Sutent

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
PSUSA/2833/ 202304	Periodic Safety Update EU Single assessment - sunitinib	25/01/2024	25/03/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2833/202304.
IB/0084	B.I.d.z - Stability of AS - Other variation	09/02/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

IA/0082	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	04/08/2021	09/11/2021	SmPC and PL	
PSUSA/2833/ 202004	Periodic Safety Update EU Single assessment - sunitinib	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/11/2020	09/11/2021	SmPC, Annex II, Labelling and PL	
IG/1245/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.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)	29/05/2020	n/a		

PSUSA/2833/201904	Periodic Safety Update EU Single assessment - sunitinib	28/11/2019	n/a		PRAC Recommendation - maintenance
N/0078	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	22/10/2020	PL	
IAIN/0077	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/10/2019	22/10/2020	SmPC and PL	
II/0073	Submission of an updated RMP version 17.2 in order to review the list of safety concerns to make it more risk proportionate based on available safety data. The updates are in line with the new GVP Module V (Rev 2) guideline and new RMP template. 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	03/10/2019	n/a		
IG/1123	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	30/08/2019	n/a		
II/0074	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	14/06/2019	n/a		

	of studies to the competent authority				
PSUSA/2833/ 201804	Periodic Safety Update EU Single assessment - sunitinib	13/12/2018	14/02/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2833/201804.
II/0070	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include paediatric study results (from studies A6181196 and ACNS1021) performed in compliance with a paediatric investigation plan (PIP). In addition the MAH took the opportunity to introduce editorial changes in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/12/2018	14/02/2019	SmPC	Please refer to Scientific Discussion "EMEA/H/C/000687/II/0070.
T/0072	Transfer of Marketing Authorisation	26/09/2018	16/10/2018	SmPC, Labelling and PL	
IG/0938/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.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)	13/07/2018	n/a		

	B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
II/0068	Update of section 4.8 of the SmPC in order to include available long-term safety data pooled from 9 MAH sponsored sunitinib clinical studies in patients with metastatic renal cell carcinoma (MRCC) as reported in a recently published literature article. Further, SmPC sections 4.4 and 4.8 have been reworded to improve readability. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and Package Leaflet and to add the unique barcode identifier in the Labelling. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	19/04/2018	SmPC, Labelling and PL	The long-term safety of sunitinib in patients with MRCC was analysed across 9 completed clinical studies conducted in the first-line, bevacizumab-refractory, and cytokine-refractory treatment settings in 5,739 patients, of whom 807 (14%) were treated for ≥ 2 years up to 6 years. In the 807 patients who received long-term sunitinib treatment, most treatment-related adverse events (TRAEs) occurred initially in the first 6 months–1 year and then were stable or decreased in frequency over time, with the exception of hypothyroidism, which gradually increased over time, with new cases occurring over the 6 year period. Prolonged treatment with sunitinib did not appear to be associated with new types of TRAEs.
II/0067	Update of sections 4.5 and 5.2 of the SmPC in order to include information regarding a possible	07/12/2017	19/04/2018	SmPC	Limited clinical data are available on the interaction between sunitinib and Breast Cancer Resistance Protein

	interaction between sunitinib and other medicinal products that are inhibitors of the efflux transporter breast cancer resistance protein (BCRP) following assessment of PAM (REC 052). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(BCRP) inhibitors and the possibility of an interaction between sunitinib and other BCRP inhibitors cannot be excluded. In vitro, sunitinib is a substrate of the efflux transporter BCRP. In study A6181038 the co administration of gefitinib, a BCRP inhibitor, did not result in a clinically relevant effect on the Cmax and AUC for sunitinib or total drug (sunitinib + metabolite). This study was a multi-center, open-label, Phase 1/2 study examining the safety/tolerability, the maximum tolerated dose, and the antitumour activity of sunitinib in combination with gefitinib in subjects with MRCC. The PK of gefitinib (250 mg daily) and sunitinib (37.5 mg [Cohort 1, n=4] or 50 mg [Cohort 2, n=7] daily on a 4-weeks on followed by 2 weeks-off schedule) when co-administered was evaluated as a secondary study objective. Changes in sunitinib pharmacokinetic parameters were of no clinical significance and did not indicate any drug-drug interactions; however, considering the relatively low number of subjects (i.e. N=7+4) and the moderate-large interpatient variability in the pharmacokinetic parameters, caution needs to be taken when interpreting the pharmacokinetic drug-drug interaction findings from this study.
PSUSA/2833/ 201704	Periodic Safety Update EU Single assessment - sunitinib	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0064	Update of section 4.1 of the SmPC in order to remove the statement 'Experience with SUTENT as first-line treatment is limited (see section 5.1)' and update of section 5.1 of the SmPC based on the final CSR of study A6181202 in fulfilment of MEA 037.2.	21/04/2017	19/04/2018	SmPC	A phase 4 multinational, multi-centre, single-arm, open-label study evaluating the efficacy and safety of sunitinib was conducted in patients with progressive, advanced/metastatic, well-differentiated, unresectable pNET.

	In addition, the MAH took the opportunity to make a minor editorial change in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				One hundred six patients (61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort) received treatment with sunitinib orally at 37.5 mg once a day on a continuous daily dosing (CDD) schedule. The investigator-assessed median PFS was 13.2 months, both in the overall population (95% CI: 10.9, 16.7) and in the treatment-naïve cohort (95% CI: 7.4, 16.8).
PSUSA/2833/ 201604	Periodic Safety Update EU Single assessment - sunitinib	01/12/2016	n/a		PRAC Recommendation - maintenance
R/0062	Renewal of the marketing authorisation.	15/09/2016	09/11/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Sutent in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0061/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	04/04/2016	n/a		

	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)				
II/0060/G	This was an application for a group of variations. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	09/11/2016	SmPC, Annex II and PL	
PSUSA/2833/ 201504	Periodic Safety Update EU Single assessment - sunitinib	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0058	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/09/2015	n/a		
II/0056	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on the adverse drug	25/06/2015	11/02/2016	SmPC and PL	Thrombotic Microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic

	reaction Thrombotic microangiopathy". The Package Leaflet is updated accordingly. Minor formatting changes were made throughout document for format consistency. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				syndrome (HUS), sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of sunitinib as monotherapy and in combination with bevacizumab. Sunitinib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	11/02/2016	PL	
IB/0057/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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	20/05/2015	n/a		

	batch control/testing takes place				
II/0054	Submission of the final overall survival (OS) analysis from Study A6181111, a multinational, randomized, double-blind, placebo-controlled, Phase 3 clinical trial in patients with progressive, well-differentiated pancreatic islet cell tumours (pNET), not amenable to surgery, radiation, or combined modality therapy with curative intent. This submission addresses the post-authorisation measure (PAM) ANX 036 and annex II has been updated accordingly. Following the assessment of the data provided, upon request by the CHMP, section 5.1 of the SmPC was updated with the 5-year OS results together with information on patients who crossed over from placebo to sunitinib treatment. 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	26/02/2015	11/02/2016	SmPC and Annex II	A total of 59 out of 85 (69.4%) patients from the placebo arm crossed over to open-label sunitinib following disease progression or unblinding at study closure. At the 5-year OS analysis, there is still a trend favouring sunitinib, with a median overall survival (OS) of 38.6 months (95% CI: 25.6, 56.4) in comparison to 29.1 months (95% CI: 16.4, 36.8) in the placebo group. OS observed after 5 years of follow-up in the extension study showed a stratified hazard ratio (HR) of 0.730, (95% CI: 0.504, 1.057; 2-sided p=0.0940).
PSUV/0052	Periodic Safety Update	18/12/2014	17/02/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0052.
II/0053/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	18/12/2014	17/02/2015	SmPC and PL	

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0050/G	This was an application for a group of variations. 1. Update of SmPC section 4.8 with the ADR 'Hypoglycaemia' and addition of the requirement to monitor for hypoglycaemia in diabetic patients and to temporarily interrupt treatment in case of symptomatic hypoglycaemia to section 4.4 of the SmPC. 2. Update of SmPC sections 4.8 to revise the ADR frequency based on the analysis of safety data from pooled clinical studies with subsequent updates to the section 4.4. The PL has been updated accordingly. Additionally, the MAH took the opportunity to introduce minor editorial changes throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	17/02/2015	SmPC and PL	In this variation the company provided updated information on some of the sunitinib side effects including decreased blood glucose. The product information was updated with the recommendation on the need to check blood glucose levels in patients with diabetes and to stop treatment if the blood glucose level is too low. Furthermore, the incidence of known side effects was also revised.
II/0051	Update of the section 5.3 of the SmPC to rectify an error in calculation of the exposure margin for male reproductive organ findings from a repeat dose rat	26/06/2014	17/02/2015	SmPC	In this variation the company amended an error in the results of some of the non-clinical tests of sunitinib, namely its effects on the reproductive system in rats. The

	toxicity study. Furthermore, the MAH took the opportunity to introduce minor editorial changes throughout the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				recalculated data confirmed the known safety aspects of this medicine.
II/0049	Submission of the final Clinical Study Report (Study A6181199) on non-interventional retrospective correlation analyses of tumour mutation status (cKit and PDGFRA) and clinical benefit from Study A6181036 (MEA 014.4). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		The results from the retrospective A6181199 study were submitted as previously requested by the CHMP. Overall, patients with primary Kit exon 9 mutation had longer OS and PFS and higher rate of response compared to patients with other mutations. However, this study suffered of the limitations typical of retrospective essays, i.e restricted sample size, lack of availability of tissue and plasma samples at repeated time points and inter-laboratory variability (mutational status was examined at local laboratories). No changes to the product information are warranted. The data from the retrospective A6181199 study do not change the benefit/risk of sunitinib for the treatment of patients with metastatic GIST that are resistant or intolerant to imatinib.
II/0048/G	This was an application for a group of variations. Update of estimated frequencies of adverse drug reactions (ADRs) in sections 4.4 and 4.8 of the SmPC further to a review of pooled clinical trial data . In addition, sections 4.4 and 4.8 of the SmPC are updated regarding mouth pain/irritation, necrotizing fasciitis and proteinuria based on post-marketing	23/01/2014	17/02/2015	SmPC, Annex II and PL	The frequency of ADRs was re-assessed by the MAH in a more conservative way (i.e, based on treatment emergent all-causality events) in comparison to what previously done (i.e, based on treatment-related events). Furthermore, the MAH has also undertaken a number of revisions to the Product Information derived from the sunitinib post-marketing pharmacovigilance activities and the internal revision of the sunitinib label: Consequently,

	experience. The Package leaflet is updated accordingly. The product information has also been updated in line with QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the MAH also proposed revisions in sections 4.4 and 4.8 of the SmPC regarding mouth pain/irritation, necrotizing fasciitis and proteinuria based on post-marketing experience.
IA/0047/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	27/09/2013	n/a		
IA/0046	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/08/2013	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2013	15/11/2013	PL	The MAH applied to include the contact details for Croatia to the list of local representatives.
IA/0043	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative	15/04/2013	n/a		

	composition - Solid pharmaceutical forms				
II/0042	Update of sections 4.4 and 4.8 of the SmPC with regards to cholecystitis further to a cumulative review conducted at the request of the PRAC in a signal recommendation. The package leaflet is updated accordingly. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version 8.3. Annex II has also been updated further to the re-classification of a post-authorisation commitment as a condition to the Marketing Authorisation. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	15/11/2013	SmPC, Annex II and PL	Based on review of a safety signal, the PRAC recommended the MAH of Sutent to perform a cumulative review of the reports concerning "Cholecystitis" and related terms, with particular focus on acalculous and emphysematous cholecystitis. In response to the PRAC recommendation and further to conducting a cumulative review, the MAH submitted this variation application including an epidemiology review, a review of MAH-sponsored nonclinical studies, and cases from the MAH's clinical trials and postmarketing reports. One cholecystitis sunitinib-related event was reported in the pooled dataset of pivotal studies and supported the MAH's proposal to include "Cholecystitis" in Table 1 of the SmPC Section 4.8 with a frequency uncommon. Sixty-seven cholecystitis cases, accounting for 68 events, have been reported in the sunitinib global safety database. Some cases were reported with fatal outcome Overall, sunitinib treatment may be associated with cholecystitis, including acalculous cholecystitis and emphysematous cholecystitis. In clinical registrational studies, the incidence of cholecystitis considered related to sunitinib treatment was 0.1%. Post-marketing cases of cholecystitis have been reported.
II/0040/G	This was an application for a group of variations. Update of section 4.4 and 4.8 of the SmPC with regards to thyroiditis and nervous system disorders further to the request of the CHMP in the assessment of PSUR 9. In addition, sections 4.4 and 4.8 of the	17/01/2013	15/11/2013	SmPC, Annex II and PL	The product information of Sutent has been updated to reflect that cases of thyroiditis have been uncommonly reported in clinical trials and through post-marketing experience. In addition, the paragraph on thyroid dysfunction in section 4.4 should be updated with data from clinical trials where TSH was monitored. "Thyroiditis"

	SmPC were updated further to review of post-marketing experience. The Package leaflet has been updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.2. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				has also been added with a frequency "uncommon" in the table adverse reactions identified through post-marketing experience. The table on adverse reactions reported in clinical trials has been updated to add "Cerebrovascular accident/ Cerebral infarction", "Reversible posterior leukoencephalopathy syndrome" and "Transient ischaemic attack" and "deep vein thrombosis" with a frequency "uncommon" and to add "blood uric acid increased" with a frequency "common". Several adverse reactions of "infections" have been added in the table adverse reactions identified through post-marketing experience.
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0039	Update of sections 4.4 and 4.8 of the SmPC with respect to the adverse reaction "oesophagitis" further to the request of the PhVWP/CHMP after review of a signal from Eudravigilance. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a	15/11/2012	15/11/2013	SmPC	Further to a signal from Eudravigilance, the MAH was requested to conduct a cumulative review of oesophagitis and propose changes to the product information as appropriate. In total, 101 medically confirmed cases of Oesophagitis events were retrieved in the safety database, including 34 registered in the MAH-sponsored interventional clinical

	PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				trials and 67 from various data sources (i.e spontaneous reports, cases reported by the health authorities and publications). Thirty seven of the 67 cases of oesophagitis events can be considered correlated to sunitinib, due to the lack of a possible alternative etiology. The majority of events recovered after temporary or permanent discontinuation of sunitinib, even if it is not possible to conclude on positive de-challenge due to concomitant specific treatment and/or hospitalization. In total, 2 fatal events were reported and one of these cases was in the data set of patients without concomitant risk factor and/or alternative aetiology. Consequently, the SmPC of Sutent has been updated to add the adveres reaction oesophagitis with a frequency "common" and to highlight that cases of oesophagitis, in some cases with fatal outcome, have been reported. The warning in section 4.4 of the SmPC on gastrointestinal disorders has also been updated accordingly.
II/0038	Update of sections 4.4 and 4.8 of the SmPC with respect to the skin and tissue disorders erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis following a request from the PhVWP/CHMP. The MAH also proposed to change the frequency of the adverse reaction pyoderma gangrenosum from unknown to rare. The Package leaflet was updated accordingly. The MAH also took the opportunity to make editorial changes and to update the list of local representatives in the Package leaflet. C.I.z - Changes (Safety/Efficacy) of Human and	18/10/2012	15/11/2012	SmPC and PL	In this variation the MAH has updated sections 4.4 and 4.8 of the SmPC and the Package leaflet with respect to the skin and tissue disorders. Severe cutaneous reactions have been rarely reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms of SJS, TEN, or EM (e.g. progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these

	Veterinary Medicinal Products - Other variation				patients also received concomitant treatment with corticosteroids or antihistamines.
IG/0169/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	08/06/2012	n/a		
IA/0036	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	04/05/2012	n/a		
IAIN/0035/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	25/04/2012	n/a		
IB/0034	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a	16/03/2012	20/09/2012	SmPC, Labelling and	

	PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH			PL	
R/0030	Renewal of the marketing authorisation.	20/10/2011	09/01/2012	SmPC, Annex II and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Sutent continues to be favourable. The CHMP is however of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The latest extension of indication of Sutent for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults has been granted recently (EMEA/H/C/687/II/21, Commission Decision 29 November 2010). In order to definitely confirm a Marketing Authorisation with unlimited validity, a larger post marketing experience is considered necessary, in particular as certain safety concerns as discussed in the assessment of the renewal and PSUR are under continuous surveillance. The CHMP decided that the MAH should continue to submit 1-yearly PSURs.
II/0032	Update of SmPC sections 4.4 regarding Tumour Haemorrhage, Tumour necrosis and Infections as well as update of SmPC section 4.8 with the adverse reaction "Pancytopenia" and information on cardiac disorders and infections, in particular "necrotising fasciitis" following request from the CHMP in the	20/10/2011	09/01/2012	SmPC and PL	Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal. Furthermore, serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are

	assessment of PSUR 8. The package leaflet has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				infections typically seen in cancer patients, e.g. respiratory, urinary tract, skin infections and sepsis. Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. Cardiac events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported through post-marketing experience. Furthermore, pancytopenia has been reported with a frequency uncommon.
II/0031/G	This was an application for a group of variations. Group of 2 Type II variations to update SmPC section 5.3 with results from a 2-year oral carcinogenicity study in rats as well as from an oral pre- and postnatal development study in rats. 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	20/10/2011	09/01/2012	SmPC	In a 2-year rat carcinogenicity study Sprague-Dawley (Crl:CD(SD)) rats (70 rats/sex for control and high dose; 60 rats/sex for low and mid dose) were given sunitinib daily via oral gavage in a cycle of 28 days of dosing followed by a 7-day treatment free period at doses of 0, 0.33, 1.0, or 3.0 mg/kg/day for at least 104 weeks. Toxicokinetic parameters have been assessed by one single test of plasma levels at week 26. Administration of sunitinib resulted in an increased incidence of pheochromocytomas and hyperplasia in the adrenal medulla of male rats given 3 mg/kg/day following >1 year of dosing (7.8 times the AUC in patients administered the recommended daily dose [RDD]). Brunner's glands carcinoma occurred in the duodenum at ?1 mg/kg/day in females and at 3 mg/kg/day in males, and mucous cell hyperplasia was evident in the glandular stomach at 3 mg/kg/day in males, which occurred at ?0.9, 7.8 and 7.8 times the AUC in patients administered the RDD, respectively. The relevance to humans of the neoplastic findings observed in the mouse (rasH2 transgenic) and rat carcinogenicity studies with sunitinib treatment is unclear. Sunitinib was evaluated in a pre-and postnatal

					development study in pregnant rats. In this study SU010398 was administered to timed pregnant Sprague-Dawley rats (20/group) as a solution in sterile water by oral gavage at doses of 0, 0.3, 1, or 3 mg/kg/day from gestation Day (GD) 6 to lactation Day (LD) 20, in order to determine the potential adverse effects of maternal (F0) exposure to SU010398 from implantation to weaning on pregnancy, parturition, and lactation of the F0 maternal animals and on the viability, growth, and functional development, including behaviour, sexual maturation, and reproduction of the F1 offspring. Maternal body weight gains were reduced during gestation and lactation at ?1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimated exposure ?2.3 times the AUC in patients administered the R
II/0028	Update of SmPC section 4.4 regarding information on thyroid dysfunction as well as early and late-onset anaemia; in addition SmPC section 4.8 as well as the Package Leaflet (PL) have been updated with regard to the adverse drug reaction "haemoptysis" as requested with CHMP assessment of FU2 021.2. In addition, the frequencies of adverse reactions reported through post-marketing experience have been recalculated in accordance with SmPC guideline. Furthermore, the MAH took the opportunity to update the version number of the RMP in Annex II as well as the List of local representatives in the PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/07/2011	18/08/2011	SmPC, Annex II and PL	Hypothyroidism was reported as an adverse event in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN- arm in the treatment-naïve MRCC study. Baseline laboratory measurement of thyroid function is recommended in all patients. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice. Although most of the reported hemorrhagic events were of

					grade 1 or 2 and mainly due to lack of control of the underlying conditions (metastatic disease, uncontrolled hypertension and thrombocytopenia), the risk of hemorrhagic AEs with sunitinb is not neglectable (26% in patients treated with sunitinib, Ayllon, Prog Urol 2010). Therefore, the adverse drug reaction "haemoptysis" has been added to SmPC section 4.8 as well as in the PL with the frequency "uncommon". The terms "anaemia" and "oedema peripheral" were already listed in the SmPC section 4.8 as very common adverse reactions. The incidence of anaemia ranged from 12.5% (MRCC) to 19.5% (GIST) in clinical trials. The incidence of oedema (oedema, oedema peripheral and oedema face) ranged from 13.4% (GIST) to 15.3% (MRCC). Most events of anaemia and oedema were mild to moderate in severity (Grades 1 and 2). However, the information in the SmPC has been amended to inform that anaemia has been observed to occur early as well as late during treatment with sunitinib; Grade 3 and 4 cases have been reported. Furthermore, the 3/X methodology in accordance with the SmPC guideline was applied for the post-marketing experien
IA/0029	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	30/05/2011	n/a		
IG/0044/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	02/03/2011	n/a	Annex II	

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
IB/0025/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.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	19/01/2011	n/a		
II/0027	Update of SmPC sections 4.4 and 4.8 with information on cases of Osteonecrosis of the jaw (ONJ) associated with co-administration of sunitinib and bisphosphonates as requested by CHMP. The respective PL sections have been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and	18/11/2010	20/12/2010	SmPC and PL	Cases of ONJ have been reported in patients treated with Sutent. The majority of cases occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk factor. Caution should therefore be exercised when SUTENT and bisphosphonates are used either simultaneously or sequentially. Invasive dental procedures are also an identified risk

	Veterinary Medicinal Products - Other variation				factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving i.v. bisphosphonates, invasive dental procedures should be avoided if possible.
II/0026/G	This was an application for a group of variations. This was an application for a group of variations. The MAH applied for an update of SmPC sections 4.4, 4.8, 4.9 and 5.3 following assessment of PSUR 7. The respective sections of the package leaflet have been updated accordingly. The MAH also took the opportunity to update Annex II deleting the DDPS version number and to revise the SmPC sections 4.2, 4.5, 4.6 and 5.1 in accordance with QRD 7.3.1 as well as performing typographical corrections. In addition the Icelandic local representative has been updated in the package leaflet. In addition, an update of SmPC section 4.4 regarding hypothyroidism as requested by CHMP with assessment of FU2 21.1 has been performed. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/11/2010	20/12/2010	SmPC, Annex II and PL	SmpC section 4.4 has been amended with new information regarding the subsections on Haematological disorders, Cardiac disorders, QT interval prolongation, Arterial Thromboembolic Events, Thyroid dysfunction, Hepatoxicity, Renal function and Impaired Wound Healing. In the postmarketing section of SmPC section 4.8 the following Adverse Drug reactions have been added with the frequency unknown: Cardiomyopathy, Pericardial effusion, Hepatitis, Impaired wound healing, Renal failure and Acute renal failure. Moreover, SmPC section 4.9 has been updated to inform that few cases of overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions. In SmPC section 5.3 information has been added regarding the carcinogenic potential of sunitinib evaluated in rasH2 transgenic mice. Gastroduodenal carcinomas, an increased incidence of background haemangiosarcomas, and/or gastric mucosal hyperplasia have been observed at doses of ?25 mg/kg/day following 1- or 6-months duration (?7.3 times the AUC in patients administered the RDD). No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day (?0.7 times the AUC in patients administered the RDD). The relevance of the carcinogenicity findings observed in the rasH2 transgenic

					mouse to humans following 1- and 6-months sunitinib treatment is unclear
II/0021	Extension of Indication	21/10/2010	29/11/2010	SmPC, Annex II and PL	
II/0022	Update of SPC sections 4.2 and 5.2 to add information for patients with renal impairment based on the data of a Phase I study (A6181106). In addition, the MAH took the opportunity to perform minor editorial changes to Annex II and 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	20/05/2010	01/07/2010	SmPC, Annex II and PL	Study A6181106 was an open-label, single-dose, parallel-group study. Three groups of subjects (healthy subjects with normal renal function [creatinine clearance [CLcr] >80 mL/minute], subjects with severe renal impairment but not requiring dialysis [CLcr <30 mL/minute] and subjects with End-Stage renal disease (ESRD) requiring hemodialysis; 8 subjects per group were enrolled and completed the study. Systemic exposures after a single dose of SUTENT were similar in subjects with severe renal impairment (CLcr<30 ml/min) compared to subjects with normal renal function (CLcr>80 ml/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function. No starting dose adjustment is required when administering SUTENT to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on hemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability
IA/0024/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	02/06/2010	n/a		

	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				
IB/0023	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	07/04/2010	n/a		
II/0018	Update of SPC sections 4.4, 4.8 and 5.1 based on the final study report for the pivotal study A6181034 for which an interim report was assessed with EMEA/H/C/687/II/001 in the year 2006. Section 4 of the package leaflet (PL) has been udpated accordingly. The MAH also took the opportunity to perform an administrative change in the zip code of the address of the manufacturer in Annex II and the PL. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC, Annex II and PL	Study A6181034 was a randomized, multi-center, international, Phase 3 study of sunitinib vs. interferon-alfa (IFN-) as first-line treatment in subjects with metastatic renal cell carcinoma (MRCC). This final analysis confirmed and extended the findings of the second interim analysis. In the primary analysis of Progression Free Survival (core radiology laboratory assessment, ITT population), the median PFS on sunitinib was more than double that on IFN- (48.3 weeks [95% CI: 46.4 to 58.3 weeks] vs. 22.1 weeks [95% CI: 17.1 to 24.0 weeks]; hazard ratio of 0.5268 [95% CI: 0.4316 to 0.6430], p<0.0001); In the first-line treatment of subjects with MRCC, sunitinib treatment resulted also in a statistically significant and clinically meaningful improvement in Time To Progression and Overall Response Rate, as compared to IFN- . Although the median Overall Survival was longer for the sunitinib arm (114.6 weeks for the sunitinib arm (95% CI: 100.1 - 142.9 weeks) and 94.9 weeks for the IFN-? arm (95% CI: 77.7 - 117.0 weeks) with a hazard ratio of 0.821 (95% CI: 0.673 - 1.001; p=0.0510 by unstratified log-

					rank), it did not reach statistical significance with the unstratified log-rank test. Treatment-related serious adverse events (TRSAEs) were reported in 23.7% of patients receiving sunitinib and in 6.9% of patients receiving IFN-?, However, the discontinuation rates due to adverse events were 20% for sunitinib and 23% for IFN-?. The adverse events reported in sunitinib-treated subjects were tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy. Overall, the safety data are consistent with the known safety profile of sunitinib, and no new safety risks were identified.
II/0016	This type II variation concerns an update of section 5.1 of the SPC with the results of study A6181004, as requested by CHMP following the assessment of FUM 016. The MAH also took the opportunity to make minor editorial amendments to the SPC. Update of Summary of Product Characteristics	24/09/2009	28/10/2009	SmPC	Study A6181004 was a phase II, randomized, double Blind, placebo-controlled study of SU011248 in the treatment of patients with imatinib mesylate (Gleevec, Glivec)-resistant or intolerant malignant gastrointestinal stromal tumour). The final analysis of Study A6181004 re-affirmed the results from the previously submitted interim analysis. The study demonstrated that sunitinib treatment improved TTP by more than 4-fold (26.6 vs. 6.4 weeks, p<0.001) compared with placebo. This resulted in an approximate 3-fold reduction in the relative risk of disease progression in subjects with GIST. In the final analysis median TTP for the sunitinib group is 26.6 weeks, with a range: 16 to 32.1 weeks. The 16 weeks are closer to the median TTP of patients in the placebo arm, i.e. 6.4 weeks. This means that there are patients whose disease is effectively kept under control by sunitinib and other patients that are possibly exposed to toxicity without any significant benefit. Adverse events reported in sunitinib-treated subjects were generally tolerable and manageable through dosing

					interruption, dose reduction, and/or standard supportive medical therapies. The final analyses of safety are consistent with the safety profile observed at the interim analysis; there have been no new safety risks identified in this study. Due to the lack of validated predictive markers and the significant difference in TTP (primary objective in this study) it is difficult to deny an option to patients who progress on imatinib. At the same time the MAH is strongly encouraged to further identify and validate predictive factors of response to sunitinib. The MAH has made a commitment in this regard.
IB/0020	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/10/2009	n/a	SmPC	
IB/0019	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	03/09/2009	n/a		
II/0015	Update of SPC sections 4.4 and 4.8 regarding the events hypersensitivity/angioedema" and "fistula" reported during post marketing. The package leaflet has been revised accordingly including revisions of section 4 to align the information presented in the PL with SPC section 4.8. Furthermore, the MAH took the opportunity to update the List of local representatives in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	20/08/2009	SmPC and PL	A cumulative safety review of hypersensitivity and angioedema was conducted by the MAH for the period 26 January 2006 to 31 July 2008. A total of 69 cases (containing 86 relevant events) reported angioedema and related events. Regarding angioedema in particular, forty-five cases reported 50 events including facial, lip, laryngeal and/or tongue swelling/edema events. Thirty-five events were considered serious and the remaining 15 events were considered non serious. Seven cases reported Hypersensitivity (3), Anaphylactic reaction (2), and Drug hypersensitivity (2). Six of the seven events were considered serious. This case series suggests that serious hypersensitivity reactions, particularly angioedema, may

					occur with sunitinib therapy. During routine data mining of the safety database for sunitinib, the adverse event "Fistula" was identified as a signal of disproportional reporting. The subsequent search in the postmarketing safety database for the period 26 January 2006 to 31 July 2008 revealed a total of 34 reported cases of all types of fistula. The most common PTs were Anal fistula (5), Enterocutaneous fistula (5), and Gastrointestinal fistula (5). Although many of the reported fistulae cases involved patients with known contributing factors (i.e. adjacent malignancy, surgery, pre-existing conditions), there were several cases which described a close temporal association between sunitinib use and fistulae which did not identify an adjacent risk factor. During the assessment the CHMP considered that in almost all the cases of ADRs (both angioedema and fistula) the treatment with Sutent was completely interrupted in order to recover the symptoms. Therefore, information regarding the management of these ADRs has been added to SPC section 4.4 together with the update of the table presenting Adverse Reactions reported through post-marketing experience.
II/0017	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	25/06/2009	03/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
X/0012	Addition of a new strength	19/03/2009	29/05/2009	SmPC, Labelling and	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance

	Annex I_2.(c) Change or addition of a new strength/potency			PL	of Sutent 37.5 mg in the treatment of unresectable and/or metastatic malignantgastrointestinal stromal tumour (GIST) after failure of imatinib mesilate treatment due to resistance or intolerance and in the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) was favourable and therefore recommended the granting of an extension to the marketing authorisation of Sutent for Sutent 35.7 mg hard capsules.
II/0014	Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	10/02/2009	SmPC and PL	This type II variation concerns an update of the SPC, upon request by CHMP following the assessment of the 4th PSUR, to update the warnings regarding pulmonary events, haematological events, renal function and venous thrombolic events in section 4.4 of the SPC, and to add the ADR 'pneumonia' to secton 4.8 of the SPC. In addition, the MAH takes the opportunity to update the contact details of the local representatives and to make editorial changes in the Package Leaflet. Revised wording in section 4.4 of the SPC: Haematological events Decreased absolute neutrophil counts of grade 3 and 4 severity were reported in 10% and 1.7% of patients on the phase 3 GIST study, respectively, and in 16% and 1.6% of patients on the phase 3 MRCC study, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 3.7% and 0.4% of patientson the phase 3 GIST study, respectively, and in 8.2% and 1.1% of patients on the phase 3 MRCC study, respectively. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None

					of these events in the phase 3 studies were fatal, but rare fatal haematological events have been reported through post-marketing experience. Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with Sutent. Venous Thromboembolic Events: Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received Sutent on clinical trials, including GIST and MRCC. Seven patients (3%) on Sutent and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thromboses (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT. Seven patients (1.9%) receiving Sutent in the phase 3 treatment-naïve MRCC study and four patients (2%) on t
II/0013	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	25/09/2008	30/10/2008	Annex II	The MAH has applied for an update of the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated to reflect the latest version agreed with the CHMP (version 1.1, dated 8 November 2007).
II/0011	Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	22/08/2008	SmPC, Annex II and PL	This type II variation concerned an update of sections 4.4 and 4.8 of the SPC with further information on fatal, serious and/or unlisted ADRs, as well as a general update

					of the ADR tables in section 4.8 of the SPC, and was submitted by the MAH upon request by CHMP following the assessment of the 3rd PSUR. Further, the MAH has updated section 4.8 of the SPC with the ADRs 'nephrotic syndrome and proteinuria', 'thrombotic microangiopathy' and 'hyperthyroidism' and, upon request by CHMP following the assessment of FU2 024.1 has added further information regarding 'QT interval prolongation' in section 4.4 of the SPC. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update annex II using standard text to include the latest version numbers of the RMP (version 3.0) and pharmacovigilance system agreed with the CHMP.
IB/0009	IB_33_Minor change in the manufacture of the finished product	26/05/2008	n/a		
IA/0010	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	31/03/2008	n/a		
IA/0008	IA_32_a_Change in batch size of the finished product - up to 10-fold	14/03/2008	n/a		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	25/01/2008	SmPC and PL	This type II variation concerns an update of section 4.8 of the SPC with information regarding the ADRs 'rhabdomyolysis and myopathy' and 'serious infections'. In addition, the Marketing Authorisation Holder took the opportunity to make a minor editorial change to the Package Leaflet. Infection and infestations: Cases of serious infection (with or without neutropoenia), in some cases with fatal outcome, have been reported.

					Musculoskeletal and connective tissue disorders: Rare cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.
II/0006	Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	22/11/2007	SmPC and PL	This type II variation has been submitted upon request by the CHMP following the assessment of the 1st PSUR and concerns an update of sections 4.4 and 4.8 of the SPC with the percentage of fatal ADRs reported/observed, section 4.8 of the SPC with a separate table with the ADRs reported post-marketing and a separate table integrating the ADRs observed in refractory and chemotherapy-naïve patients. Further, the MAH has made editorial changes to section 4.4 of the SPC and included further information on baseline TSH testing. In addition, the MAH takes the opportunity to update section 4.2 of the SPC to include two types of dose modification recommendations. The Package Leaflet has been updated accordingly.
II/0005	Addition of new presentations New presentation(s)	20/09/2007	24/10/2007	SmPC, Labelling and PL	The MAH applied for a new pack size of 28 capsules consisting of Aclar/PVC blister with aluminium foil for all strengths of SUTENT. The MAH took also the opportunity to apply for a combined package leaflet for all the strengths and to update the contact details for the local representatives.
IA/0004	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	23/02/2007	n/a		
II/0002	Update of Summary of Product Characteristics	14/12/2006	17/01/2007	SmPC	The MAH applied for a type II variation to update sections 4.2, 4.4, 4.8 and 5.2 of the SPC with information on hepatically impaired patients based on the results of Study

					A6181079 and to add information on 'Torsade de Pointes' based on 1 case observed in an ongoing clinical trial. In addition, the MAH took the opportunity to make some minor editorial changes to the SPC and Package Leaflet. Hepatic impairment: Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of Sutent were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. Sutent was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN (Upper Limit of Normal) or, if due to liver metastasis, > 5.0 x ULN. No dose adjustment is recommended when administering Sutent to patients with mild or moderate (Child-Pugh Class A and B) hepatic impairment. Pancreatitis has been observed rarely (<1%) in patients receiving Sutent for GIST or Metastatic Renal Cell Carcinoma. Hepatic failure was observed in <1% of solid tumor patients treated with Sutent. If symptoms of pancreatitis or hepatic failure are present, patients should have Sutent discontinued and be provided with appropriate supportive care. QT Interval prolongation: QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies. At

					approximately twice therapeutic concentrations, Sutent has been shown to prolong the QTcF interval (Frederica's Correction). There were no patients with greater than grade 2 (CTCAE v3.0) QT/QTc interval prolongation. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including 'Torsade de pointes'. 'Torsade de pointes' has been observed in <0.1% of Sutent-exposed patients. Sutent should be used
II/0001	Extension of Indication & switch from conditional to normal Marketing Authorisation Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	11/01/2007	SmPC, Annex II and PL	The MAH submitted a Type II variation, which included efficacy and safety data from an analysis of Study A6181034 (A phase III randomised study of sunitinib versus interferon-alfa as first line systemic therapy for patients with metastatic renal cell carcinoma) in order to fulfill the Specific Obligation. The MAH, on the basis of the results of Study A6181034, requested to extend the indication to include first-line treatment of patients with advanced and/or metastatic renal cell carcinoma (MRCC). SPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been amended and the PL has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SPC and PL. As part of this application, the MAH also requested a switch from a conditional to a 'normal' marketing authorisation in accordance with Article 7 of Regulation (EC) No 507/2006. Please refer to the Scientific Discussion "Sutent-H-C-687-II-01"
IA/0003	IA_21_a_Submission of Ph. Eur. certificate for	08/12/2006	n/a		

	excipient - from approved manufacturer				