Zelboraf

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
IG/1730	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2024		SmPC and PL	
IA/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	15/09/2023	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).

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/9329/ 202208	Periodic Safety Update EU Single assessment - vemurafenib	26/04/2023	26/06/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9329/202208.
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2023	26/06/2023	PL	
IB/0062/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	18/11/2022	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IA/0061/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name	01/03/2022	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2021	18/02/2022	PL	
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2021	18/02/2022	PL	
IA/0058	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	12/02/2021	18/02/2022	SmPC	
IB/0057/G	This was an application for a group of variations. 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 B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	24/09/2020	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0056	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/07/2020	n/a		
PSUSA/9329/ 201908	Periodic Safety Update EU Single assessment - vemurafenib	12/03/2020	n/a		PRAC Recommendation - maintenance
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/10/2019	22/10/2020	SmPC and PL	Caution should be used when administering Vemurafenib with strong CYP3A4/PgP inhibitors. Patients co-treated with such agents should be carefully monitored for safety, and dose modifications applied if clinically indicated.
PSUSA/9329/ 201808	Periodic Safety Update EU Single assessment - vemurafenib	14/03/2019	n/a		PRAC Recommendation - maintenance
IB/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/08/2018	18/02/2019	SmPC and PL	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	18/02/2019	PL	
IA/0051/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	03/08/2018	n/a		

	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.7 - Administrative change - Deletion of manufacturing sites				
II/0048/G	This was an application for a group of variations. Update of the SmPC section 5.2 with the information on mean bioavailability of vemurafenib at steady state together with information on renal elimination based on the phase I study GO28395. Submission of the CSR from the study GO27826: A Phase III, Randomised, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically Resected, Cutaneous BRAF-Mutant Melanoma at High Risk for Recurrence. Minor editorial changes have been included in the PI. The RMP version 11.0 has also been updated. 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	17/05/2018	18/02/2019	SmPC	The bioavailability at steady state ranged between 32 and 115% (mean 64%) relative to an intravenous microdose, in a phase I study with uncontrolled food conditions in 4 patients with BRAF V600 positive malignancies. Renal elimination does not appear to be of importance for vemurafenib elimination, whereas biliary excretion of unchanged compound may be an important route of elimination.
T/0047	Transfer of Marketing Authorisation	20/02/2018	06/04/2018	SmPC,	

				Labelling and PL	
PSUSA/9329/ 201708	Periodic Safety Update EU Single assessment - vemurafenib	08/03/2018	n/a		PRAC Recommendation - maintenance
II/0042/G	This was an application for a group of variations. Update of the SmPC section 4.8 with information on radiation toxicity based on the data from study MO25515 (MEA 006) [An Open-Label, Multicenter Study to Assess the Safety of RO5185426 (Vemurafenib) in Patients with Metastatic Melanoma] Submission of study GP28492 (MEA 010) [ZeSS: A Prospective Observational Safety Study of Patients with BRAFV600 Mutation-positive Unresectable or Metastatic Melanoma Treated with Vemurafenib (Zelboraf)]. The RMP version 10.3 is also submitted. 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	01/03/2018	18/02/2019	SmPC	In this variation the MAH updated the section 4.8 of the SmPC with the information on potentiation of radiation toxicity and added 'potentiation of radiation toxicity' as an adverse reaction with the frequency common.
IG/0887	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)	29/01/2018	n/a		

II/0043	Update of section 4.8 of the SmPC in order to update the safety information following results from pooled safety analysis of the final results from pivotal phase II (NP22657 BRIM-2) and pivotal phase III (NO25026 BRIM-3) trials. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor changes to the SmPC and Package Leaflet in order to improve clarity and consistency of the information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	06/04/2018	SmPC and PL	This variation updates the section 4.8 Undesirable effects of the SmPC and the corresponding sections of the Package leaflet with 1) revised frequencies of ADRs occurring in patients treated with vemurafenib in the phase II or phase III study and events originating from safety reports across all trials; 2) inclusion of the terms keratoacanthoma, electrocardiogram QT interval prolonged and iridocyclitis in the ADR table. Additionally the section 4.6 is revised to include a clarification that although no teratogenicity was seen in non-clinical species, vemurafenib may be expected to cause foetal harm based on its mechanism of action.
IB/0045	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	05/12/2017	n/a		
IB/0041	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	04/07/2017	n/a		
PSUSA/9329/ 201608	Periodic Safety Update EU Single assessment - vemurafenib	23/03/2017	18/05/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9329/201608.
II/0039	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include the paediatric clinical data from the Zelboraf NO25390 (BRIM-P) study in conclusion	23/02/2017	18/05/2017	SmPC	The safety and efficacy of vemurafenib in children less than 18 years old have not been established. A phase I dose-escalation study evaluating the use of vemurafenib in six

	to the assessment of procedure EMEA/H/C/002409/P46/033. 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				adolescent patients with stage IIIC or IV BRAF V600 mutation positive melanoma was conducted. All patients treated were at least 15 years of age and weighed at least 45 kg. Three patients were treated with vemurafenib 720 mg twice daily, and three patients were treated with vemurafenib 960 mg twice daily. The maximum tolerated dose could not be determined. Although transient tumour regressions were seen, the best overall response rate (BORR) was 0% (95% CI: 0%, 46%) based on confirmed responses. The study was terminated due to low enrollment. Limited pharmacokinetic data from six adolescent patients aged between 15 and 17 years with stage IIIC or IV BRAF V600 mutation positive melanoma suggest that vemurafenib pharmacokinetic characteristics in adolescents are generally similar to those in adults. No new safety signals were observed in a clinical study with six adolescent patients.
IAIN/0040/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 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	19/12/2016	n/a		

II/0037	Update of section 4.5 of the SmPC in order to include information on Drug-drug interaction with rifampicin. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the RMP (final version 10.2) and to request modification of MEA 012 part 2 "Study GO29475: Two-part steady-state interaction study with rifampin (3YP3A4 inducer). Furthermore, the MAH is requesting changes of due dates for 3 category 3 final study reports (GO29475 (MEA011), MO25515 (MEA006) and GP28492 (MEA010)). The MAH is also including request for deletion from the RMP of the study NO25390 (MEA 005) to reflect the Paediatric Product Specific Waiver for treatment of melanoma as agreed with the PDCO on 24 April 2016. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	18/05/2017	SmPC	In a clinical study, co-administration of a single dose 960 mg of vemurafenib with rifampicin, significantly decreased the plasma exposure of vemurafenib by approximately 40%, resulting in an AUClast geometric mean ratio (with/without rifampin) of 0.61 (90%CI:0.48-0.78).
R/0034	Renewal of the marketing authorisation.	21/07/2016	22/09/2016	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Zelboraf in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0033	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/06/2016	n/a		
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	25/05/2016	n/a		

	authorisation, including the RMP - Other variation				
IB/0035	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	04/05/2016	n/a		
II/0031/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to add information on Drug-drug interaction of vemurafenib with tizanidine (a CYP1A2 substrate). In addition, the MAH took the occasion to bring the PI in line with the latest QRD template version 10. The RMP (version 10.0) is updated accordingly. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to update the RMP with a proposed new due date for the final clinical study report of study GO28052 and with implementation of the recommendation received during procedure EMEA/H/C/002409/LEG 031 regarding agranulocytosis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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	01/04/2016	22/09/2016	SmPC and Annex II	Vemurafenib is a moderate CYP1A2 inhibitor. Repeated doses of 960 mg BID vemurafenib increased Cmax and AUCinf of a single 2 mg dose of tizanidine (a CYP1A2 sensitive substrate) approximately 2.2 and 4.7 -fold, respectively. In another clinical trial when a single dose of caffeine was co-administered after repeat dosing with vemurafenib for 15 days, an average 2.6-fold (maximum up to 10-fold) increase in caffeine plasma exposure after vemurafenib treatment was observed. Vemurafenib may thus increase the plasma exposure of substances predominantly metabolised by CYP1A2 (e.g. agomelatine, alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, theophylline) and dose adjustments may be considered, if clinically indicated.

II/0030	Update of sections 4.4 and 4.8 of the SmPC in order to add safety information on acute kidney injury. The Package Leaflet and the RMP are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	22/09/2016	SmPC and PL	Renal toxicity, ranging from serum creatinine elevations to acute interstitial nephritis and acute tubular necrosis, has been reported with vemurafenib. Serum creatinine should be measured before initiation of treatment and monitored during treatment as clinically indicated. Blood creatinine increased is added to the SmPC as a common adverse drug reaction (ADR) and acute interstitial nephritis and acute tubular necrosis are added as rare ADRs.
II/0029	Update of section 5.1 of the SmPC with results from study (MO25653) which assessed safety and efficacy of vemurafenib in V600-mutation positive metastatic melanoma patients with previously-treated brain metastases. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	22/09/2016	SmPC	A single-arm, multicentre study (N=146) of vemurafenib was conducted in adult patients with histologically confirmed metastatic melanoma harbouring the BRAF V600 mutation and with brain metastases. A total of 146 patients were enrolled. The primary efficacy objective of the study was best overall response rate (BORR) in the brain of metastatic melanoma patients with previously untreated brain metastases, as assessed by an independent review committee (IRC). Evaluation of the efficacy of vemurafenib using BORR in the brain of previously treated patients was a secondary objective. 16 (17.8%) patients with previously untreated metastases and 10 (17.9%) patients with previously treated metastases responded. The results were comparable with those observed in the respective dabrafenib study BREAK-MB. For more information, please refer to the Summary of Product Characteristics.
PSUSA/9329/ 201508	Periodic Safety Update EU Single assessment - vemurafenib	17/03/2016	n/a		PRAC Recommendation - maintenance
IA/0032	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	21/12/2015	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0028	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	03/12/2015	n/a		
II/0024/G	This was an application for a group of variations. Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to update information on the risk of potentiation of radiation toxicity and the risk of progression of pre-existing pancreatic adenocarcinoma with KRAS mutation. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC and PL	Cases of radiation recall and radiation sensitization have been reported in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens).The frequency of this adverse reaction is unknown since radiation treatment information including radiation dosage information is not routinely collected in spontaneous safety reports. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Cases of progression of pre-existing pancreatic adenocarcinoma with KRAS mutation have rarely been observed with the use of vemurafenib.
II/0023	Update of section 4.4 and 4.5 of the SmPC in order to update the Drug-Drug interaction information following finalisation of study GO28394 (A phase I, open-label, multicentre, 3-period, fixed sequence study to investigate the effect of vemurafenib on the pharmacokinetics of a single dose of digoxin in	24/09/2015	28/10/2015	SmPC and PL	Vemurafenib may increase the plasma exposure of medicinal products that are P-gp substrates. Caution should be exercised, dose reduction and/or additional drug level monitoring for P-gp substrate medicinal products with narrow therapeutic index (NTI) (e.g. digoxin, dabigatran etexilate, aliskiren) may be considered if these medicinal

	patients with BRAFV600 mutation-positive metastatic malignancy – MEA 013). The RMP has been updated according to the information discussed in the variation. In addition, MAH took this occasion to introduce editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				products are used concomitantly with vemurafenib.
II/0025	Update of sections 5.1 and 5.2 of the SmPC in order to update the safety information based on the study NP25396. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2015	28/10/2015	SmPC	Updated information on the kinase inhibitory activity of vemurafenib against different BRAF kinases and on Zelboraf have been introduced in the product information after analysis of from the food effect NP25396 study.
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
II/0021/G	This was an application for a group of variations. Submission of a revised RMP in order to reflect that the MAH should no longer perform MEA 004 (study in severe hepatic impaired patients) and to extend the timelines of the submission of the final study report for study MO25515 (MEA 006). The MAH took the	21/05/2015	n/a		

	opportunity to revise the RMP with other minor changes. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IB/0022	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)	16/04/2015	28/10/2015	SmPC	
II/0018	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning and the adverse reaction for pancreatitis reported with a frequency "uncommon" further to a cumulative review conducted by the MAH. The Package Leaflet is updated accordingly. The MAH also took the opportunity to make minor editorial changes in the Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	28/10/2015	SmPC and PL	Cumulative reviews for pancreatitis have been performed by the MAH for Zelboraf and analysis of the data justify the addition of a new warning and of this term as an adverse drug reaction in the product information.
PSUSA/9329/ 201408	Periodic Safety Update EU Single assessment - vemurafenib	12/03/2015	n/a		PRAC Recommendation - maintenance

IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
PSUV/0016	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0017	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	24/07/2014	n/a		
II/0015/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC with the new ADR of drug-induced liver injury and a description of liver laboratory abnormalities following a review of pre-clinical studies conducted by the MAH, epidemiologic studies, published literature and the MAH's safety and clinical database. Section 4.8 is also being updated with neutropenia as a new ADR following treatment with Zelboraf. The PL is being updated accordingly. 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	26/06/2014	16/12/2014	SmPC and PL	Further to a review of hepatotoxicity cases observed in the setting of DRESS syndrome, the adverse drug reaction (ADR) of hepatotoxicity with concurrent use of ipilimumab and the identification of three potential Hy's law cases in the vemurafenib arm of the GSK sponsored MEK116513 phase II clinical trial, it was considered that liver injury, sometimes severe, constitutes an adverse drug reaction (ADR) for vemurafenib. In addition, neutropenia was considered as an ADR based on a cumulative review of available information on vemurafenib cases reporting granulocytopenia and related terms from pre-clinical data, epidemiologic studies, published literature and the Marketing Authorisation Holder's database with cut-off date of September 2013.

	new quality, preclinical, clinical or pharmacovigilance data				
PSUV/0012	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0014	Update of section 4.8 of the SmPC with panniculitis as a new ADR of treatment with vemurafenib with frequency "common" in follow-up to the assessment of the 2nd PSUR. The PL is updated accordingly. The MAH also took the opportunity to make some editorial changes to the SmPC. 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	20/02/2014	16/12/2014	SmPC and PL	Based on cases of panniculitis reported with vemurafenib during pharmacovigilance monitoring, a cumulative search for relevant cases was conducted in the Marketing Authorisation Holder's pharmacovigilance database and in the literature. The search reported 26 cases (28 events), and causality was assessed as likely for 85% (n=22) of cases, while there was insufficient information for the remaining 15% (n=4) cases. The most frequently reported event was panniculitis (n=16), followed by erythema nodosum (n=7), vasculitis (n=4) and one event of fat necrosis. In conclusion, panniculitis (including related events such as erythema nodosum) is a common Adverse Drug Reaction of vemurafenib.
II/0013	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	20/02/2014	n/a		
II/0011/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC to include chronic myelomonocytic leukaemia (CMML) and drug reaction with eosinophilia and systemic symptoms (DRESS) as new ADRs based on post-	18/12/2013	16/12/2014	SmPC and PL	The MAH submitted a drug safety report following a request from the ASNM over concerns on reported cases of malignancies observed in patients treated with vemurafenib. The literature review retrieved two cases of vemurafenib-induced malignancy progression in patients treated with vemurafenib. In both cases, RAS mutation was

	marketing experience. The MAH also took the opportunity to make minor editorial changes. The PL was updated accordingly. The requested group of variations 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				implicated, confirmed in one case (CMML) and suspected in the other case (pancreatic adenocarcinoma). From the MAH safety database, 450 cases were retrieved in the search for malignancy cases. 27 cases were classified as: new malignancies (n=23); aggravation of existing malignancies (n=3) and recurrence of past malignant neoplasm (n=1). Tumours from four of the 27 cases (15%) were shown to have confirmed genetic mutations of interest (EGFR, NRAS, CDKN2A). In addition, the MAH performed a cumulative review from the safety database as well as literature search on reports of cases of DRESS syndrome in patients receiving vemurafenib. In addition to the two DRESS SAEs reported in study M025515, post-marketing data reported seven cases as either likely or possibly identified as DRESS syndrome.
II/0010	Update to section 5.1 of the SmPC with the addition of updated survival data from study NO25026. The MAH took also the opportunity to introduce minor formatting changes to the SmPC. The requested variation proposed amendments to the Summary of Product Characteristics. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	18/12/2013	SmPC	In order to fulfil the post-authorisation measure MEA008, the MAH submitted updated survival analyses from study NO25026. From the data cutoff of December 20, 2012, the HR for OS was 0.78, with a median survival of 9.7 months in the dacarbazine treated patients compared to 13.6 months in the vemurafenib treated patients. The subgroup analyses are also consistent with previous results where patients with elevated LDH, tumour stage M1C and ECOG PS1 showed a consistent similar trend in favour of vemurafenib.
II/0007	Update of section 4.5 of the SmPC to revise the wording on interactions between vemurafenib and BCRP inhibitors at the CHMP's request following the assessment of MEA 014. The Package Leaflet was updated accordingly. Furthermore, the PI is being	27/06/2013	18/12/2013	SmPC, Annex II and PL	Following the assessment of the in vitro study 1052335 on the effect of vemurafenib as inhibitor and substrate on BCRP efflux transporter section 4.5 of the SmPC has been updated with the possible interaction between vemurafenib and other anticancer drugs which are substrates of BCRP

	brought in line with the latest QRD template version 9.0. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				transport system.
IA/0009	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/06/2013	n/a		
II/0008	Update of section 4.4 of the SmPC to add a warning with regard to the combined use of vemurafenib and ipilimumab at the CHMP's request following the results of the clinical trial CA184161. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet with the contact in Croatia. 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	30/05/2013	18/12/2013	SmPC and PL	In a Phase I trial, asymptomatic grade 3 increases in transaminases (ALT/AST >5 x ULN) and bilirubin (total bilirubin >3x ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.
II/0005/G	This was an application for a group of variations.	17/01/2013	18/12/2013	SmPC, Annex II and PL	As part of the post-authorisation obligation, the MAH submitted updated survival analyses from study NO25026.

	Update of survival data in section 5.1 of the SmPC, following the assessment of the specific obligation on the updated survival analyses from the pivotal trial NO25026. The obligation in Annex II has been considered fulfilled. In addition, the MAH updated section 4.8 of the SmPC with the adverse drug reacion "dizziness" which had been omitted in error. 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				From the data cutoff of 1st February 2012, the HR for OS was 0.70, with a median survival of 9.7 months in the dacarbazine treated patients compared to 13.6 months in the vemurafenib treated patients and a HR for PFS was 0.38 with a median PFS of 1.64 and 6.78 months, respectively. Subgroup analyses by LDH, tumour stage and ECOG status showed a consistent similar trend in favour of vemurafenib.
II/0003	Update of section 4.4 and 4.8 of the SmPC in order to include safety information following two reports of non-cutaneous squamous cell carcinoma (non-cuSCC) in patients treated with vemurafenib in clinical trials. In addition, the ADR table in section 4.8 was updated with "new primary melanoma" and "QT prolongation", which had already been reported, in order to include events originating across all trials. Furthermore, the MAH made minor editorial changes to the SmPC to improve consistency throughout by	17/01/2013	18/12/2013	SmPC, Annex II and PL	Two cases of non-cutaneous small cell carcinoma (non-cuSCC) were identified following a search of the MAH's safety database. Based on the data, the MAH updated section 4.4 and 4.8 of the SmPC to include information on non-cuSCC and to reflect the new frequency of the adverse drug reaction with vemurafenib treatment. In addition, the ADR table in section 4.8 was updated with "new primary melanoma" and "QT prolongation", which already appeared in the description section in 4.8, in order to include events originating across all trials. The PL was amended

	updating table numbers and typographical errors. The PL has been updated accordingly. Furthermore, the PL is being brought in line with the latest QRD template version 8.2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				accordingly.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
II/0004	Update of section 4.5 of the SmPC in order to update the safety information on the inhibition of cytochrome CYP2C8 in vitro. Correction of a minor typographical error was also included. No changes were included in the PL. 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	15/11/2012	20/12/2012	SmPC	In the new study 1047985, the inhibition of CYP2A6, 2B6, 2C8 and 2E1 by vemurafenib on human liver microsomal cytochrome P450-mediated metabolic activities were compared with the effect of specific control inhibitors. The results showed that vemurafenib did not strongly inhibit CYP2A6, 2B6 or 2E1 (IC50 values were >100 µM) in vitro but was shown to inhibit CYP2C8 with an IC50 value of approximately 12 µM. Based on the results, vemurafenib is unlikely to cause clinically relevant inhibition of cytochrome CYP2A6, 2B6 or 2E1 in vivo but could potentially inhibit CYP2C8 and impact exposure of concomitant drugs whose major clearance route relies of this pathway. Thus, the SmPC section 4.5 has been updated to reflect the new information on CYP2C8.
II/0002	Update of sections 4.4 and 5.1 of the SmPC with the sequencing results for BRAF V600 for all patients from the pivotal study NO25026 (BRIM-3). The Package Leaflet remains unchanged.	15/11/2012	20/12/2012	SmPC	The MAH provided updated analyses of the sequencing of patients tumours for BRAFV600 mutations. In total 673 patients had tumours analysed retrospectively by sequencing for BRAF mutation status. 57 patients out of 673 were found to have BRAF V600K mutations. Although

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				limited by the low number of patients, efficacy analyses for overall survival, progression free survival and confirmed best overall response among these patients with V600K-positive tumours suggest similar treatment benefit of vemurafenib.
II/0001	Update of sections 4.2 and 5.2 of the SmPC in order to include new wording on the posology and the effect of food on the relative bioavailability of vemurafenib as a consequence of the results from the interim analysis of the food-effect study NP25396. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	20/12/2012	SmPC and PL	Results from study NP25398, a study designed to investigate the effect of food on the pharmacokinetics of a single oral dose of vemurafenib, showed that food (high fat meal) increased the relative bioavailability of a single 960 mg dose of vemurafenib. The geometric mean ratios between the fed and fasted states for Cmax and AUC were 2.6 and 4.7 fold, respectively. The median Tmax was increased from 4 to 8 hours when a single vemurafenib dose was taken with food. Thus, it is recommended to take vemurafenib with or without food, but consistent intake of both daily doses on an empty stomach should be avoided as it may lead to significantly lower steady state exposure than consistent intake of vemurafenib with or a short time after a meal.