Glivec

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0132/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.a.4.a - Change in coating weight of oral dosage	27/03/2023		SmPC 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).

	forms or change in weight of capsule shells - Solid oral pharmaceutical forms B.II.a.2.a - Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries 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 B.II.a.1.b - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in scoring/break lines intended to divide into equal doses				
IA/0131/G	This was an application for a group of variations. 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	17/10/2022	n/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				
IA/0130	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	17/10/2022	n/a		
PSUSA/1725/ 202105	Periodic Safety Update EU Single assessment - imatinib	27/01/2022	22/03/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1725/202105.
II/0129	Update of section 4.8 of the SmPC in order to add pemphigus with frequency rare and osteonecrosis with frequency uncommon to the list of adverse drug reactions based on an analysis of pre-clinical data, scientific literature, clinical trial datasets, Novartis pharmacovigilance database, EVDAS and other safety databases. The Package Leaflet is updated accordingly. The MAH is also taking the opportunity to align section 4 of the PL with the already approved ADR section of the SmPC as a number of ADRs is not reflected accurately. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/02/2022	03/02/2023	SmPC and PL	SmPC new text: In "Table 1 Tabulated summary of adverse reactions" the following are added: Skin and subcutaneous tissue disorders: Pemphigus is added with frequency rare Musculoskeletal and connective tissue disorders: "Osteonecrosis" replaces the term "Avascular necrosis/hip necrosis" and frequency is changed to Uncommon from unknown For more information, please refer to the Summary of Product Characteristics.

IB/0128	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	08/12/2021	22/03/2022	SmPC, Labelling and PL	
IB/0127/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.d - Change in the specification parameters	03/12/2021	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.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 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.z - Change in control of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a				

	starting material/reagent/intermediate for AS - Other variation B.I.a.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				
IA/0126/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.6 - Administrative change - Change in ATC Code/ATC Vet Code	11/08/2021	22/03/2022	SmPC, Annex II, Labelling and PL	
N/0123	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/04/2021	21/05/2021	PL	
IA/0124/G	This was an application for a group of variations. 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 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	22/02/2021	n/a		
IB/0122/G	This was an application for a group of variations.	01/02/2021	21/05/2021	SmPC, Annex	

	C.I.7.b - Deletion of - a strength C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority			II, Labelling and PL	
IA/0121	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	15/12/2020	n/a		
IB/0120/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.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	22/10/2020	21/05/2021	Annex II and PL	

	in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)				
IA/0119/G	This was an application for a group of variations. 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	07/07/2020	n/a		

	new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - 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) 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				

II/0117	Update of section 4.6 of the SmPC to include that women of childbearing potential must be advised to use effective contraception and stop breast-feeding during treatment and for at least 15 days after stopping treatment with imatinib, based on a company review of the company Core Data Sheet. The PL has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	21/05/2021	SmPC and PL	The SmPC section 4.6 has been updated as follows: • Women of childbearing potential must be advised to use effective contraception during treatment and for at least 15 days after stopping treatment with imatinib • Women should not breastfeed during treatment and for at least 15 days after stopping treatment with imatinib. • In non-clinical studies, the fertility of male and female rats was not affected, although effects on reproductive parameters were observed (see section 5.3). The PL has been updated accordingly.
IB/0118/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.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.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	24/03/2020	n/a		

	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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				

	B.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.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS				
II/0115	Submission of an updated RMP version 12.1 in order to revise the lists of safety concerns in EU RMP and align with the current GVP Rev 2 based on the PRAC advice received on the latest PSUR (11-May-2015 to 10-May-2018). 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	16/01/2020	n/a		
IAIN/0116/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.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	14/08/2019	03/04/2020	Annex II and PL	

	Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IA/0114/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.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	10/05/2019	03/04/2020	SmPC, Annex II, Labelling and PL	
PSUSA/1725/ 201805	Periodic Safety Update EU Single assessment - imatinib	31/01/2019	28/03/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1725/201805.
IA/0112/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.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	27/09/2018	n/a		

	Deletion of certificates (in case multiple certificates exist per material)				
T/0110	Transfer of Marketing Authorisation	16/05/2018	25/06/2018	SmPC, Labelling and PL	
II/0109	Update of section 4.4 of the SmPC to add a new warning regarding phototoxicity, and section 4.8 of the SmPC to add the new ADR 'pseudoporphyria' with a frequency of 'not known'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the 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	22/03/2018	25/06/2018	SmPC and PL	Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
II/0108	Update of SmPC section 4.4 based on the final CSR for study STI571A2405; the International Study for Chronic Myeloid Leukaemia (CML) in childhood and adolescents (I-CML-Ped Study). The provision of the study report addresses the post-authorisation measure MEA 162.8. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	25/06/2018	SmPC	In an observational study in the CML paediatric population, a statistically significant decrease (but of uncertain clinical relevance) in median height standard deviation scores after 12 and 24 months of treatment was reported in two small subsets irrespective of pubertal status or gender. Close monitoring of growth in children under imatinib treatment is recommended.
IB/0107/G	This was an application for a group of variations.	14/02/2017	n/a		

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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				
II/0106	Update of section 4.8 of the SmPC to update the safety information on the existing ADR 'musculoskeletal pain including myalgia' so as to inform that musculoskeletal pain during treatment with imatinib or after discontinuation has been observed in post-marketing. The Package Leaflet has been updated accordingly. Further, the MAH has taken the opportunity to merge the SmPCs of the different strengths of the same pharmaceutical form i.e. 50 mg and 100 mg hard capsules, and 100 mg and 400 mg film coated tablets, respectively, and to align the annexes with version 10 of the QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	10/11/2016	08/05/2017	SmPC, Annex II, Labelling and PL	N/A

	data				
II/0103	Submission of an updated RMP version 11.0 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
II/0104	Update of section 5.1 of the SmPC, upon request by the CHMP, to reflect the results of Study CSTI571L2401, an observational registry collecting long-term safety and efficacy data in patients with myeloid neoplasms with platelet derived growth factor receptor beta rearrangement (MPN with PDGFRB rearrangement) treated with imatinib mesylate, in fulfilment of the post-authorisation measure MEA 168.8. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	08/05/2017	SmPC	An observational registry (study L2401) was conducted to collect long-term safety and efficacy data in patients suffering from myeloproliferative neoplasms with PDGFR- β rearrangement and who were treated with Glivec. The 23 patients enrolled in this registry received Glivec at a median daily dose of 264 mg (range: 100 to 400 mg) for a median duration of 7.2 years (range 0.1 to 12.7 years). Due to the observational nature of this registry, haematologic, cytogenetic and molecular assessment data were available for 22, 9 and 17 of the 23 enrolled patients, respectively. When assuming conservatively that patients with missing data were non-responders, CHR was observed in 20/23 (87%) patients, CCyR in 9/23 (39.1%) patients, and MR in 11/23 (47.8%) patients, respectively. When the response rate is calculated from patients with at least one valid assessment, the response rate for CHR, CCyR and MR was 20/22 (90.9%), 9/9 (100%) and 11/17 (64.7%), respectively.

II/0100	Submission of the Final Clinical Study Report for Study CSTI571A2403: "A global Gleevec/Glivec and Tasigna Pregnancy Exposure Registry" (Category 3). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	08/05/2017	SmPC	The MAH provided the results of the pregnancy registry CSTI571A2403 with the objective to monitor pregnancies exposed to imatinib in order to estimate the prevalence of birth defects. An analysis of the scientific literature of pregnancy women treated with imatinib was also provided in the context of this variation. In view of the information gathered, a possible role of imatinib in causing foetal anomalies could not be completely ruled out. Therefore, an update to section 4.6 of the SmPC was agreed to reflect the know information the issue, to read as follows: Women of childbearing potential Women of childbearing potential must be advised to use effective contraception during treatment. Pregnancy There are limited data on the use of imatinib in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Glivec. Studies in animals have however shown reproductive toxicity (see section 5.3) and the potential risk for the foetus is unknown. Glivec should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.
IB/0105	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/08/2016	08/05/2017	Annex II	
IAIN/0102	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2016	08/05/2017	SmPC and PL	

IB/0101/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.b - Change to in-process tests or limits	25/04/2016	n/a		

	applied during the manufacture of the finished product - Addition of a new test(s) and limits				
IB/0099	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/03/2016	n/a		
II/0098/G	This was an application for a group of variations. Submission of a revised RMP (finally agreed version 8.1) in order to provide with: • Exclusion of potential drug interactions with acetaminophen/ paracetamol and Glivec/Glivec (imatinib mesylate). • Exclusion of the elderly population as missing information. • Throughout the RMP, the title of missing information "renal impairment" and "hepatic impairment" has been updated as "Use in patients with renal impairment" or "use in patients with hepatic impairment. • Safety actions taken since the last update included Drug Rash with Eosinophilia and System Symptoms, Gastric Antral Vascular Ectasia and Chronic renal failure. Change of due dates of final study reports for three category 3 studies: CSTI571A2405, CSTI571A2403 and CSTI571L2401. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	28/01/2016	n/a		

	authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/1725/ 201505	Periodic Safety Update EU Single assessment - imatinib	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0096	Update of sections 4.4 and 4.8 of the SmPC in order to include chronic renal failure as an adverse drug reaction and a warning related to renal insufficiency following PRAC recommendation. 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	26/02/2015	14/01/2016	SmPC and PL	In this variation, the following wording has been added to section 4.4 of the SmPC: "Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be prescribed in accordance with standard treatment guidelines." In addition, "renal failure chronic" has been added to section 4.8 of the SmPC and Package Leaflet under a frequency “not known”.

II/0095	Update of SmPC section 4.4 to include information about 'Gastric Antral Vascular Ectasia' (GAVE) under the existing warning 'Gatrointestinal haemorrhage', and SmPC section 4.8 to add GAVE as a new ADR. Further, SmPC section 4.8 has been aligned with current guidelines regarding table layout and estimation of frequencies of adverse reactions. In addition, the MAH took the opportunity to introduce standard text in the SmPC and Package Leaflet regarding additional monitoring in line with the latest QRD templates, and to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	14/01/2016	SmPC	Gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. When needed, discontinuation of Glivec treatment may be considered.
II/0093/G	This was an application for a group of variations. A.1 - To change the address of the marketing authorisation holder, Novartis Europharm Limited, from Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom, to Frimley Business Park, Camberley GU16 7SR, United Kingdom. A.1 - Administrative change - Change in the name and/or address of the MAH	03/12/2014	14/01/2016	SmPC, Labelling and PL	C.I.4 was withdrawn during the procedure
IG/0443	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	20/08/2014	n/a		

	(excluding manufacturer for batch release)				
IA/0092	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/06/2014	n/a		
IAIN/0091	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	19/06/2014	18/07/2014	SmPC and PL	
II/0090	Update of section 4.8 of the SmPC in order to include the term "Drug rash with eosinophilia and systemic symptoms" (DRESS) under the SOC Skin and subcutaneous disorders with a frequency of unknown further to the PRAC request following the assessment of a cumulative review of cases of DRESS. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH took the opportunity of this variation to add and correct information in the PL to bring it in line with the SmPC. Editorial changes were also proposed to the SmPC. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	24/10/2013	18/07/2014	SmPC and PL	A cumulative safety review of cases of DRESS reported in patients treated with Glivec was conducted by the MAH following the PRAC request further to the assessment of the PSUR covering the period 11 May 2009 to 10 May 2012. The MAH retrieved 12 cases of DRESS. Three of the reported cases had a positive re-challenge (patients re-experienced the reaction after reintroduction of Glivec). Three cases showed a positive de-challenge (patient recovering after drug withdrawal). In one case the DRESS was confirmed with a skin biopsy. The section 4.8 of the SmPC was therefore updated to add DRESS as an adverse drug reaction.
II/0089	Update of section 5.3 of the SmPC in order to reflect the results of a juvenile development toxicology	25/07/2013	18/07/2014	SmPC, Annex II and PL	The Applicant submitted results of juvenile toxicity studies which did not show new target organs than those

	study. In addition, the MAH took the opportunity to reflect in the PL the adverse drug reaction of "bleeding in the eyes" which was already listed in section 4.8 of the SmPC and update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				previously identified. In the juvenile toxicology study, effects upon growth, delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m2. In addition, mortality was observed in juvenile animals (around weaning phase) at approximately 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m2. Section 5.3 of the SmPC was updated to reflect this new information.
II/0080	Extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC. The Package Leaflet was updated in accordance. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/05/2013	27/06/2013	SmPC, Annex II and PL	Please refer to Scientific Discussion Glivec-H-406-II-80-VAR.
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.	24/04/2013	n/a		

	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				
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0085	Update of sections 4.2 and 5.1 of the SmPC in order to reflect paediatric data related to rare diseases. The Package Leaflet was proposed to be 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	15/11/2012	27/06/2013	SmPC and PL	As part of the PIP on the rare diseases conditions (myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement, Kit (CD 117)-positive gastrointestinal stromal tumours (GIST) and dermatofibrosarcoma protuberans (DFSP)), the MAH was required to submit a report on the extrapolation of efficacy from adult to paediatric patients including a complete evaluation of adult and paediatric data on disease pathophysiology in the adult versus the paediatric population, available safety, dose/PK exposure, dose/efficacy, PK exposure-efficacy data in children treated with imatinib in these rare diseases indications, and a review of published cases in the literature. The efficacy data reported in paediatric subjects appear to be replicating the adults' outcomes, for all indications but GIST. However, the level of evidence available cannot support a new indication. As an outcome of the review of this application, the CHMP agreed to the update of sections 4.2 and 5.1 of

					the SmPC. The PL is updated accordingly.
II/0084	Update of section 4.8 undesirable effects of the SmPC in order to include the term subdural haematoma with the CIOMS frequency of "uncommon". The Package Leaflet is 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	15/11/2012	27/06/2013	SmPC and PL	Following the review of 9 cases of subdural hematoma (SDH) in study STI571, the MAH updated the SmPC to include SDH as an adverse drug reaction in section 4.8 undesirable effects of the SmPC. The PL is updated accordingly.
IAIN/0086	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	09/11/2012	27/06/2013	SmPC and PL	
II/0082	Update of sections 4.4 and 4.5 of the SmPC to update the information on interaction with potent strong CYP3A4 inhibitors and CYP3A4 substrates with narrow therapeutic window as well as to provide guidance on the use of low molecular weight heparin as an alternative to warfarin. In addition, section 4.4 has been updated to clarify the information pertaining to hypereosinophilic syndrome (HES) and cardiac disease. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications	20/09/2012	23/10/2012	SmPC and PL	Further to the CHMP recommendation, the MAH conducted a review of available data related to interaction with potent strong CYP3A4 inhibitors and CYP3A4 substrates with narrow therapeutic window as well as guidance on the use of low molecular weight heparin as an alternative to warfarin. In addition the MAH clarified the information pertaining to hypereosinophilic syndrome (HES) and cardiac disease. Sections 4.4 and 4.5 of the SmPC have been updated.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
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 system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	17/08/2012	n/a		
IAIN/0081	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/07/2012	n/a		
IB/0079/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.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.a - Change to batch release arrangements	09/03/2012	n/a		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions				
IG/0148/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	22/02/2012	n/a		

	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				
II/0070	Update of section 4.2 Posology and method of administration of the SmPC to indicate that the length of treatment in the clinical trial supporting the adjuvant treatment of adult patients following resection of GIST was 36 months following results of the CSTI571BFI03 study (FUM 180). Section 5.1 Pharmacodynamic properties of the SmPC has also been updated to reflect the efficacy data of the study. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC	A randomised phase III study (CSTI571BFI03) comparing the 12-month vs 36-month administration of imatinib in high risk patients of recurrence in the adjuvant treatment of adult patients following resection of GIST has been carried out. Outcomes from the primary endpoint, Recurrence free survival (RFS), have shown a positive result with a HR of 0.46 (95% CI: 0.32-0.65). RFS probability estimates at 12 months were 93.7% in the 12-month arm and 95.9% in the 36-month arm. Interestingly, the difference increased at 60.1% vs 86.6% at 36 months respectively. All the sensitivity analyses on the primary endpoint support this finding. In addition, even though the data on OS are not fully mature, OS results are in favour of 36-month treatment arm, HR of 0.45 (95% CI 0.22-0.89). Section 4.2 of the SmPC was therefore updated to indicate that the length of treatment in the clinical trial supporting the adjuvant treatment of adult patients following resection of GIST was 36 months following results of the CSTI571BFI03 study and section 5.1 of the SmPC was updated to include efficacy data from the study.
II/0073	Update of section 4.4 special warnings and precautions to include patients with history of renal	15/12/2011	20/01/2012	SmPC	The review of the clinical safety database of Glivec identified that patients with history of renal failure have a

	failure as a caution regarding the risk of oedema and fluid retention as requested by the CHMP following the assessment of the risk management plan version 4.0 (RM2 176.2). C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				higher risk of developing oedema and fluid retention. It was therefore requested by CHMP to update section 4.4 special warnings and precautions to include patients with history of renal failure as a caution regarding the risk of oedema and fluid retention
II/0072	Update of section 4.6 Fertility pregnancy and lactation of the SmPC to introduce a sub-section on fertility. Section 4.7 Effects on ability to drive and use machines of the SmPC was updated to include somnolence as one of the undesirable effects experienced by patients treated with Glivec. The PL has been amended accordingly. In addition, the MAH took the opportunity of this variation to bring the PI in line with the latest QRD template version 8.0 and included minor editorial comments C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/12/2011	20/01/2012	SmPC, Annex II, Labelling and PL	Following the review of the Novartis Argus safety database and in line with the QRD template version 8.0, the MAH updated section 4.6 Fertility pregnancy and lactation of the SmPC to introduce a sub-section on fertility and section 4.7 Effects on ability to drive and use machines of the SmPC to include somnolence as one of the undesirable effects experienced by patients treated with Glivec.
IA/0077	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/12/2011	n/a		

II/0071	Following a revision of its Core Data Sheet (CDS), the MAH updated section 5.1 of the SmPC to include a mechanism of action sub-section. In addition existing information in section 4.5 of the SmPC related to interactions with medicinal products were reflected in section 4.4. Other editorial changes are included in sections 4.2, 4.4 and 4.5. 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	14/12/2011	SmPC	The MAH has conducted a systematic review of information on the mechanism of action of imatinib from the published literature. As a result of these publications imatinib could be an inhibitor of DDR1 and DDR2 tyrosine kinase autophosphorylation which can be included together with the previously established mechanism of action in section 5.1 of the SmPC. Other modifications of sections 4.2, 4.4 and 4.5 of the SmPC have been introduced in order to reduce redundancy in the text and improve clarity.
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		
IA/0069	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	26/07/2011	n/a		
IA/0068/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement	15/07/2011	n/a		

	or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
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/0064	This type II variation concerns an update of section 4.5 of the Summary of Product Characteristics (SmPC) to revise information regarding drug-drug interaction with paracetamol. In addition, the MAH took the opportunity of this variation to correct the number of patients in the GIST study included in section 5.1 of the SmPC. Minor editorial amendments have also been made to the Annex II. C.I.4 - Variations related to significant modifications	14/04/2011	23/05/2011	SmPC and Annex II	The MAH submitted the results of a non-randomized, open-label study CSTI571A2107 investigating the effects of Glivec on the pharmacokinetics of acetaminophen/paracetamol in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase (CML-CP). The results of the study showed that Glivec in vitro inhibition of O-glucuronidation has not been observed in vivo following the administration of Glivec 400 mg and paracetamol 1000 mg. Higher doses of Glivec and paracetamol have not been studied.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0063	This type II variation concerns an update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to include information regarding growth retardation in children following the review of the Novartis global safety database, clinical trial data and published literature. 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	20/01/2011	21/02/2011	SmPC and PL	Case reports from the literature as well as small retrospective case series indicate that imatinib may affect longitudinal bone growth in children, especially in the pre-pubertal period. The limited number of events from both the literature and from spontaneous reports is insufficient to assess magnitude or reversibility of the impact of drug administration. Sections 4.4 and 4.8 of the SmPC have been updated to reflect this new information.
IB/0066/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place 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	10/01/2011	n/a		

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0065/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method 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	10/01/2011	n/a		
IG/0032/G	This was an application for a group of variations.	21/12/2010	n/a		

	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 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				
II/0062	This type II variation concerns an update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to include information regarding the risk of tumour lysis syndrome as	18/11/2010	20/12/2010	SmPC, Annex II and PL	Further to a signal of Tumour lysis syndrome (TLS) in relation to Glivec (imatinib), the MAH was requested by the CHMP to conduct a cumulative safety review of all cases of TLS (FUM 184).

	requested by the CHMP following the assessment of FUM 184. The Package leaflet has been updated accordingly. Annex II has been revised to delete the version number of the DDPS. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				A search of the Global database retrieved 61 reports of tumour lysis. Upon medical review it was determined that 11 reports were not to be considered TLS under the case definition. It was also determined that 1 additional report of TLS was not related to Glivec. Based on the review of the 50 remaining reports, a causal relationship between TLS and Glivec treatment is deemed to be possible. The SmPC was updated in section 4.4 and 4.8 and the package leaflet has been updated accordingly.
IA/0067/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	17/12/2010	n/a		

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		
IA/0061/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	04/08/2010	n/a		
IB/0060	To register an alternative secondary packaging for the drug substance. B.I.c.1.z - Change in immediate packaging of the AS - Other variation	18/05/2010	n/a		
II/0059	This type II variation concerns an update of section	18/02/2010	26/03/2010	SmPC, Annex	"Palmoplantar erthrodysesthesia syndrome" was a new

	4.8 of the SmPC to include palmoplantar erythrodysesthesia syndrome as a post-marketing adverse reaction further to the CHMP request following the assessment of PSUR 10. The Package leaflet has been updated accordingly. In addition, the MAH proposed further improvements to the Package Leaflet and took into account results from a user consultation. Furthermore, the MAH updated the list of local representatives in the Package Leaflet. The MAH also took the opportunity to update the Product information in line with the latest QRD template (version 7.3). Update of Summary of Product Characteristics and Package Leaflet			II, Labelling and PL	signal identified during the period covered by PSUR-10 (11 May 2008 - 10 May 2009). A cumulative review included 10 cases, two of them with positive rechallenge. The CHMP concluded that this reaction should be added in section 4.8 "Undesirable effects" of the SmPC as a post-marketing adverse reaction with a frequency "not known". This information has also been included in section 4 "Possible side effects" of the Package Leaflet, coded with not known frequency: "Reddening and/or swelling on the palms of the hands and soles of the feet which may be accompanied by tingling sensation and burning pain".
II/0058	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	26/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 4.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation, the CHMP concluded that the submitted DDPS contained all required elements.
II/0050	Update of section 5.1 of the SPC concerning an efficacy update based on the availability of a 84 month data analysis from the pivotal phase III study (CSTI571A0106) in newly diagnosed CML patients. This variation also fulfills the MAH follow-up measure	19/03/2009	29/04/2009	SmPC	Updated efficacy results based on the availability of a 84 month data analysis from the pivotal phase III study (CSTI571A0106) in newly diagnosed CML patients were evaluated. The results regarding the primary endpoint are positive. The outcomes appear to be very similar in regard

	(FUM 128) related to the submission of the annual update of this clinical study, including molecular results. Update of Summary of Product Characteristics				to the last update (at 72 months). The response remains durable. No new relevant safety concerns have been raised.
II/0049	Update to section 4.2 to the posology for HES/CEL and update of the information on distribution in human milk under section 4.6, addition of Rhabdomyolysis, myopathy, Acute Generalized Exanthematous Pustulosis, ovarian haemorrhage, hemorrhagic ovarian cyst under section 4.8 and update of the information on overdose under section 4.9 of the SPC. The Package Leaflet has been updated accordingly. Furthermore, the SPC and Package Leaflet have been updated according to the latest QRD template. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	29/04/2009	SmPC and PL	A number of investigators have shown that all patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) that have reduced or discontinued the treatment with Glivec have experienced a haematological or molecular relapse. As a consequence, section 4.2 "Posology and Method of administration" was updated to include a statement: Treatment should be continued as long as the patient continues to benefit. The MAH submitted two recent publications on the distribution of imatinib and its major metabolite, CGP 74588, into breast milk in lactating women. However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking imatinib should not breast feed. Section 4.8 of the SPC"Undesirable Effects" was updated with the addition of rhabdomyolysis, myopathy, Acute Generalized Exanthematous Pustulosis, ovarian haemorrhage, hemorrhagic ovarian cyst. The information update on imatinib overdose under section 4.9 of the information of the SPC was updated. The Package Leaflet has been updated accordingly. Furthermore, the SPC and Package Leaflet have been updated according to the latest QRD template.

II/0048	Extension of indication to include the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment. Update of Summary of Product Characteristics	19/03/2009	29/04/2009	SmPC and Annex II	Please refer to Scientific Discussion document (H-406-II-48-AR).
IA/0057	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0056	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0055	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0054	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0053	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0052	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0051	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/01/2009	n/a		
IA/0047	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	19/05/2008	n/a		

II/0045	Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	20/11/2007	SmPC and PL	The MAH has applied to update section 4.4 of the SPC on the observed increase in hepatotoxocity when used in combination with chemotherapy and section 4.8 to add the Adverse Events "toxic epidermal necrolysis", "lichenoid keratosis" and "lichen planus". The ATC code under section 5.1 was updated and typographical errors in Table 1 of section 4.8 of the SPC have also been corrected. The Package Leaflet has also been updated accordingly and also to reflect a number of adverse events that were already mentioned in the SPC. Furthermore, the contact details for the Slovakian and Latvian local representatives have been updated in the Package Leaflet.
IA/0046	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	21/08/2007	n/a		
S/0043	Annual re-assessment.	22/02/2007	13/04/2007	SmPC, Annex II, Labelling and PL	
II/0042	Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	28/03/2007	SmPC and PL	Update of the adverse drug reaction table in section 4.8 of the SPC, and to provide further information on congestive heart failure in imatinib treated patients. Furthermore, the contact details for Bulgaria and Romania have been added in the list of local representatives in section 6 of the Package Leaflet.
II/0041	The MAH has applied to update section 4.5 of the SPC with pharmacokinetic data regarding the effects of the co-administration with a CYP2D6 substrate (metoprolol) and CYP3A4 inducers (enzyme-inducing	22/02/2007	28/03/2007	SmPC	Update of section 4.5 of the SPC with pharmacokinetic data regarding the effects of the co-administration with a CYP2D6 substrate (metoprolol) and CYP3A4 inducers

	antiepileptic drugs and St. John's wort). Update of Summary of Product Characteristics				(enzyme-inducing antiepileptic drugs and St. John's wort).
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/02/2007	n/a	PL	
II/0040	Update of Summary of Product Characteristics	18/10/2006	28/11/2006	SmPC	Update of sections 4.2, 4.4 and 5.2 of the SPC with the results of a phase I clinical pharmacology study in patients with varying degrees of renal dysfunction, following the assessment of specific obligation data.
II/0039	Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	28/11/2006	SmPC and PL	Update of section 4.4 of the SPC (Special warnings and precautions for use) to include: hypothyroidism in patients receiving levothyroxine following thyroidectomy, as well as section 4.8 (Undesirable effects) to include: hepatic necrosis, anaphylactic reactions and acute respiratory failure following the assessments of the 5th, 6th and 7th PSURs. The Package Leaflet has also been updated accordingly.
II/0038	Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	28/11/2006	SmPC	Update of Section 5.1 of the SPC with the 60 month data analysis from phase II study (CSTI571A0106) in newly diagnosed adult CML patients, which was part of the follow-up measures related to the approval of the indication. In addition, an existing statement in Section 4.1 of the SPC was amended to clarify that this is the only indication for Glivec where controlled trials have been perfomed, and to include the standard statements in the SPC and PL regarding Exceptional Circumstances.
II/0035	Extension of Indication	18/10/2006	28/11/2006	SmPC and PL	Extension of the currently approved indications to include "Treatment of adult patients with hypereosinophilic

					syndrome (HES) and/or chronic eosinophilic leukaemia (CEL)" with FIP1L1-PDGFRa rearrangements.
II/0032	Extension of Indication	18/10/2006	28/11/2006	SmPC, Annex II and PL	Extension of the current indication for the "Treatment of adult patients with myelodysplastic/myeloproliferative diseases (MD/MPD) associated with PDGFR gene rearrangements".
R/0037	Renewal of the marketing authorisation.	27/07/2006	21/09/2006	SmPC, Annex II, Labelling and PL	
II/0036	Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	13/09/2006	SmPC and PL	Update of paediatric information in sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SPC on the basis of the data from the phase II clinical study (2108) in paediatric patients with CML, sponsored by the US NCI/COG.
II/0031	Extension of Indication	27/07/2006	13/09/2006	SmPC and PL	Additional indication: "Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy and of adult patients with relapsed or refractory Ph+ ALL as monotherapy".
II/0030	Extension of Indication	27/07/2006	13/09/2006	SmPC and PL	Extension of the current indication to include: "Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)".
S/0029	Annual re-assessment.	26/01/2006	20/03/2006	SmPC, Annex II, Labelling and PL	Annual reassessment of specific obligations and follow-up measures.
II/0028	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	Changes in the SPC section 4.8 in order to include 3 rare serious ADRs: aseptic necrosis of the bone, diverticulitis and gastrointestinal perforation following the 6th PSUR

					conclusions .The PL is updated accordingly.
II/0027	Update of Summary of Product Characteristics	26/01/2006	28/02/2006	SmPC	Update of the SPC section 5.3 to reflect new animal carcinogenicity findings.
II/0033	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	23/02/2006	27/02/2006		Change to the synthetic process for the active substance, imatinib mesilate. This resulted in changes to the specifications and control procedures for the active substance.
IB/0026	IB_17_b_Change in the storage conditions for the active substance	18/10/2005	n/a		
IB/0025	IB_17_a_Change in re-test period of the active substance	18/10/2005	n/a		
IB/0024	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	18/10/2005	n/a	SmPC	
II/0022	Update of Summary of Product Characteristics and Labelling	26/05/2005	08/07/2005	SmPC and PL	Update of the SPC and PL on safety and efficacy results from the clinical studies and post-marketing data relevant to the approved GIST indication.
II/0021	Update of Summary of Product Characteristics and Labelling	26/05/2005	08/07/2005	SmPC and PL	Update of the SPC and PL on safety and efficacy results from the clinical studies and post-marketing data relevant to the approved CML indication.
II/0020	Update of Summary of Product Characteristics	21/04/2005	02/06/2005	SmPC	Revision of the SPC section 5.3 in order to include preclinical carcinogenicity findings.
S/0019	Annual re-assessment.	20/01/2005	31/03/2005	Annex II	Annual reassessment of specific obligations and follow-up measures.
IA/0023	IA_08_b_01_Change in BR/QC testing - repl./add.	07/03/2005	n/a		

	manuf. responsible for BR - not incl. BC/testing				
IB/0017	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	02/12/2004	n/a		
IA/0018	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/11/2004	n/a		
IA/0016	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/06/2004	n/a		
IB/0014	Addition of the following pack sizes: 90 x 400 mg film-coated tablets IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/05/2004	25/05/2004	SmPC, Labelling and PL	
IB/0013	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/05/2004	25/05/2004	SmPC, Labelling and PL	
IB/0012	Addition of the following pack size: 90 x 400 mg film-coated tablet. IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/05/2004	25/05/2004	SmPC, Labelling and PL	
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2004	n/a	PL	
S/0011	Annual re-assessment.	21/01/2004	31/03/2004	Annex II	

X/0007	X-3-iv_Change or addition of a new pharmaceutical form X-3-iii_Addition of new strength	24/07/2003	11/11/2003	SmPC, Labelling and PL	
X/0006	X-3-iv_Change or addition of a new pharmaceutical form X-3-iii_Addition of new strength	24/07/2003	11/11/2003	SmPC, Annex II, Labelling and PL	
II/0008	Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	14/07/2003	SmPC and PL	
S/0010	Annual re-assessment.	19/03/2003	30/06/2003	Annex II	
I/0005	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	13/12/2002	07/01/2003		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	19/12/2002	SmPC and PL	
II/0003	Extension of Indication	19/09/2002	19/12/2002	SmPC and PL	
II/0002	Extension of Indication	19/09/2002	19/12/2002	SmPC and PL	
II/0001	Extension of Indication	21/02/2002	24/05/2002	SmPC, Annex II and PL	