Nexavar

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/0046	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	25/06/2018		SmPC, Annex II and PL	
IA/0045/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of	02/05/2018	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).

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	specification limits B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2017		Labelling and PL	
PSUSA/2773/ 201612	Periodic Safety Update EU Single assessment - sorafenib	01/09/2017	n/a		PRAC Recommendation - maintenance
IA/0043	B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	28/07/2017	n/a		
T/0042	Transfer of Marketing Authorisation	12/06/2017	06/07/2017	SmPC, Labelling and PL	
IA/0041/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	10/05/2017	n/a		
IAIN/0039/G	This was an application for a group of variations.	16/03/2017	06/07/2017	Annex II and PL	

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2016	06/07/2017	PL	
PSUV/0037	Periodic Safety Update	25/09/2014	21/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0037.
II/0035	Extension of the indication for the treatment of progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. The SmPC was revised in order to add warnings on the risk of bleeding, hypocalcaemia and TSH suppression as well as reflect relevant non-clinical and clinical safety and efficacy data in patients with differentiated thyroid carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest	25/04/2014	23/05/2014	SmPC and PL	See Scientific Discussion: "H-690-VAR-II-35-en"

	QRD template version 9.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2014	31/01/2014	PL	
II/0034/G	This was an application for a group of variations. Update of section 4.4 of the SmPC to delete the warning on limited experience with the use of Nexavar in elderly, and update of section 4.8 of the SmPC to add hypokalaemia, proteinuria and nephrotic syndrome as new adverse reactions and include updated information on interstitial lung like events based on the results of a safety review. The Package Leaflet is updated accordingly. Furthermore, Annex II is being brought in line with the latest QRD template version 8.3. 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	21/02/2013	31/01/2014	SmPC, Annex II and PL	Based on the results of a safety review performed by the MAH, the product information has been revised to include the following new adverse reactions: hypokalaemia (frequency common), proteinuria (frequency common) and nephrotic syndrome (frequency rare). Regarding hypokalaemia, decreased potassium was observed in 5.4% and 9.5% of Nexavar-treated patients compared to 0.7% and 5.9% of placebo patients, in two studies respectively. Most reports of hypokalaemia were low grade (CTCAE Grade 1). In these studies CTCAE Grade 3 hypokalaemia occurred in 1.1% and 0.4% of Nexavar treated patients and 0.2% and 0.7% of patients in the placebo group. There were no reports of hypokalaemia CTCAE grade 4. In addition, a cumulative review on fatal interstitial lung disease (ILD) identified 11 cases for which the causality to sorafenib was at least possible. Hence, the product information has been updated to reflect that ILD adverse reactions may have a life-threatening or fatal outcome and that such events are either uncommon or less frequent than uncommon. Cumulative safety data also showed that there were no differences of clinical relevance in the safety profile of elderly versus non-elderly patients treated with sorafenib and therefore the warning that there is limited experience with

					the use of Nexavar in elderly in was deleted from the SmPC.
II/0032	Update of SmPC section 4.8 and PL regarding the adverse reactions hypocalcaemia and toxic epidermal necrolysis as well as a change of SmPC section 4.5 regarding interaction with carboplatin based on already assessed data with II/18G. The MAH also took the opportunity to update the PI in accordance with QRD version 8 rev 1 including corrections to the List of Local Representatives. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	The analysis of hypocalcaemia in patients treated with sorafenib in the phase 3 placebo controlled studies showed that the exposure adjusted incidence rate of treatment emergent Adverse Events of hypocalcaemia and hypocalcaemia from laboratory measurements was higher in the sorafenib group compared to placebo. The majority of events of hypocalcaemia were low grade (grades 1 and 2) and were identified through routine laboratory measurements with no serious clinical consequences. Hypocalcaemia was added as ADR of common frequency to SmPC section 4.8. Drug-induced toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are closely related, although their severity and outcome are different. Stevens-Johnson syndrome is already included in SmPC section 4.8 as rare adverse reaction. Following a review of the safety database, the MAH retrieved 4 cases with clinical features consistent of TEN reported with Nexavar used in monotherapy in the post-marketing setting. Toxic Epidermal Necrolysis was added as ADR of rare frequency to SmPC section 4.8
IAIN/0033/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	20/06/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system 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/0031/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.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.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	06/01/2012	27/06/2012	Annex II and PL	
II/0028	Update of SmPC section 4.8 with the adverse drug reactions "rhabdomyolysis" and "leucocytoclastic vasculitis" under the frequency category "rare" as requested by CHMP with assessment of PSUR 8. The PL has been amended accordingly. The MAH also took the opportunity to update the List of Local Representatives.	22/09/2011	24/10/2011	SmPC and PL	With the assessment of PSUR 8 it was noted by CHMP that in Eudra Vigilance there were 11 cases "leucocytoclastic vasculitis" in total, although only 7 were valid after excluding three cases with insufficient information and one duplicated case. Based on these cases including two positive dechallenges and a PRR 2.56 (95%CI: 1.28 - 5.13) the term "leucocytoclastic vasculitis" has been added to SmPC section 4.8 and PL section 4 with the frequency "rare".

	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				The MAH performed a cumulative search for cases potentially consistent with rhabdomyolysis; this search identified a total of 391 cases. Rhabdomyolysis was reported in 12 cases and 11 were medically confirmed. Statins were used as a concomitant medication in 2 patients and glycyrrhizic acid were used in additional 2 cases. The CHMP considered with the assessment of PSUR 8 that two cases with rhabdomyolysis during sorafenib treatment experienced a positive rechallenge. A positive rechallenge is generally regarded as strong indication for causality. Further it was noted that symptoms from muscles were commonly expressed by patients treated with sorafenib indicating a muscle impact by sorafenib. Therefore, the term "rhabdomyolysis" has been added to SmPC section 4.8 and PL section 4 with the frequency "rare".
IA/0029/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	15/08/2011	n/a	SmPC, Annex II, Labelling and PL	
II/0027	Update of the existing warning in SmPC section 4.4 regarding information on higher mortality observed in the subset of patients with squamous cell carcinoma of the lung treated with sorafenib in combination with	23/06/2011	01/08/2011	SmPC	Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell

	platinum-based chemotherapies with results from a second phase III trial. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with sorafenib as add-on to paclitaxel/carboplatin, the HR for overall survival was found to be 1.81 (95% CI 1.19; 2.74) and as add-on to gemcitabine/cisplatin 1.22 (95% CI 0.82; 1.80). No single cause of death dominated, but higher incidences of respiratory failure, haemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.
R/0024	Renewal of the marketing authorisation.	14/04/2011	29/06/2011	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 Nexavar continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0026/G	This was an application for a group of variations. This was an application for a group of variations. The respective scope of the variations was to update SmPC section 4.5 regarding new data from an interaction study investigating sorafenib in combination with cisplatin. Furthermore, update of SmPC sections 4.2, 4.4 and 5.2 with respect to sorafenib pharmacokinetics in patients with hepatic impairment. 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 of	17/03/2011	02/05/2011	SmPC and PL	Study results of a phase I single-center, open-label, non-randomized study to determine the pharmacokinetics, safety and tolerability, and tumor response profile of sorafenib as continuous dosing in combination with gemcitabine and cisplatin in patients with Stage IIIB or Stage IV non-small-cell lung cancer or other advanced solid tumors showed no clinically relevant interactions. The results of the recent multi-center, open-label, non-randomized, phase I study of oral sorafenib to assess the pharmacokinetics and safety in subjects with hepatic impairment and healthy volunteers. confirmed that the sorafenib pharmacokinetics were not altered in subjects with hepatic impairment with Child-Pugh class A and B. Therefore, in hepatocellular carcinoma (HCC) patients with Child-Pugh A

	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				or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and B non-HCC patients were similar to the PK in healthy volunteers.
IA/0025/G	This was an application for a group of variations. 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.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	12/01/2011	n/a	Annex II	
II/0022/G	This was an application for a group of variations. This was an application for a group of variations. The respective scope of the variations was to update SmPC section 4.5 with information on the interaction between sorafenib and cyclophosphamide as well as to update SmPC section 4.8 re-including the term "radiation pneumonitis" as clarification of the uncommon adverse reaction "interstitial lung disease-like events". These changes follow the recommendation provided with the CHMP assessment of the Periodic Safety Update Report (PSUR) 7. In addition, the MAH proposed to remove "carboplatin"	21/10/2010	26/11/2010	SmPC and PL	Study 12347 was designed to examine the effect of sorafenib on cyclophosphamide, a CYP2B6 substrate, in vivo. In this study, concomitant administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 in vitro with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinical meaningful inhibition. These data suggest that sorafenib at

	from section 2 of the PL as the term was erroneously included in this section of the PL during the previous variation II/18G, although no pharmacokinetic interaction between carboplatin and sorafenib was demonstrated. Furthermore, an update of SmPC sections 4.4, 4.8 and 5.1 regarding QT prolongation; to include a warning on QT prolongation in section 4.4, a rare adverse reaction in section 4.8, and information about the underlying Clinical Pharmacology Study in section 5.1 has been performed. The PL has been updated accordingly. 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				the recommended dose of 400 mg twice daily may not be an in vivo inhibitor of CYP2B6 or CYP2C8. Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant in vivo inhibition of CYP2C9 by sorafenib may be expected to be low. However, patients taking warfarin or phenprocoumon should have their INR checked regularly. A single arm clinical trial of 400 mg bid sorafenib in male patients with cancer specifically designed to evaluate cardiovascular safety. In this clinical pharmacology study, QT/QTc measurements were recorded in 31 patients at baseline (pre-treatment) and post-treatment. After one 28-day treatment cycle, at the time of maximum concentration of sorafenib, QTcB was prolonged by 4 ±19 msec and QTcF by 9 ±18 msec, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring. Sorafenib should be used with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic med
IB/0023/G	This was an application for a group of variations. B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.c.2.b - Change in test procedure for an excipient -	20/09/2010	n/a		

	Deletion of a test procedure if an alternative test procedure is already authorised B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.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)				
IB/0021/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	02/09/2010	n/a	SmPC	
II/0018/G	This was an application for a group of variations.	22/07/2010	26/08/2010	SmPC, Annex II, Labelling	Administration of paclitaxel (225 mg/m2) and carboplatin (AUC = 6) with sorafenib (? 400 mg twice daily),

	This was an application for a group of variations. The respective scope of the variations was to update SmPC section 4.5 regarding interaction between sorafenib and capecitabine as well as to update SmPC section 4.8 with the ADR "drug-induced hepatitis" in accordance with assessment of PSUR 6. The Package Leaflet (PL) has been updated accordingly. Furthermore, an update of SmPC section 4.5 regarding interaction between sorafenib and paclitaxel/carboplatin has been performed. Also SmPC section 4.8 has been updated with ADRs "angioedema" and "radiation recall dermatitis". The PL has been updated accordingly. In addition, the MAH took the opportunity to update the Product Information in line with QRD version 7.3.1 as well as to update the List of Local Representatives in the PL. Administration of paclitaxel (225 mg/m2) and carboplatin (AUC = 6) with sorafenib (? 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel. Co-administration of paclitaxel (225 mg/m2, once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected. These data indicate no need for dose adjustments			and PL	administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel. Co-administration of paclitaxel (225 mg/m2, once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected. These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown. Co-administration of capecitabine (750-1050 mg/m2 twice daily, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unknown. In the assessment of PSUR 6 the CHMP noted that for sorafenib, cumulatively 6 events of hepatitis and 31 events of hepatic failure have been reported. Based on the identification by the MAH of 8 cases potentially consistent with drug induced hepatitis the term "drug induced hepatitis"

	when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown. Co-administration of capecitabine (750-1050 mg/m2 twice daily, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted admi 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				with life-threatening or fatal outcome has been added to SmPC section 4.8. Based on a case report describing radiation recall dermatitis following initiation of sorafenib, two additional cases identif
IB/0020	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	30/07/2010	n/a		

IA/0019	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	30/07/2010	n/a		
IG/0009/G	This was an application for a group of variations. 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 C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure 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	18/06/2010	n/a	Annex II	
IB/0017	IB_10_Minor change in the manufacturing process of the active substance	18/01/2010	n/a		
II/0016	Update of SPC section 4.8 to change the frequency of the term "congestive heart failure" to "common" and to include further information on this adverse drug reaction, as well as to add the term "interstitial lung	22/10/2009	23/11/2009	SmPC and PL	The present analysis performed by the MAH regarding heart failure has used the Global Integrated Analysis dataset consisting only of data from the MAH sponsored Phase 1 to Phase 3 sorafenib monotherapy clinical studies. In these

	disease-like events" with the frequency "uncommon" following CHMP assessment of PSUR 6. Furthermore, safety information from a study in non-small lung cancer patients has been added to SPC section 4.4. The package leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				company sponsored clinical trials congestive heart failure was reported as an adverse event in 1.9% of patients treated with sorafenib. Based on the review of the submitted documentation the CHMP considered that there is a likely increase in patients experiencing congestive heart failure. Therefore, upgrading the frequency category to "common" for the term "congestive heart failure" was supported. Furthermore, additional information related to congestive heart failure was added to SPC section 4.8. The potential association of sorafenib with an increase in the reporting rate for "interstitial lung disease" was evaluated by the MAH. Of the 57 cases identified by the search, there was in 16 cases information presented within the case for the candidate event that suggested a clear alternative cause, but that a potential role of sorafenib could not be ruled out. In 7 cases, the MAH considered that available information was consistent with a diagnosis of potentially drug-induced ILD. Therefore, the term "interstitial lung disease-like events" has been added to SPC section 4.8. A randomized controlled trial comparing safety and efficacy of carboplatin and paclitaxel plus or minus sorafenib in chemonaive patients with Stage IIIB-IV Non-Small Cell Lung Cancer was stopped early, when the independent Data Monitoring Committee concluded that the study would not meet its primary endpoint of improved overall survival. Safety events were generally consistent with those previously reported. However, higher mortality was observed in the subset of patients with squamous cell carcinoma of the lung treated with sorafenib and carboplatin and paclitaxel versus those treated with carboplatin and paclitaxel alone (HR 1.81, 95% CI 1.19-2.74). No definitive

					cause w
II/0015	Update of Detailed Description of the Pharmacovigilance System Update of DDPS (Pharmacovigilance)	24/09/2009	15/10/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 9.7) to reflect the integration of the companies' pharmacovigilance systems (Bayer and Schering AG). Consequently, Annex II has been updated with the standard text including new version number of the agreed DDPS.
II/0012	The MAH applied to update of SPC sections 4.4, 4.5 and 5.2 to include information on co-administration with Neomycin or other antibiotics that might interfere with enterohepatic circulation of sorafenib. Furthermore SPC section 4.8 is updated to include the ADRs 'hyperthyroidism' and 'Steven-Johnson syndrome' as well as to change the ADR 'erythema multiforme minor' to 'erythema multiforme'. The Package Leaflet has been revised accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	24/07/2009	SmPC and PL	The MAH submitted the results of an interaction study to address the concern that the action of antibiotics in the gastrointestinal tract could interfere with the enterohepatic recycling of sorafenib. Sorafenib is metabolised in part by glucuronidation. The glucuronide conjugate of sorafenib is secreted into the gastrointestinal tract via the bile. Some microbes of the gastrointestinal flora release glucuronidases which can cleave the sorafenib conjugate, thereby releasing free drug that can be reabsorbed. The hypothesis to be tested in Study 12348 was whether partial or complete eradication of the gastrointestinal flora could diminish the extent of sorafenib re-absorption, thereby decreasing the systemic exposure of sorafenib. Study 12348 was an open-label, randomised, two-period sequential treatment study conducted in 28 healthy male volunteers. Neomycin was chosen as the test antibiotic because of published reports that it effectively reduced glucuronidase activity. Neomycin was shown to decrease sorafenib Area Under the Curve (AUC) by 54%, probably due to eradication of gastrointestinal bacterial glucorinidase activity, and thereby a decrease in the enterohepatic recycling of sorafenib. It cannot be excluded that other antibiotics that affect the

					gastrointestinal flora might have a similar effect on sorafenib. Therefore, a warning in SPC section 4.4 regarding co-administration of neomycin or other antibiotics that cause major ecological disturbances of the gastrointestinal microflora may lead to a decrease in sorafenib bioavailability has been included. The risk of reduced plasma concentrations of sorafenib should be considered before starting a treatment course with antibiotics. Furthermore, additional information has been added to SPC sections 4.5 and 5.2. In addition, the ADRs 'hyperthyroidism' and 'Steven-Johnson syndrome' have been added to SPC section 4.8 as uncommon event and the ADR 'erythema multiforme minor' was changed to 'erythema multiforme'.
T/0013	The MAH applied for the transfer of the Marketing Authorisation of Nexavar from Bayer Healthcare AG to Bayer Schering Pharma AG. Transfer of Marketing Authorisation	18/03/2009	07/04/2009	SmPC, Annex II, Labelling and PL	The MAH applied for the transfer of the Marketing Authorisation of Nexavar from Bayer Healthcare AG to Bayer Schering Pharma AG. The transfer will take place on 1 September 2009.
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	13/03/2009	n/a	Annex II and PL	
II/0011	Update of Summary of Product Characteristics Update of Summary of Product Characteristics	22/01/2009	02/03/2009	SmPC	This type II variation concerns an update of section 5.1 of the SPC to include the results of the Asian hepatocellular carcinoma study 11849 (Study 4), upon request by the CHMP following the assessment of the Follow-Up Measure FU2 021.1. Study 11849 (Study 4) was a Phase III, international,

					multi-centre, randomised, double blind, placebo-controlled study that evaluated the clinical benefit of sorafenib 400 mg (2 x 200 mg tablets) twice daily (bid) versus placebo, both added to Best Supportive Care, in 226 patients with advanced hepatocellular carcinoma (Child-Pugh A only). This study, conducted in China, Korea and Taiwan confirmed the findings of the pivotal study (Study 3) with respect to the favourable benefit-risk profile of Nexavar (HR (OS): 0.68, p = 0.01414). In the prespecified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread) of both Study 3 and 4, the hazard ratio consistently favoured Nexavar over placebo. Exploratory subgroup analyses suggested that patients with distant metastases at baseline derived a less pronounced treatment effect.
II/0010	Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	25/11/2008	SmPC and PL	This variation concerned an update of the SPC to delete information in sections 4.4 and 4.5 on the potential risk of decreased sorafenib exposure when administered concomitantly with substances that increase gastric pH. The MAH has provided data from a 3-way, single-dose crossover study in healthy male volunteers, evaluating the effect of food (moderate-fat meal) and the effect of concomitant omeprazole treatment on the bioavailability of sorafenib (the fed study arm was included to serve as a comparison of pH-related effects beyond those attributable to food). It was shown that daily treatment with a 40 mg omeprazole led to a mean increase in gastric pH from 1 to 4, but had no effect on sorafenib bioavailability. It was therefore concluded that anti-acidic treatment would not be expected to have a clinically meaningful effect on sorafenib exposure.

					In addition, the MAH applied to add a recommendation for monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction in section 4.2 and to add the ADR "renal failure" to section 4.8 of the SPC. The MAH has provided a review of sorafenib data relevant to 'renal dysfunction'. Based on this analysis it is considered that there is little evidence to support a primary nephrotoxic potential of sorafenib. However, due to the possible indirect action through the induction of diarrhoea, vomiting, dehydration with subsequent possible volume depletion and hypotension, that is associated with sorafenib, it is considered that sorafenib may have the potential to contribute to the development of renal dysfunction through pre-renal mechanisms. The Package Leaflet has been updated accordingly.
IA/0009	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	09/07/2008	n/a		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	19/03/2008	18/04/2008	SmPC and PL	The MAH applied for a type II variation to update section 4.4 of the SPC with a statement on gastrointestinal perforation and to add the ADRs 'cholecystitis' and 'cholangitis' in section 4.8 of the SPC. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the annexes and to update the list of local representatives in the Package Leaflet. Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking Nexavar. In some cases this was not associated with apparent

					intra-abdominal tumor. In case of gastrointestinal perforation, Nexavar therapy should be discontinued.
II/0007	Update of Summary of Product Characteristics	20/09/2007	29/10/2007	SmPC	The MAH applied for a type II variation to update sections 4.2 and 5.2 of the SPC, based on the results of Study 11804, with further recommendations for patients with renal impairment. In four Phase I clinical trials, steady state exposure to sorafenib was similar in patients with mild or moderate renal impairment compared to the exposures in patients with normal renal function. In a clinical pharmacology study (single dose of 400 mg sorafenib), no relationship was observed between sorafenib exposure and renal function in subjects with normal renal function, mild, moderate or severe renal impairment. No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.
II/0006	Update of Summary of Product Characteristics	20/09/2007	29/10/2007	SmPC	This variation concerned a modification of a statement in section 5.2 of the SPC regarding potential differences in pharmacokinetics between Asian and Caucasian patients. The MAH has provided data from a new pharmacokinetic study in healthy volunteers, comparing the exposure in Caucasian and Asian (Japanese and Chinese) subjects under controlled conditions. In addition, a new population pharmacokinetic analysis was undertaken, wherein pharmacokinetic data from several single-agent phase I studies were analysed. These new data support the deletion of the statement in section 5.2 of the SPC regarding potential differences in pharmacokinetics between Asian and Caucasian patients. However, the Committee considered that the following new text should be included in section 5.2

					of the SPC: "There are no clinically relevant differences in pharmacokinetics between Caucasian and Asian subjects."
II/0005	"Treatment of hepatocellular carcinoma". Extension of Indication	20/09/2007	29/10/2007	SmPC and PL	This variation concerned an extension of indication to include treatment of hepatocellular carcinoma. Section 4.1, 4.4, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been amended accordingly. In addition, the MAH took the opportunity to make some minor editioral changes to the SPC and Package Leaflet and to update the list of local representatives in the Package Leaflet. Please refer to the Scientific Discussion "Nexavar-H-C-690-II-005".
II/0004	Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	22/08/2007	SmPC and PL	The Marketing Authorisation Holder applied for a type II variation to add the ADR 'keratoacanthoma/ squamous cell cancer of the skin' in section 4.8 of the SPC. The Package Leaflet has been updated accordingly. Based on individual case reports and rather circumstantial mechanistic reasoning, a causal relationship between development of 'keratoacanthoma/ squamous cell cancer of the skin' and sorafenib therapy is considered sufficiently likely to justify the inclusion of these events in section 4.8 of the SPC, and the proposed incidence figure is accepted. It is advised that pre-cancerous lesions such as those of the urinary system and mouth are followed with special care.
II/0003	Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	The Marketing Authorisation Holder applied for a type II variation to update section 4.5 of the SPC with information on potential interaction of sorafenib with docetaxel and to make a consequential change to section 4.4. The Package Leaflet

					has been amended accordingly. Caution is recommended when sorafenib is co-administered with docetaxel. Docetaxel (75 or 100 mg/m2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle with a 3-day break in dosing around administration of docetaxel) resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel.
II/0002	Update of Summary of Product Characteristics	14/12/2006	24/01/2007	SmPC	The MAH applied for a type II variation to update section 4.5 of the SPC with the results of interaction study 11883 of sorafenib and rifampicin with a consequential change to section 4.4. Inducers of metabolic enzymes: Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.
II/0001	Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	03/01/2007	SmPC and PL	The MAH applied for a type II variation to update section 4.8 of the SPC with the ADRs "congestive heart failure", "reversible posterior leucoencephalopathy", "gastrointestinal perforation" and to add a qualifyer to indicate that certain ADRs may have a fatal outcome. The Package Leaflet has

					been updated accordingly. In addition, the MAH took the opportunity to add Bulgarian and Romanian local representatives to the Package Leaflet and to make some minor linguistic changes to the Annexes.