Tasigna

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
IAIN/0128/G	This was an application for a group of variations. 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 -	28/11/2024		Annex II and PL	

[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).

	Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/2162/202401	Periodic Safety Update EU Single assessment - nilotinib	03/10/2024	n/a		PRAC Recommendation - maintenance
IA/0127/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	05/09/2024	n/a		
IA/0126	A.7 - Administrative change - Deletion of manufacturing sites	14/06/2024	n/a		
IAIN/0124/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of	04/03/2024	n/a		

	manufacturing sites				
IA/0123/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.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.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	11/01/2024	n/a		
IAIN/0122/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	24/11/2023		Annex II and PL	

	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.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IB/0121	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	13/11/2023	n/a		
IB/0119/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	05/10/2023	n/a		

	variation 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0120/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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)	01/09/2023	n/a		
IB/0118/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	31/05/2023	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate 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.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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				
IA/0117	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	07/11/2022	n/a		
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
II/0115/G	This was an application for a group of variations. C.I.4: Update of section 4.8 of the SmPC in order to update the ADRs frequency category based on pooled safety data from 13 interventional clinical studies, 5 of which have not been previously	19/05/2022	13/06/2023	SmPC and PL	As part of this update, the safety pool was substantially expanded. The updated safety profile is based on pooled data from 3,422 patients treated with Tasigna in 13 clinical studies in the approved indications: adults and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the

	assessed (CAMN107A2303 - 120 months data; CAMN107A2404; CAMN107E2401; CAMN107ECN02 and CAMN107EIC01). In addition, the MAH took the opportunity to merge the current 2 SmPCs (one for 150mg and one for 50mg/200mg) into one single SmPC, by including all information from the 150mg SmPC into the 50mg/200mg SmPC; and to implement editorial changes. The Package Leaflet is proposed to be updated accordingly. A.6: Update of nilotinib ATC code based on the last update of the WHO ATC index. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data A.6 - Administrative change - Change in ATC Code/ATC Vet Code				chronic phase (5 clinical studies with 2,414 patients), adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib (6 clinical studies with 939 patients) and paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib (2 clinical studies with 69 patients). These pooled data represents 9,039.34 patient-years of exposure. The safety profile of nilotinib is consistent across indications. The most common adverse reactions (incidence ≥15%) from the pooled safety data were: rash (26.4%), upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis) (24.8%) headache (21.9%), hyperbilirubinaemia (including blood bilirubin increased) (18.6%), arthralgia (15.8%), fatigue (15.4%), nausea (16.8%), pruritus (16.7%) and thrombocytopenia (16.4%). For more information, please refer to the Summary of Product Characteristics.
IA/0114/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	09/12/2021	n/a		

	manufacturer of a novel excipient				
IB/0113/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture 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	12/11/2021	n/a		
PSUSA/2162/ 202101	Periodic Safety Update EU Single assessment - nilotinib	02/09/2021	n/a		PRAC Recommendation - maintenance
IA/0112/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	06/08/2021	n/a		
II/0109	Update of SmPC sections 4.4, 4.8, 5.1 based on the 5-year follow up data from the study CAMN107A2203 in paediatric patients. Annex II D has been updated to reflect the fulfilment of the obligation to conduct the post authorisation efficacy study (PAES). The Package leaflet is updated accordingly. In addition,	24/06/2021	28/03/2022	SmPC, Annex II and PL	The product information has been updated with the final results of the mentioned paediatric study. CAMN107A2203 was a Phase II, open-label, multi-center study evaluating the efficacy and safety of nilotinib 230 mg/m2 twice daily conducted in 58 pediatric patients with Ph+ CML (33 patients were resistant or intolerant to

	the Tasigna EU RMP version 25 has been updated to remove the corresponding additional pharmacovigilance activity and the missing information 'Long-term follow-up in paediatric patients'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				imatinib or dasatinib, and 25 patients were newly diagnosed). The results provided with this final five-year data are clinically relevant, are in line with the previous observed effects and also confirm the long-term efficacy. As for the updated safety this is in general consistent with the known safety profile of nilotinib established in adult patients with Ph+ CML-CP dosed at 400 mg b.i.d. Some issues are identified; increases of transaminases and bilirubin as well as the incidence of bilirubin elevation based on laboratory assessments were more common observed in pediatric population. Paediatric CML-CP patients should be monitored for hepatic safety and the nilotinib dose adjusted or interrupted as needed The risk of growth retardation in the paediatric population is still present and has been further elucidated in the product information. However, the therapeutic benefit of treating CML in pediatric patients outweighs the risk of growth and development effects. This is also considered an important identified risk in the risk management plan.
IAIN/0111/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.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	05/05/2021	28/03/2022	SmPC, Annex II, Labelling and PL	

	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.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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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/0107	Submission of the 5 year data including data on late relapses from the ongoing studies ENESTfreedom (CAMN107I2201): A Phase II, single-arm, open-label, multicenter nilotinib TFR study in patients with BCR-ABL1 positive CML-CP, who had achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment and ENESTop (CAMN107A2408): A Phase II, single-arm, open-label, multicenter study, evaluating TFR in patients with BCR-ABL1-positive CML-CP who achieved a sustained molecular response of MR4.5 on nilotinib	11/03/2021	28/03/2022	SmPC	Section 5.1 of the SmPC has been updated to include the 5 years data for the study ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408), in which TFR (Treatment Free Remission) data after 48 weeks and 264 weeks are summarized in a newly created table.

	treatment after switching from imatinib to nilotinib. Consequently, the RMP (version) 23 is being updated to remove the additional pharmacovigilance activity 'collection and submission of data on late relapses from the ongoing studies ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408)' and the safety concern 'risk of resistance (in TFR)'. 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				
PSUSA/2162/ 202001	Periodic Safety Update EU Single assessment - nilotinib	17/09/2020	16/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2162/202001.
IA/0108/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	12/11/2020	n/a		

	manufacturer of a novel excipient				
II/0106	Update of the section "4.8 Undesirable effects" of the SmPC with 'Facial paralysis' with the frequency unknown. Section "4 possible side effects" of the package leaflet has been updated accordingly. The QRD template version 10.1 has been implemented as part of this PI update. The Annex III has been updated accordingly. Editorial changes have been made to the Annex II to follow the new QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/09/2020	16/11/2020	SmPC, Annex II, Labelling and PL	
II/0103	Update of the RMP version 22.1 following the PRAC request to add 'growth retardation' to the list of important identified risks, and study AMN107A2203 as an additional pharmacovigilance activity for the important identified risk of 'growth retardation' to the pharmacovigilance plan. The MAH took the opportunity to revise the list of safety concerns in the EU RMP, in line with the GVP Module V (rev 2) recommendations and implemented the requested changes from PRAC. In addition, the additional pharmacovigilance activity of 'collection of gene signature data in patients who relapse on TFR compared to patients who relapse on treatment' has been deleted from the EU RMP as previously agreed during the procedure	11/06/2020	n/a		

	EMEA/H/C/000798/PAM/MEA/051.1. Other updates to reflect current study status are proposed through the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IA/0105/G	This was an application for a group of variations. B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation 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.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	29/05/2020	n/a		

	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 - 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/0102/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.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	09/03/2020	16/11/2020	Annex II and PL	

	manufacturing sites 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				
IAIN/0101	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	11/12/2019	16/11/2020	Annex II and PL	
PSUSA/2162/ 201901	Periodic Safety Update EU Single assessment - nilotinib	19/09/2019	14/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2162/201901.
IAIN/0100/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	14/10/2019	n/a		
IAIN/0098/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	26/10/2018	n/a		

	manufacturing site for the FP - Primary packaging site				
PSUSA/2162/ 201801	Periodic Safety Update EU Single assessment - nilotinib	06/09/2018	n/a		PRAC Recommendation - maintenance
II/0095	Update of section 4.6 of the SmPC to include the recommendation that women should not breast-feed during Tasigna treatment and for 2 weeks after the last dose. The Package Leaflet has been updated accordingly. Further, the MAH took the opportunity to implement minor editorial changes, corrections and/or additions in the SmPC and Package Leaflet based on data already submitted and assessed previously, including the alignment of section 4 of the Package Leaflet with section 4.8 of the SmPC, the completeness of the list of excipients in SmPC section 6.1 and minor changes to SmPC sections 4.4 and 4.5. Furthermore, the MAH took the opportunity to update the contact details in the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/07/2018	11/07/2019	SmPC and PL	n/a
II/0092	Submission of an updated RMP version 21.1 in order to delete the important identified risk 'Myelosuppression', to implement changes in the definition of the identified risks 'Hepatotoxicity' and 'Fluid retention', and to reflect the discontinuation of the educational material as additional risk	12/07/2018	11/07/2019	Annex II	

	minimisation measure. Annex II has been updated accordingly. 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				
IG/0950	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)	18/06/2018	n/a		
T/0094	Transfer of Marketing Authorisation	26/03/2018	26/04/2018	SmPC, Labelling and PL	
IA/0093/G	This was an application for a group of variations. 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	22/02/2018	n/a		

	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)				
IA/0091	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	10/01/2018	n/a		
X/0088/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency	14/09/2017	15/11/2017	SmPC, Labelling and PL	
PSUSA/2162/ 201701	Periodic Safety Update EU Single assessment - nilotinib	01/09/2017	n/a		PRAC Recommendation - maintenance
II/0084/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC based on the results from: - Study CAMN107I2201 (ENESTfreedom: A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) who achieved a sustained deep molecular response;	21/04/2017	24/05/2017	SmPC, Labelling and PL	For further information please refer to the published Assessment Report: Tasigna H-798-II-84-G-AR

	- Study CAMN107A2408 (ENESTop): A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in patients with Ph+ CML-CP who achieved a sustained deep molecular response on nilotinib treatment after switching from imatinib treatment; The Package Leaflet has been updated accordingly. Additional changes to the Labelling were implemented in line with the latest QRD template version 10. An updated RMP, version 19.1, was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0089	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	10/04/2017	n/a		
II/0087	Submission of the final CSR from the clinical drug-drug interaction study CAMN107A2132. An updated RMP version 17 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	15/12/2016	n/a		N/A

	of studies to the competent authority				
II/0083	Submission of a revised RMP version 15.1 in order to introduce minor administrative changes and updated epidemiological information. 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	13/10/2016	n/a		N/A
IA/0086	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	15/09/2016	n/a		
PSUSA/2162/ 201601	Periodic Safety Update EU Single assessment - nilotinib	02/09/2016	n/a		PRAC Recommendation - maintenance
IG/0712	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)	03/08/2016	n/a		
II/0080	Submission of the final Clinical Study Report (CSR) for study CSTI571A2403, "A global Gleevec/Glivec and Tasigna Pregnancy exposure Registry" (category 3) in fulfilment of the Tasigna Post-authorisation Measure MEA-038 C.I.13 - Other variations not specifically covered	26/05/2016	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0082	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2016	22/05/2017	SmPC and PL	
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	23/03/2016	n/a		
IA/0078/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.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	03/12/2015	n/a		
II/0073	Update of Annex II of the product information with the submission of the results of the pivotal phase III study in adult patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) (study CAMN107A2303). In addition, section 5.1 has also been amended. Package leaflet has been updated accordingly. The RMP has also been updated.	24/09/2015	02/06/2016	SmPC, Annex II and PL	Update of Annex II of the product information with the submission of the results of the pivotal phase III study in adult patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) (study CAMN107A2303). In addition, section 5.1 has also been amended. Package leaflet has been updated accordingly. The RMP has also been updated.

	In addition, the Marketing authorisation holder (MAH) took the opportunity to correct some minor errors. 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				
PSUSA/2162/ 201501	Periodic Safety Update EU Single assessment - nilotinib	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0075	Update of section 5.3 of the SmPC in order to amend the safety information based on the results from a 26-week oral gavage carcinogenicity study in 001178 T. 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 new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	02/06/2016	SmPC	The MAH performed dose finding study as well as a 26-week carcinogenicity study in Tg.rasH2 mice. The MAH is updating section 5.3 of the SmPC in order to add new safety information based on the results from a 26-week oral gavage carcinogenicity study. Furthermore, the MAH has included "skin malignancy" as a new potential risk in the RMP. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).
IAIN/0077	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	29/05/2015	02/06/2016	SmPC, Labelling and PL	

IB/0076	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	27/05/2015	02/06/2016	SmPC, Labelling and PL	
IA/0072/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	06/03/2015	n/a		
II/0071	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	18/12/2014	n/a		
II/0070/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH	03/12/2014	15/12/2014	SmPC, Labelling and PL	
PSUV/0069	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance

II/0068	Update of sections 4.4 and 4.5 of the SmPC further to the results of a drug-drug interaction study using multiple doses of nilotinib in combination with midazolam. The package leaflet is updated accordingly. The MAH also took the opportunity to make editorial changes to sections 4.5 and 5.2 of the SmPC to improve clarity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	15/12/2014	SmPC and PL	In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure (AUC and Cmax) of oral midazolam (a substrate of CYP3A4) 2.6 fold and 2.0 fold, respectively. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolised by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.
II/0067	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC further to 60 month data analysis from the phase III multicentre, open-label, randomised study CAMN107A2303 of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) (ANX 40.3). The package leaflet has been updated accordingly. Annex II has also been updated in order to correct an inconsistency with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	15/12/2014	SmPC, Annex II and PL	Sections 4.2 and 4.4 of the SmPC have been updated to further clarify the monitoring of lipid profiles. SmPC sections 4.4, 4.8 and 5.1 have been updated further to the available 60-month data analysis, the median time on treatment ranged from 59.5 to 60.7 months. The rates of MMR at 60 months were higher in the nilotinib arms compared to the imatinib arm: 49.1% in the imatinib arm, 62.8% in the nilotinib 300 mg bid arm and 61.2% in the nilotinib 400 mg bid arm (p=0.0008 for nilotinib 300 mg bid arm versus imatinib and p=0.0030 for nilotinib 400 mg bid arm versus imatinib). Furthermore, the information on other secondary endpoints e.g. Best complete cytogenetic response, rates of BCR-ABL/ABL ratio ≤0.01% and ≤0.0032%, Progression to accelerated phase or blast crisis on treatment and Overall Survival have been updated as well.
II/0065	Update of sections 4.4 and 4.8 of the SmPC with regards to fluid retention and oedema and	20/03/2014	15/12/2014	SmPC and PL	Fluid retention and oedema Severe forms of fluid retention such as pleural effusion,

	cardiovascular events, further to the request of the PRAC during the assessment of PSUR 8. The Package leaflet is updated accordingly. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly (see section 4.2 for instructions on managing non-haematological toxicities). Cardiovascular events Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. In this clinical study with a median on-therapy time of 48 months, Grade 3 4 cases of cardiovascular events included peripheral arterial occlusive disease (1.1% and 0.4% at 300 mg and 400 mg nilotinib twice daily, respectively), ischemic heart disease (2.2% and 3.2% at 300 mg and 400 mg nilotinib twice daily, respectively) and ischemic cerebrovascular events (0.7% and 1.4% at 300 mg and 400 mg nilotinib twice daily, respectively). Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during Tasigna therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors (see section 4.2 for instructions on managing non-haematological toxicities).
IB/0066/G	This was an application for a group of variations.	05/02/2014	n/a		

	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.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.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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.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.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				
II/0064	Update of section 4.6 of the SmPC to add a recommendation to use highly effective	18/12/2013	15/12/2014	SmPC and PL	Following review of existing data related to pregnancy, the product information of Tasigna has been updated to

	contraception for up to two weeks after ending treatment with Tasigna. 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				recommend that women of childbearing potential have to use highly effective contraception during treatment with Tasigna and for up to two weeks after ending treatment. Section 4.6 of the SmPC was therefore updated.
II/0062	Update of sections 4.2, 4.4 and 4.8 of the SmPC with recommendation for monitoring blood glucose levels before and during Tasigna therapy. The package leaflet is updated accordingly. Editorial changes and corrections to the SmPC were also made. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	15/12/2014	SmPC and PL	The review of all available data shows that nilotinib has been reported to increase blood glucose levels. In a phase III study in newly diagnosed CML patients, 5.8 % and 6.5% of the patients treated with 400 mg nilotinib and 300 mg nilotinib twice daily, respectively, showed a Grade 3-4 elevation in blood glucose. It is recommended that the glucose levels be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.
II/0060	Update of sections 4.2 and 4.4 of the SmPC to recommend lipid monitoring prior to initiating Tasigna therapy and as clinically indicated during treatment. The package leaflet is updated accordingly. The product information is also updated in line with QRD template version 9.0. The contact details in the Netherlands are also updated in the list of local representatives in the package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	20/12/2013	SmPC, Annex II and PL	In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice daily showed a Grade 3-4 elevation in cholesterol; no Grade 3-4 elevations were however observed in the 300 mg twice daily dose group. It is recommended that the lipid profile be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated.

II/0058	Update of sections 4.8 and 5.1 of the SmPC further to 48 month data analysis from the phase III multicentre, open-label, randomised study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) (CAMN107A2303). The package leaflet has been updated accordingly. The MAH also proposed minor editorial changes and to update Annex II in line with the latest QRD template (version 8.3). The contact details of the local representative in Croatiahave also been added in the package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	20/12/2013	SmPC, Annex II and PL	SmPC sections 4.8 and 5.1 have been updated further to the available 48 month data analysis, the median duration of exposure available is now 48.0 months (range 0.1 – 58.7 months). The rates of MMR at 48 months were higher in both nilotinib arms compared to the imatinib arm:43.8% in the imatinib arm, 59.1% in the nilotinib 300 mg bid arm, and 55.2% in the nilotinib 400 mg bid arm ($p<0.0001$ for the comparison of nilotinib 300 mg bid arm vs. imatinib). Furthermore, the information on other secondary endpoints e.g. Best complete cytogenetic response, rates of BCR-ABL/ABL ratio ≤0.01% and ≤0.0032%, Progression to accelerated phase or blast crisis on treatment and Overall Survival have been updated as well.
IG/0296/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated 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 or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	24/04/2013	n/a		
IA/0056	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/03/2013	n/a		

II/0051/G	This was an application for a group of variations. Update of section 4.5 of the SmPC with regards to the concomitant use of nilotinib and gastric pH-elevating agents. Update of section 5.2 of the SmPC to include study results regarding the relative bioavailability of nilotinib. The Package leaflet is updated accordingly. Annex II has also been updated in line with the latest QRD template version 8.2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	20/12/2013	SmPC, Annex II and PL	The MAH of Tasigna conducted a study to evaluate the effects of two gastric pH-elevating agents, famotidine and an antacid preparation, on the pharmacokinetics of nilotinib in healthy subjects. No significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of Tasigna was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Tasigna. In the same study as above, administration of an antacid (aluminium hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of Tasigna also did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of Tasigna. In addition, the MAH conducted a pharmacokinetic study in healthy subjects to evaluate the relative bioavailability. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3) relative bioavailability of nilotinib capsule is approximately 50%.
IB/0055	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)	16/01/2013	n/a		
IB/0054	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)	16/01/2013	20/12/2013	SmPC	

IB/0053/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/12/2012	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
R/0047	Renewal of the marketing authorisation.	19/07/2012	20/09/2012	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Tasigna continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Tasigna, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted with unlimited validity. The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP.
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance	17/08/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0046	Update of sections 4.8 and 5.1 of the SmPC further to 36 month data analysis from the phase III multicenter, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) (CAMN107A2303). The package leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC and PL	SmPC sections 4.8 and 5.1 have been updated further to the available 36 month data analysis, the median duration of exposure available is now 36.4 months (range 0.1 – 46.7 months). The rates of MMR at 36 months were higher in both nilotinib arms compared to the imatinib arm: 38.5% in the imatinib arm, 58.5% in the nilotinib 300 mg bid arm, and 57.3% in the nilotinib 400 mg bid arm ($p<0.0001$ for the comparison of each nilotinib arm vs. imatinib). Furthermore, the information on other secondary endpoints e.g. Best complete cytogenetic response, rates of BCR-ABL/ABL ratio ≤0.01% and ≤0.0032%, Progression to accelerated phase or blast crisis on treatment and Overall Survival have been updated as well.
IAIN/0049	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	08/06/2012	n/a		
IAIN/0048	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	03/05/2012	27/06/2012	SmPC	
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance	22/02/2012	n/a		

	system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0044	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	27/01/2012	n/a		
II/0037	Update of 4.8 of the SmPC in order to add the adverse reaction peripheral arterial occlusive disease with a frequency "uncommon" and to consequently delete the adverse reaction arteriosclerosis obliterans. The Package Leaflet is updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	19/12/2011	SmPC and PL	The Marketing Authorisation Holder conducted a review further to receipt of reports of peripheral arterial occlusive disease (PAOD) and considered the need to add this adverse reaction in section 4.8 of the SmPC with a frequency "uncommon". Based on review of reports of PAOD, as well as of the literature, the CHMP considered that available PAOD information should be included in the product information. In addition, the term 'arteriosclerosis obliterans' has been deleted from the product information as it is represented by the term 'peripheral arterial occlusive disease'.
IAIN/0043/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.a - Replacement or addition of a	15/12/2011	n/a		

	manufacturing site for the FP - Secondary packaging site				
II/0036	Update of section 5.3 of the Summary of Product Characteristics with the results of a 2-year oral carcinogenicity study in rats further to the request of the CHMP (FUM 007). The MAH also took the opportunity to update the contact details of the local representatives in Poland and Romania in the package leaflet.	20/10/2011	22/11/2011	SmPC and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) committed to submit the final report for the carcinogenicity studies (FUM 007). Consequently, the MAH submitted the results from a 2-year carcinogenicity study in Wistar Hannover rats. In this study, the major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, endothelial cell hyperplasia, inflammation and/or epithelial hyperplasia).There was no evidence of carcinogenicity in the 2-year rat carcinogenicity study upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level were representing approximately 2x to 3x human daily steady-state exposure (based on AUC) to nilotinib at the dose of 800 mg/day. The Summary of Product Characteristics has been updated accordingly.
IG/0113/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	11/11/2011	n/a		
IB/0038/G	This was an application for a group of variations.	15/09/2011	15/09/2011	SmPC, Labelling and	

	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			PL	
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	11/07/2011	n/a		
II/0034	Update of sections 4.8 and 5.1 of the SmPC and of the Package Leaflet further to 24 month data	19/05/2011	17/06/2011	SmPC, Annex	SmPC section 4.8 has been updated further to the available 24 month data analysis, the median duration of exposure

	analysis from the phase III multicenter, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) (CAMN107A2303). The Risk Management Plan version number (version 9) has also been updated in Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II and PL	available is now 25 months (range 0.1 – 35.4 months). At the time of the analysis for the 24 month data all 846 patients had completed 24 months of treatment (or discontinued earlier). The primary efficacy endpoint was major molecular response (MMR) at 12 months. For the secondary endpoint MMR at 24 months, the rate was higher in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (61.7% versus 37.5%) as well as in the nilotinib 400 mg twice daily arm compared to the imatinib arm (59.1% versus 37.5%). MMR was achieved at 12 months and maintained at 24 months without loss of MMR in between in 42% (95% CI: 36.0-47.8%) of patients in the nilotinib 300 mg twice daily group, 39% (95% CI: 33.4-45.1%) of patients in the nilotinib 400 mg twice daily group and 20% (95% CI: 15.9-25.7%) of patients in the imatinib arm (p<0.0001). Of the patients achieving an MMR at 12 months, 93% in the nilotinib arm and 92% in the imatinib arm maintained their MMR at 24 months. Furthermore, the information on other secondary endpoints e.g. Best complete cytogenetic response, rates of BCR-ABL/ABL ratio <=0.01% and <=0.0032%, Progression to accelerated phase or blast crisis on treatment and Overall Survival have been updated as well.
II/0033	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and the package leaflet with information regarding tumour lysis syndrome. The MAH also took the opportunity to update the contact details of the local representatives in Poland and Romania in the	14/04/2011	23/05/2011	SmPC and PL	Cases of Tumour Lysis Syndrome (TLS) have been reported with Tasigna. TLS is at increased risk of occurring in patients with high tumour burden with or without specific tumour therapy. Tumour therapy is likely to increase the risk of TLS. Dehydration and baseline high uric acid levels also increase the risk of TLS. Consequently, in patients at

	package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				increased risk of TLS and in patients whose malignancy is sensitive to Tasigna therapy, the potential exists for TLS to occur with Tasigna therapy. Therefore, a warning has been included in the product information of Tasigna to indicated that, due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with Tasigna. This adverse reaction has also been included with a rare frequency in section 4.8 "undesirable effects" of the Summary of Product Characteristics.
IA/0035/G	This was an application for a group of variations. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	19/05/2011	19/05/2011	SmPC, Labelling and PL	
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest	21/12/2010	n/a	Annex II	

	wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
X/0028	Annex I_2.(c) Change or addition of a new strength/potency	23/09/2010	20/12/2010	SmPC, Labelling and PL	The MAH submitted an extension application to the marketing authorisation for a new strength: 150 mg hard capsules, in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) . Please refer to Scientific Discussion Tasigna-H-798-X-28-AR.
II/0029	Extension of indication of Tasigna in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in the chronic phase. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC and the package leaflet have been updated. Annex II has	23/09/2010	20/12/2010	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Tasigna-H-798-II-29-AR.

	been updated to included the updated version of the risk management plan (version 8.1). The Marketing Authorisation Holder also took the opportunity to update the product information with the latest QRD template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0025/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated 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 or updated 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 or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	20/10/2010	n/a		
II/0032/G	This was an application for a group of variations. to update in testing monograph for the Tasigna 200 mg hard capsules B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant	23/09/2010	28/09/2010		

	effect on the overall quality of the finished product B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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 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/0031	Update of sections 4.8 and 5.1 of the Summary of Product Characteristics further to 24-months follow up safety and efficacy data from the Phase II study CAMN107A2101 for patients with imatinib-resistant or intolerant chronic myelogenous leukaemia in chronic phase and in accelerated phase. The final study report for CAMN107A2101 was requested with FUM 032 and FUM033. In addition, a correction to SmPC section 4.4 has been introduced based on	22/07/2010	26/08/2010	SmPC and PL	The clinical development program for nilotinib consisted of a clinical trial with a Phase IA dose escalation study and a Phase II dose expansion study in imatinib-resistant/intolerant Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in chronic phase (CP) and accelerated phase (AP). The primary endpoints were Major Cytogenetic Response (MCyR) (? 35% Ph+) for CML-CP and confirmed Hematologic Response (HR) for CML-AP.

	these follow-up data. Section 4 of the package leaflet has been updated accordingly. The MAH also took the opportunity to update the list of local representatives in the package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The MAH now provided the 24-months follow up safety and efficacy data from the Phase II study CAMN107A2101. The data now reflect exposure to Tasigna in 458 patients, 321 patients with imatinib-resistant or intolerant CML in CP and 137 patients in AP treated at the recommended dose of 400 mg twice daily. The median duration of exposure in days was 561 (1 1,096) for the CML-CP patients and 264 (2 1,160) for the CML-AP patients. Chronic Phase The MCyR rate in 321 CP patients was 51%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting Tasigna treatment and these were sustained. Of the patients who achieved MCyR, 77% (95% CI: 70% - 84%) were maintaining response at 24 months. Patients with a Complete Hematological Response (CHR) at baseline achieved a MCyR faster (1.9 vs. 2.8 months). Of CP patients without a baseline CHR, 70% achieved a CHR, median time to CHR was 1 month and median duration of CHR was 32.8 months. The estimated 24-month overall survival rate in CML-CP patients was 87%. Accelerated Phase The overall confirmed HR rate in 137 AP patients was 50 %. Most responders achieved a HR early with Tasigna treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 24.2 months). Of the patients who achieved HR, 53% (95% CI: 39% - 67%) were maintaining response at 24 months. The estimated 24-month overall survival rate in CML-AP

					patients was 70%.
II/0027	Update of the Detailed Description of the Pharmacovigilance system (DDPS) to version 8.0, including a change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number of the agreed DDPS. Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	23/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
IA/0030/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.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	12/03/2010	n/a		
II/0026	Update of section 4.5 of the Summary of Product Characteristics (SPC) with the results of a drug-drug interaction study with warfarin, further to the request of the CHMP (FUM 010). Annex II was also	19/11/2009	22/12/2009	SmPC, Annex II and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the commitment to conduct a clinical drug-drug interaction study with a substrate of CYP2C9 (FUM 010).

	updated in line with the latest QRD template (version 7.3) and the Marketing Authorisation Holder also took the opportunity to update the version number of the Risk Management Plan with the latest agreed version 6. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				The MAH conducted a phase I two-period crossover, single blind, single-center study to evaluate the pharmacokinetics of warfarin upon co-administration with nilotinib in healthy subjects. In this single-dose drug-drug interaction study 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib did not result in any changes in warfarin pharmacokinetic parameters or warfarin pharmacodynamics measured as prothrombin time (PT) and international normalised ratio (INR). There are no steady-state data. This study suggests that a clinically meaningful drug-drug interaction between nilotinib and warfarin is less likely up to a dose of 25 mg of warfarin. Due to lack of steady-state data, control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended. Section 4.5 of the Summary of Product Characteristics has been updated accordingly.
II/0025	To introduce an additional manufacturer for the an intermediate used in the manufacture of the drug substance is proposed. As a result slight modifications to the process are introduced with regard a catalyst and a solvent. Quality changes	24/09/2009	07/10/2009		
II/0018	Update of section 4.5 of the SPC, with the results	23/07/2009	06/08/2009	SmPC and PL	At the time of the granting of the initial marketing

	from a drug-drug interaction study with esomeprazole (FUM 012). Section 4.4 has been updated accordingly to remove the precautionary statement on concomitant use with antacids, H2 blockers, or proton pump inhibitors. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				authorisation, the Marketing Authorisation Holder (MAH) made the commitment to provide the results of a drug-drug interaction study with proton pump inhibitor in healthy subjects (FUM 012). The MAH conducted a phase I clinical trial with the primary objective to determine the effect of esomeprazole (a proton pump inhibitor) on the pharmacokinetics of a single oral dose of Tasigna (nilotinib) in healthy subjects and the secondary objective to assess the safety and tolerability of a single oral dose of nilotinib given alone and concomitantly with esomeprazole in healthy subjects. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in Cmax and 34% decrease in AUC0-?). The CHMP agreed that the study results suggest a modest reduction in the rate and extent of nilotinib absorption when co-administered with esomeprazole. Such an effect is unlikely to have clinically significant consequences for nilotinib therapy. Nilotinib can be used with esomeprazole or other proton pump inhibitors as needed. The Product Information has been updated accordingly.
II/0016	Update of section 4.9 of the Summary of Product Characteristics further to reports of overdose. Update of Summary of Product Characteristics	23/07/2009	06/08/2009	SmPC	The Marketing Authorisation Holder (MAH) of Tasigna has conducted a review further to reports of overdose. Based on the available information, the MAH proposed to change section 4.9 Overdose of the SPC as follows:

					"Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other medicinal products. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered. In the event of overdose, the patient should be observed and appropriate supportive treatment given."
II/0015	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) further to cases of sudden death. The Marketing Authorisation Holder (MAH) also took the opportunity to correct sections 4.4 and 4.5 of the SPC where moxifloxacin was listed as a medicinal product inhibiting CYP3A4 instead of a medicinal product that may prolong QT. The Package Leaflet has been updated accordingly. Minor editorial changes have also been made to the SPC and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	06/08/2009	SmPC and PL	Sudden death was identified as a potential risk in February 2006, at which time the Marketing Authorisation Holder of Tasigna (nilotinib) had received 6 reports of sudden and/or unexpected deaths in patients in clinical trials of nilotinib. Further to a cumulative review, a total of 14 cases of sudden cardiac deaths have been identified from clinical trials and compassionate use programs up to the cut-off date of 31 January 2009. The CHMP considered that all fourteen cases identified as sudden cardiac death involve patients who had cardiac disease, either known at the time of study entry or as determined upon autopsy, or who had significant cardiac risk factors. For six of the 14 cases, a causal role for nilotinib could not be ruled out. Therefore, the following warning was added to section 4.4 of the Summary of Product Characteristics (SPC) of Tasigna: "Sudden Death Uncommon cases (0.1 to 1%) of sudden deaths have been

					reported in patients receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors." Section 4.8 of the SPC and the relevant section of the Package Leaflet have also been updated accordingly.
IB/0024	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	04/08/2009	n/a		
II/0017	Update of section 4.8 of the Summary of Product Characteristics to add the term "myelosuppression" further to the request from the CHMP in the assessment of the 2nd PSUR. Update of Summary of Product Characteristics	25/06/2009	27/07/2009	SmPC	Myelosuppression is common in CML patients treated with tyrosine kinase inhibitors, especially at treatment onset when the CML clone accounts for most of the haematopoiesis. Myelosuppression was a common finding with Tasigna. Thrombocytopenia, neutropenia and anaemia were the most frequently reported grade 3 and 4 laboratory abnormalities in the core safety patient population of the initial marketing authorisation application. Myelosuppression is an identified risk in the Tasigna Risk Management Plan and is continuously monitored. The current Summary of Product Characteristics already includes events indicative of myelosuppression including thrombocytopenia, neutropenia, anaemia, febrile neutropenia and pancytopenia. However, further to the assessment of the 2nd PSUR, the CHMP requested that the term "myelosuppression" be added.
IA/0023	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2009	n/a		

IA/0022	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2009	n/a		
IA/0021	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2009	n/a		
IA/0020	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2009	n/a		
IA/0019	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2009	n/a		
II/0008	Update of sections 4.4, 4.5 and 5.2 of the SPC with pharmacokinetic results from a study of nilotinib in combination with imatinib, a P-gp substrate, further to the request of the CHMP (FUM 011). Update of Summary of Product Characteristics	23/04/2009	08/06/2009	SmPC	At the time of the granting of the initial marketing authorisation, the marketing authorisation holder made the commitment to assess the pharmacokinetics of Tasigna (nilotinib) in combination with imatinib, a P-gp substrate. A phase I multicenter, dose escalation study of AMN107 in combination with imatinib on a continuous daily dosing schedule in adult patients with imatinib-resistant gastrointestinal stromal tumors (GIST) was conducted. The results of this study showed that concomitant administration of nilotinib with imatinib (a substrate and moderator of Pgp and CYP3A4), had a slight inhibitory effect on CYP3A4 and/or P-gp. The AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%. These changes are unlikely to be clinically important. This study also showed that nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

					The Product Information has been updated accordingly.
II/0006	Update of DDPS (Pharmacovigilance)	19/03/2009	21/04/2009	Annex II	Update of the Detailed Description of Pharmacovigilance System (DDPS) to version 3.0. Consequently, Annex II of the Product Information is updated with the agreed version number of the DDPS (version 3.0) and the latest agreed version number of the Risk Management plan (version 5.0).
II/0007	Update of section 4.2 and 4.4 of the SPC with the results from a pharmacokinetic study in patients suffering from various degrees of hepatic impairment, further to the request from the CHMP (FUM 016). Update of Summary of Product Characteristics	19/02/2009	07/04/2009	SmPC	At the time of the granting of the initial marketing authorisation, the marketing authorisation holder made the commitment to assess the pharmacokinetics of Tasigna (nilotinib) in subjects with impaired hepatic function and healthy subjects with normal hepatic function (FUM 016). A phase I, single-center, open-label, single oral dose, parallel study was conducted to assess the pharmacokinetics of 200 mg of nilotinib in subjects with impaired hepatic function and healthy subjects with normal hepatic function. The results of this study showed that hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in patients with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. No obvious association between degree of hepatic impairment and exposure has been shown. The predicted steady-state Cmax of nilotinib showed an increase of 29%, 18% and 22% respectively. Cmax exposure appears significantly lower in subjects with

					hepatic impairment and with an apparent association to the degree of hepatic impairment. This is unlikely to be of clinical relevance. Based on these results, dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution. The Product Information has been updated accordingly.
II/0009	Update of section 4.5 of the SPC, further to the request from the CHMP with the results from a drug-drug interaction study with the CYP3A4 inducer rifampicin (FUM 009). Update of Summary of Product Characteristics	22/01/2009	26/02/2009	SmPC	At the time of the granting of the initial marketing authorisation, the applicant made the commitment to provide the results of a Phase I open-label, two period, single center study to assess the effect of 600 mg daily oral dose of rifampin (CYP3A4 inducer) on the pharmacokinetics of a single 400 mg oral dose of AMN107 in healthy subjects (FUM 009). This study showed that rifampicin, a potent CYP3A inducer decreases nilotinib Cmax by 64 % and reduces nilotinib AUC by 80%. The CHMP considered that rifampicin and nilotinib should not be used concomitantly and that other medicinal products that induce CYP3A4 are likewise likely to reduce exposure to nilotinib to a clinically relevant extent. The Product Information has been updated accordingly.
IA/0014	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/01/2009	n/a		
IA/0013	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/01/2009	n/a		

IA/0012	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/01/2009	n/a		
IA/0011	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/01/2009	n/a		
IA/0010	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/01/2009	n/a		
II/0005	Update of section 5.3 of the SPC further to the request from the CHMP following the assessment of pre- and postnatal development study in rats (FUM 008). Update of Summary of Product Characteristics	20/11/2008	05/01/2009	SmPC	As a part of the initial marketing authorisation, the Marketing Authorisation Holder committed to conduct an oral pre- and postnatal development (Segment III) study in rats (FUM 008). Further to the request from the CHMP following the assessment of FUM 008, section 5.3 of the SPC has been updated to reflect the key findings of this study, as follows: Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, premature fusion of the facial bones (fused maxilla/zygomatic), visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. In a pre- and postnatal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. Exposure to nilotinib in females at No-Observed-Adverse-

					Effect-Levels was generally less or equal to that in humans at 800 mg/day.
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	02/09/2008	n/a		
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	02/09/2008	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	04/08/2008	n/a	SmPC	
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/12/2007	n/a		