parameters. The clinical relevance of these findings on human fertility is unknown. In a two-year carcinogenicity study in male and female rats, oral administration of ponatinib at 0.05, 0.1 and 0.2 mg/kg/day in males and at 0.2 and 0.4 mg/kg/day in females did not result in any tumorigenic effects. The 0.8 mg/kg/day dose in females resulted in a plasma exposure level generally lower or equivalent to the human exposure at the range of dose from 15 mg to 45 mg daily. A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland was observed at that dose. The clinical relevance of this finding for humans is not known.

	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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2016	25/08/2016	SmPC and PL	
PSUSA/10128 /201506	Periodic Safety Update EU Single assessment - ponatinib	28/01/2016	22/03/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10128/201506.
II/0028	Update of sections 4.4 and 4.8 of the SmPC to update the existing warning on vascular occlusion in relation to renal artery stenosis and to add the term as a new adverse drug reaction with frequency uncommon, accordingly. The Package Leaflet is updated accordingly. In addition, the updated RMP version 13.1 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to	28/01/2016	22/03/2016	SmPC and PL	Arterial and venous thrombosis and occlusions, including renal artery stenosis (associated with worsening, labile or treatment-resistant hypertension), and the need for urgent revascularization procedures have occurred in Iclusig-treated patients. Hypertension may contribute to risk of arterial thrombotic events, including renal artery stenosis. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating

	new quality, preclinical, clinical or pharmacovigilance data				for renal artery stenosis.
IB/0026/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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.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.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	05/01/2016	n/a		

X/0023	Annex I_2.(c) Change or addition of a new strength/potency	24/09/2015	27/11/2015	SmPC, Labelling and PL	
IB/0025	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/10/2015	n/a		
PSUSA/10128 /201412	Periodic Safety Update EU Single assessment - ponatinib	23/07/2015	18/09/2015	SmPC and PL	Please refer to Iclusig PSUSA/00010128/201412 EPAr: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0021/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 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.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	06/05/2015	08/09/2015	SmPC, Annex II, Labelling and PL	

	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.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - 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.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.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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				

II/0020	Update of section 5.2 of the SmPC based on the results of study No. ARP490 (In Vitro Protein Binding of Ponatinib in Plasma from Subjects with Normal and Impaired Hepatic Function). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/03/2015	08/09/2015	SmPC	
II/0017	Update of sections 4.8 and 5.1 of the SmPC with further safety and efficacy information based on the updated Clinical Study report of Study AP24534-10-201 (PACE). The Package leaflet has been updated accordingly. The RMP is updated accordingly. Further, the MAH took this opportunity to update the RMP as per the requests received during the referral procedure (EMEA/H/C/002695/A-20/0003). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	08/09/2015	SmPC and PL	Updated data has been provided from the pivotal phase II study with a data extraction date of 6 January 2014, with a median follow up of 27.9 months, representing 659 patient-years of exposure. The additional efficacy and safety data are consistent with the known profile of Iclusig. As a consequence Sections 4.8 and 5.1 of the SmPC have been updated, including clear reference to the data extraction date.
IB/0016/G	This was an application for a group of variations. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a	02/02/2015	08/09/2015	SmPC and PL	

	new specification parameter to the specification with its corresponding test method B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IB/0019/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.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 B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	16/01/2015	n/a		
A20/0003	Pursuant to Article 20 of Regulation (EC) No 726/2004, further to the evaluation of data relating to pharmacovigilance, the European Commission requested on 27 November 2013 the opinion of the Agency on whether the marketing authorisations of Iclusig should be maintained, varied, suspended or revoked.	23/10/2014	15/01/2015	SmPC, Annex II and PL	Please refer to the PRAC assessment report: Iclusig EMEA/H/C/002695/A-20/0003

PSUV/0014	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IB/0018/G	This was an application for a group of variations. 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.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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/12/2014	n/a		
II/0012	Submission of a study as part of the pharmacovigilance plan. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/10/2014	n/a		
PSUV/0009	Periodic Safety Update	24/07/2014	18/09/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0009.
IAIN/0015	A.1 - Administrative change - Change in the name and/or address of the MAH	17/09/2014	15/01/2015	SmPC, Labelling and PL	
IAIN/0013	C.I.8.a - Introduction of or changes to a summary of	14/08/2014	n/a		

	Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location				
IA/0011/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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	22/05/2014	n/a		
II/0005/G	This was an application for a group of variations. Update of section 4.5 of the SmPC with the results of a drug-drug interaction study with rifampicin (Study AP24534-12-107); Update of sections 4.4, 4.5, 5.2 of the SmPC and the Package Leaflet with the results of a drug-drug interaction study with lansoprazole conducted as a post-authorisation measure of the RMP (Study AP24534-12-108, MEA 008); Update of sections 4.2, 4.4, 4.5 and 5.2 of the SmPC with the results of a study in patients with chronic hepatic impairment conducted as a post-authorisation measure of the RMP (Study AP24534-12- 109, MEA 001);	22/05/2014	18/09/2014	SmPC and PL	Drug-drug interaction study with rifampicin (Study AP24534-12-107): Co-administration of a single 45 mg dose of Iclusig in the presence of rifampin (600 mg daily), a strong CYP3A inducer, to 19 healthy volunteers, decreased the AUC0-∞ and Cmax of ponatinib by 62% and 42%, respectively, when compared to administration of ponatinib alone. Co administration of strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort with ponatinib should be avoided, and alternatives to the CYP3A4 inducer should be sought, unless the benefit outweighs the possible risk of ponatinib underexposure. Drug-drug interaction study with lansoprazole (Study AP24534-12-108): Co-administration of Iclusig with a

	Update of sections 4.5 of the SmPC and the Package Leaflet with regard to interaction with CYP3A4 inhibitors further to the results physiologically-based pharmacokinetic modelling to determine the impact of different ketoconazole dosing regimens, conducted as a post-authorisation measure of the RMP (Study ARI-001A, MEA 004); Update of section 5.2 of the SmPC in order to reflect the results of an in vitro study conducted to determine whether co-administered drugs that are highly bound to human plasma proteins can displace ponatinib from its binding sites (Study ARP350); Update of section 4.6 of the SmPC with regards to information on contraception further to the results of a study in cultured human hepatocytes on the potential for ponatinib to induce cytochrome P450 (CYP) enzymes, conducted as a post-authorisation measure of the RMP (Study XT133050, MEA 003); Submission of follow-up study analyses of plasma samples and metabolite profile conducted as a post-authorisation measure of the RMP (Study ARP395, MEA 005); The RMP has been updated accordingly and to implement changes requested by the PRAC/CHMP. In addition, the MAH took the opportunity to made editorial corrections to the SmPC and to correct the package leaflet side effects in line with the SmPC. 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				potent inhibitor of gastric acid secretion resulted in a minor reduction in ponatinib Cmax without a reduction in AUC0-∞. Study in patients with chronic hepatic impairment (Study AP24534-12- 109): Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with severe hepatic impairment. Interaction with CYP3A4 inhibitors (Study ARI-001A): Caution should be exercised and a reduction of the starting dose of Iclusig to 30 mg should be considered with concurrent use of strong CYP3A inhibitors such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice. Plasma protein binding (Study ARP350): Ponatinib is not displaced by concomitant administration of ibuprofen, nifedipine, propranolol, salicylic acid, or warfarin. Information on contraception (Study XT133050): It is unknown whether ponatinib affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used. Plasma samples and metabolite profile (Study ARP395): The metabolite profile of the post 24-hr plasma samples was consistent with that of the pre 24-hr samples, and no new metabolites were detected in the post 24-hr plasma.

	obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority 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.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority 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				
IB/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/04/2014	n/a		
II/0007	Update of section 5.3 of the SmPC in order to reflect the new data from study 902650 investigating the potential toxicity of ponatinib in juvenile Sprague-	20/03/2014	18/09/2014	SmPC	The new data from a toxicity study in juvenile Sprague-Dawley rats (study 902650) show that ponatinib administration resulted in deaths related to inflammatory

	Dawley rats. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				effects at 3.0 mg/kg/day after 6 or 7 days of treatment. These deaths were attributed to an inflammatory process resulting in multiple organ failure. Decreases in body weight gain were evident at doses of ≥ 0.75 mg/kg/day during the pre-weaning and early post-weaning treatment phases, which recovered during a post-treatment phase from Day 35 to 63 pp. No other adverse changes in developmental parameters (vaginal opening, preputial separation or bone measurements) were observed. As a consequence of this new data, section 5.3 of the SmPC has been updated.
II/0006	Submission of data from an in-vitro study to characterize potential effects of ponatinib on platelet aggregation in humans (study No. 600075). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/03/2014	n/a		The study conducted in order to further characterize potential effects of ponatinib on platelet aggregation. No significant inhibition of platelet aggregation was observed with ponatinib concentrations of 0.07 and 0.7 µg/mL. Significant inhibitory effects of ponatinib were observed only at a highest test concentration (7 µg/mL) that is 100 times higher than the estimated plasma Cmax in human patient at the recommended therapeutic dose.
IA/0008/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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	28/02/2014	n/a		

IB/0004	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	16/01/2014	n/a		
II/0002	Update of sections 4.2, 4.4, 4.8 of the SmPC in order to add a warning regarding the risk of developing arterial and venous thrombotic events in patients treated with Iclusig. 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	21/11/2013	20/12/2013	SmPC and PL	Review of data from clinical studies, including two ongoing studies (a phase I dose-finding study and a pivotal phase II study), showed a higher incidence of arterial and venous thrombotic events in patients treated with Iclusig than was observed at the time of marketing authorisation. In the phase I study, follow-up data from September 2013 showed a rate of serious occlusive vascular events of 22% (18 out of 81 patients) while in the phase II study the rate was 13.8% (62 out of 449 patients). In addition, in a recently discontinued phase III study comparing Iclusig with imatinib, there was a higher number of occlusive vascular events reported in the Iclusig arm, although the data from this study are still preliminary. As a consequence, sections 4.2, 4.4 and 4.8 of the SmPC were updated in order to include recommendations not to use Iclusig in patients with a history of heart attack or stroke, unless the potential benefits of treatment outweigh the risks. The cardiovascular status of patients should be assessed and cardiovascular risk factors actively managed before starting treatment with Iclusig and cardiovascular status should continue to be monitored and optimised during treatment. Hypertension should be controlled during treatment with Iclusig and healthcare professionals should consider interrupting treatment if hypertension is not

					controlled. Finally patients should be monitored for evidence of vascular occlusion or thromboembolism, and treatment should be interrupted immediately if this occurs. Finally, the terms retinal vein occlusion and visual impairment were included in section 4.8 of the SmPC.
IAIN/0001/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation A.1 - Administrative change - Change in the name and/or address of the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/08/2013	20/12/2013	SmPC, Labelling and PL	