Bosulif

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
T/0032	Transfer of Marketing Authorisation	11/07/2018	02/08/2018	SmPC, Labelling and PL	
IA/0034	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/07/2018	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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X/0026	Extension application to add a new strength of 400 mg film-coated tablets Annex I_2.(c) Change or addition of a new strength/potency	22/03/2018	22/05/2018	SmPC, Annex II, Labelling and PL	
II/0025/G	This was an application for a group of variations. Extension of Indication to include treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML) for Bosulif based on study AV001. In addition, the MAH updated the SmPC with safety and efficacy information from studies B1871006 and B1871008. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 4.1 was agreed during the procedure. Furthermore, the Annex IIIA is brought in line with the latest QRD template version 10. 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/02/2018	23/04/2018	SmPC, Labelling and PL	Please refer to Scientific Discussion: Bosulif H-2373-II-25-G-AR

IA/0029	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	05/04/2018	n/a		
II/0028	Update of section 5.2 of the SmPC following further analyses of the pharmacokinetic (PK) data from Study B1871044 that has been already submitted to the EMA previously. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/03/2018	22/05/2018	SmPC	Following administration of a single intravenous dose of 120 mg bosutinib to healthy subjects, bosutinib had a mean (% coefficient of variation [CV]) volume of distribution of 2,331 (32) L, suggesting that bosutinib is extensively distributed to extra vascular tissue. In healthy subjects given a single intravenous dose of 120 mg bosutinib, the mean (%CV) terminal elimination half life was 35.5 (24) hours, and the mean (%CV) clearance was 61.9 (26) L/h.
R/0027	Renewal of the marketing authorisation.	14/12/2017	08/02/2018	SmPC, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Bosulif, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10073 /201703	Periodic Safety Update EU Single assessment - bosutinib	28/09/2017	n/a		PRAC Recommendation - maintenance
R/0023	Renewal of the marketing authorisation.	26/01/2017	24/03/2017	SmPC and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and

					therefore recommends the renewal of the conditional MA for Bosulif, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUSA/10073 /201603	Periodic Safety Update EU Single assessment - bosutinib	13/10/2016	08/12/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10073/201603.
IAIN/0021	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2016	08/12/2016	SmPC and PL	
IB/0020	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	01/02/2016	n/a		
R/0019	Renewal of the marketing authorisation.	19/11/2015	07/01/2016		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Bosulif, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUSA/10073 /201503	Periodic Safety Update EU Single assessment - bosutinib	24/09/2015	23/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10073/201503.
II/0018	Update of section 5.2 of the SmPC in order to update the Pharmacokinetic properties information after analysis of final study report for study B1871044 (open label, randomised, 2-period crossover study to evaluate absolute bioavailability of bosutinib in healthy subjects) in fulfilment of MEA 005.2; in	22/10/2015	07/01/2016	SmPC, Annex II and PL	Following administration of a single dose of bosutinib (500 mg) with food in healthy subjects, the absolute bioavailability was 34%.

	addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor errors in the Package Leaflet, to combine the SmPC of the 100 mg and 500 mg presentations and to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0014/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to include further information related to concomitant use of Bosulif with CYP3A inhibitors based on the results of Study B1871041, and in order to reflect the results of Study B1871043 submitted to fulfil MEA 003.2 and undertaken to investigate the drug interaction potential with regard to bosutinib being a P-gp inhibitor. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 3.1 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.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	23/11/2015	SmPC and PL	In a study of 20 healthy subjects, in whom a single dose of 125 mg aprepitant (a moderate CYP3A inhibitor) was co administered with a single dose of 500 mg bosutinib under fed conditions, aprepitant increased bosutinib Cmax by 1.5-fold, and bosutinib AUC in plasma by 2.0-fold, as compared with administration of bosutinib alone. In a study of 27 healthy subjects, in whom a single dose of 500 mg bosutinib was co-administered with a single dose of 150 mg dabigatran etexilate mesylate (a P-glycoprotein (P-gp) substrate) under fed conditions, bosutinib did not increase Cmax or AUC of dabigatran in plasma, as compared with administration of dabigatran etexilate mesylate alone. The study results indicate that bosutinib does not exhibit clinically relevant P gp inhibitory effects.

N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	23/11/2015	PL	
IB/0016/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/05/2015	n/a		
PSUSA/10073 /201409	Periodic Safety Update EU Single assessment - bosutinib	12/03/2015	n/a		PRAC Recommendation - maintenance
R/0010	Renewal of the marketing authorisation.	18/12/2014	26/02/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional Marketing Authorisation for BOSULIF, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0011	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	13/01/2015	n/a		

	authorisation, including the RMP - Other variation				
IB/0013	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)	23/12/2014	23/11/2015	SmPC	
II/0008	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	26/02/2015	SmPC	
PSUV/0007	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0009	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/08/2014	n/a		
II/0001	Update of sections 4.2, 4.4 and 5.2 of the SmPC further to the results of study B1871020 in patients with renal impairment conducted as a post-authorisation measure (MEA 006) and population pharmacokinetic modelling. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/05/2014	23/06/2014	SmPC and PL	Based on population pharmacokinetic modelling, a daily dose of 400 mg in patients with moderate renal impairment and a daily dose of 300 mg in patients with severe renal impairment are predicted to result in a similar AUC to that seen in patients with normal renal function receiving 500 mg daily. Consequently, in patients with moderate renal impairment (CrCL 30 to 50 mL/min, calculated by the Cockroft-Gault formula), the recommended dose of bosutinib is 400 mg daily (see sections 4.4 and 5.2). In patients with severe renal impairment (CrCL <30 mL/min, calculated by the Cockroft-Gault formula), the recommended dose of bosutinib is 300 mg daily (see sections 4.4 and 5.2). Dose escalation to 500 mg once daily for patients with moderate renal impairment or to 400 mg once daily in patients with severe renal impairment may be considered in

					those who did not experience severe or persistent moderate adverse reactions, under any of the following circumstances. Long-term treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. It is important that renal function is assessed prior to treatment initiation and closely monitored during therapy with bosutinib, with particular attention to those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, ACE inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs (NSAIDs).
IB/0006	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	22/05/2014	23/06/2014	SmPC, Labelling and PL	
IB/0005	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	13/05/2014	n/a		
PSUV/0003	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
R/0002	Renewal of the marketing authorisation.	21/11/2013	20/02/2014	SmPC, Annex II and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Bosulif, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.

					The product information has been updated in line with QRD template version 9. The details of the local representative in Croatia have been added in the package leaflet.