Stivarga

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/0027	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/08/2018		SmPC and PL	
PSUSA/10133 /201709	Periodic Safety Update EU Single assessment - regorafenib	26/04/2018	25/06/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10133/201709.
R/0025	Renewal of the marketing authorisation.	22/03/2018	22/05/2018	SmPC and PL	

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

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II/0024/G	This was an application for a group of variations. Submission of final results from two non-clinical pharmacokinetic studies (study investigating the substrate characteristics and the inhibitory potential of major human plasma metabolites towards OATP1B1 and OATP1B3; study investigating the hepatobiliary disposition of regorafenib and its metabolites in human hepatocytes and the inhibitory potential of regorafenib and metabolites M-2 and M-5 towards BSEP) and study 16671 using physiologically-based pharmacokinetic (PBPK) modelling investigating CYP3A4, UGT1A9 and P-gp inhibition. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2017	n/a		
T/0023	Transfer of Marketing Authorisation	29/06/2017	07/08/2017	SmPC, Labelling and PL	
II/0020	Extension of indication for Stivarga to include treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; as a consequence, sections 4.1, 4.2,	04/07/2017	02/08/2017	SmPC, Labelling and PL	Please refer to the scientific discussion Stivarga-H-C-2573-II-0020

	4.4, 4.8 and 5.1 of the EU SmPC are updated. The package leaflet and RMP (version 5.2) have been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.0. In addition, as set out in Annex IV, the CHMP, with reference to Article 8 of Regulation (EC) No 141/2000, considers by consensus Stivarga to be similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to the authorised orphan medicinal product Nexavar for the same therapeutic indication. However, the holder of the marketing authorisation for Nexavar has given his consent to the applicant. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0022/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/06/2017	07/08/2017	Annex II and PL	

PSUSA/10133 /201609	Periodic Safety Update EU Single assessment - regorafenib	21/04/2017	12/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10133/201609.
II/0018	SmPC sections 4.2 and 5.2 are updated based on results from phase 1 study which evaluated the pharmacokinetics and safety of regorafenib in cancer subjects with severe renal impairment compared to cancer subjects without or with mild renal impairment. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	27/01/2017	SmPC and PL	The objectives of the Phase 1 trial (study 16653) were to characterize the pharmacokinetics of regorafenib and its 2 pharmacologically active metabolites M-2 and M-5 and to measure the amount of drug excreted in urine as its metabolites M-7 and M-8 in locally advanced and / or metastatic solid tumours cancer subjects with severe renal impairment when compared to the control group (cancer subjects with normal or mildly impaired renal function). Pharmacokinetics was evaluated following single dose administration of 160 mg regorafenib and after dosing for 21 days with 160 mg regorafenib QD. The results show that exposure to regorafenib, M-2 and M-5 was not increased in subjects with severe renal impairment compared to subjects with normal renal function. Excretion of M7and M8 in urine were decreased in renal impaired subjects, but this did not result in higher regorafenib, M-2 nor M5 exposure. Overall, the pharmacokinetics of 160 mg regorafenib was not affected by severe renal impairment. This is consistent with the previously provided PBPK modelling in the MAA.
II/0019	The Marketing authorisation holder (MAH) took the opportunity to update Annex II to remove condition relating to provision of data on biomarkers from the ceased COAST trial (15983). Furthermore, minor editorial changes were introduced in the Product Information. The RMP has been updated accordingly and in order to remove the safety concern in patients with severe hepatic impairment following the parallel ongoing variation EMEA/H/C/002573/II/0018.	15/12/2016	27/01/2017	SmPC and Annex II	

	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				
II/0015/G	This was an application for a group of variations. Update of section 4.8 of the SmPC based on the results from Study 15967 (CONSIGN), a Phase 3b trial in patients with metastatic colorectal cancer. In addition, the MAH took the opportunity to provide long-term results from Study 14874 (GRID addendum CSR), a pivotal phase 3 trial in patients with gastrointestinal stromal tumour (GIST). A revised RMP version 4.1 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	14/10/2016	SmPC	The safety profile of regorafenib in a phase III B study conducted in 2872 patients with metastatic colorectal cancer whose disease had progressed after treatment with standard therapies was consistent with the known safety profile of regorafenib.
II/0016	Update of section 4.5 of the SmPC based on the final study results of Study 16674; a Phase 1 drug-drug interaction study undertaken to determine the effect of multiple doses of regorafenib on the pharmacokinetics of probe substrates of transport proteins P-gp and BCRP in patients with advanced	17/03/2016	14/10/2016	SmPC, Annex II and PL	Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in Cmax. This indicates that co-administration of regorafenib may increase the plasma concentrations of other

	solid malignant tumours. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor changes to Annex II to reflect the latest version of the QRD template (9.1), and to update the contact details of the local representative in Norway and the name of the local representative in Portugal in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates. Clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction.
IA/0017	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	20/01/2016	n/a		
PSUSA/10133 /201503	Periodic Safety Update EU Single assessment - regorafenib	22/10/2015	16/12/2015	SmPC	Please refer to Stivarga PSUSA/00010133/201503 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0013	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/11/2015	14/10/2016	SmPC	
II/0014/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to delete the warning regarding patients with KRAS mutant tumours based on a biomarker report from the CONCUR (15808) study (ANX 002.4 and 002.3). In addition, the MAH has submitted the final biomarker analysis from the CORRECT trial (14387). The Annex	22/10/2015	16/12/2015	SmPC and Annex II	Based on biomarker analyses, there is no need to differentiate between patients whose tumours are KRAS mutant or wild-type for the purposes of prescribing Stivarga to eligible patients.

	II has been updated accordingly. Moreover, the updated RMP version 3.5 was agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0011	Submission of study results from retrospective biomarker analyses from the pivotal GRID trial (14874) in order to fulfil the post-authorisation measure laid down in the RMP. The requested variation leads to amendments to the Risk Management Plan (RMP). The requested variation proposed no amendments to the SmPC. An updated Risk Management Plan (RMP) has been submitted as part of the variation. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/06/2015	n/a		
II/0008	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect final results from study 15808 (CONCUR; a randomized, double blind, placebo controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic CRC who have progressed after Standard therapy). The MAH took also the opportunity to introduce minor corrections	21/05/2015	16/12/2015	SmPC and PL	

	and editorial changes throughout the PI. The RMP has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2015	16/12/2015	SmPC	
PSUSA/10133 /201409	Periodic Safety Update EU Single assessment - regorafenib	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0009/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/03/2015	n/a		
IB/0006	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/02/2015	n/a		
PSUV/0004	Periodic Safety Update	23/10/2014	16/12/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0004.
II/0005	Submission of the final results of study 14814 (cardiovascular safety study) according to the Risk Management Plan. The aim of the study was to	20/11/2014	n/a		The results of the cardiovascular safety study 14814 do not suggest that regorafenib induces QTc prolongation or a decrease in LVEF. In view of this, no modification of the

	evaluate the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and left ventricular ejection fraction (LVEF). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				product information or further action over this issue is considered necessary. The positive benefit/risk ratio of regorafenib for the approved indications remains unchanged
II/0001	Extension of indication in the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The list of local representatives was also updated in the package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/06/2014	28/07/2014	SmPC and PL	Please refer to the Scientific Discussion Stivarga-H-C-2573-II-01
IB/0003/G	This was an application for a group of variations. To change the due date for the submission of the biomarker data for CONCUR (study 15808) listed as condition to the Marketing Authorization in Annex II QRD, and also stated in the EU RMP part IV, 2.section Table 2-1. To extend the due date for the PAM for CONCUR (study 15808) to 31 December 2014.	02/06/2014	28/07/2014	Annex II	

	To extend the timelines for the primary completion of CONSIGN (15967) CSR to allow a significant follow-up time for all patients. The RMP and the Annex II are updated accordingly. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUV/0002	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance