SUMMARY OF RISK MANAGEMENT PLAN FOR ZELBORAF (VEMURAFENIB)

This is a summary of the risk management plan (RMP) for Zelboraf. The RMP details important risks of Zelboraf, how these risks can be minimized, and how more information will be obtained about Zelboraf's risks and uncertainties (missing information).

Zelboraf's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zelboraf should be used.

This summary of the RMP for Zelboraf should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zelboraf's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Zelboraf is authorized for the treatment of adult patients with *BRAF*^{V600} mutation-positive unresectable or metastatic melanoma. It contains vemurafenib as the active substance and it is given by oral administration.

Further information about the evaluation of Zelboraf's benefits can be found in Zelboraf's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

Important risks of Zelboraf, together with measures to minimize such risks and the proposed studies for learning more about Zelboraf's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Zelboraf are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zelboraf. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Cutaneous Squamous Cell Carcinoma • Progression of RAS Mutant Malignancy • Liver Injury • QTc Prolongation • Acute Kidney Injury
Important potential risks	• Non-cutaneous Squamous Cell Carcinoma • Drug-drug Interaction
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important identified risk: Cutaneous Squamous Cell Carcinoma	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Age (≥ 65 years), chronic sun exposure and prior skin cancer were identified as significant risk factors in the Phase III (NO25026) and Phase II (NP22657) clinical trials.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Progression of RAS Mutant Malignancy	
Evidence for linking the risk to the medicine	DSR1061632, DSR 1055138 and DSR 1071912.
Risk factors and risk groups	There is an excess risk of subsequent primary tumors in the melanoma population compared with what would be expected for a non-melanoma population.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PIL:** Section 2 (What you need to know before you take Zelboraf) Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations (see section 4.8). Carefully consider benefits and risks before administering vemurafenib to patients with a prior or concurrent cancer associated with RAS mutation.This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Liver Injury	
Evidence for linking the risk to the medicine	Clinical trial data and DSR 1058568.
Risk factors and risk groups	There are no identified risk factors for the occurrence of “liver injury” AEs in vemurafenib-treated patients. Baseline values of liver function tests were not a significant covariate in the population pharmacokinetic analysis for predicting elevated liver function values on treatment.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be measured before initiation of treatment and monitored monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption or with treatment discontinuation (see sections 4.2 and 4.8). This has been adequately captured in Section 4.4of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine’s legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: QTc Prolongation	
Evidence for linking the risk to the medicine	Clinical trial data.
Risk factors and risk groups	In the general population, QTc prolongation appears to occur more frequently in females. Inherited genetic polymorphisms or mutations with low penetrance, involving the same gene loci associated with phenotypically expressed long-QT syndrome, may underlie individual idiosyncrasies to the acquired form in many, if not most, cases. Some individuals have QT prolongation throughout life without any manifest arrhythmias, while others are highly susceptible to symptomatic arrhythmias, particularly torsades de pointes (Braunwald's heart disease: a textbook of cardiovascular medicine). There were no other risk factors or risk groups identified with vemurafenib use.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PIL:** Section 2 (What you need to know before you take Zelboraf) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored Initiation of treatment with vemurafenib is not recommended in patients with QTc>500 milliseconds (ms). Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose. Permanent discontinuation of vemurafenib treatment is recommended if the QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription

Important identified risk: QTc Prolongation	
	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Evidence for linking the risk to the medicine	DSR 1066831 (Forman et al., 2013)
Risk factors and risk groups	AKI as defined by the Risk Injury Failure Loss End-Stage Renal Disease (RIFLE) criteria is common amongst patients with cancers. The risk varies with the cancer type but is highest amongst patients with multiple myeloma, leukemia, gastrointestinal, and kidney cancers (Christiansen et al., 2011) Male gender, hypertension, diabetes, CKD, and at-risk concomitant medications such as diuretics, ACE-I, and NSAIDs.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Serum creatinine should be measured before initiation of treatment and monitored during treatment as clinically indicated (see Sections 4.2 and 4.8). This has been adequately captured in Section 4.4of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Non-cutaneous Squamous Cell Carcinoma	
Evidence for linking the risk to the medicine	Several cases of non-cutaneous SCC were reported in the clinical trials, while no disproportionality was observed in the randomized clinical trial.
Risk factors and risk groups	Individuals with one malignancy have an increased risk of developing a second malignancy. Since cuSCC has been observed in melanoma patients receiving vemurafenib, it was considered appropriate to monitor for the occurrence of such carcinomas in other sites.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PIL:** Section 2 (What you need to know before you take Zelboraf) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should undergo a head and neck examination prior to initiation of treatment and every 3 months during treatment. In addition, patients should undergo a chest Computerised Tomography (CT) scan, prior to treatment and every 6 months during treatment. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. This has been adequately captured in Section 4.4of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Drug-drug Interaction	
Evidence for linking the risk to the medicine	Because there is a lack of information regarding DDIs the following clinical studies will be the evidence source in addition to the DDI study NP22676 and *in vitro* study of potential effect of vemurafenib on CYP2A6, CYP2B6, CYP2C8 and CYP2E1 activity: GO29475: Steady-state interaction study with itraconazole (CYP3A4 inhibitor) GO28052: Interaction study with rifampicin. This study evaluated the effect of rifampicin on the PK of a single oral 960 mg dose of vemurafenib. Co-administration of rifampicin (CYP3A4 inducer and of glucuronidation) decreased plasma exposure of a single 960 mg vemurafenib by approximately 40%. Interaction study (GO28396) with tizanidine (CYP1A2), multiple oral doses of vemurafenib increased single-dose tizanidine exposure approximately 4.2-, 4.7-, and 2.2-fold in AUClast, AUCinf, and C_{max}, respectively. An in vitro study to evaluate the potential effect of vemurafenib to inhibit CYP2A6, CYP2B6, CYP2C8, and CYP2E1 was performed. Neither CYP2A6, CYP2B6 nor CYP2E1-selective activities of human liver microsomes tested were strongly inhibited by vemurafenib. In each case, IC50 values were $>$100 µM. Vemurafenib was shown to inhibit CYP2C8 with an IC50 value of approximately 12µM. Based on these observations, vemurafenib is unlikely to cause clinically relevant inhibition of cytochrome CYP450s CYP2A6, CYP2B6 nor CYP2E1 in vivo. In contrast, vemurafenib was found to inhibit microsomal CYP2C8 activity which could potentially impact exposure of concomitant drugs whose major clearance route relies on this enzymatic pathway. Clinical drug interaction Study GO28394 using a P-gp substrate drug (digoxin) demonstrated that multiple oral doses of vemurafenib (960 mg twice daily) increased the exposure of a single oral dose of digoxin, with an approximately 1.8 and 1.5 fold increase in digoxin AUClast and C_{max}, respectively. Additionally, in vitro inhibition and substrate properties of vemurafenib for human in breast cancer resistance protein (BCRP), bile salt export pump (BSEP), and multidrug resistance associated protein (MRP2) transport proteins were investigated. Results confirm that vemurafenib is an inhibitor of human BCRP and BSEP in vitro. The substrate potential of vemurafenib for BCRP was tested using a cellbased monolayer assay system. The results showed that vemurafenib was actively effluxed by MDCKII-BCRP cells, confirming that it is a substrate of human BCRP in vitro (Report 1052335). The substrate potential for MRP2 and BSEP was not assessed using this assay due to the lack of availability of MRP2 and BSEP expressing cell lines. It was concluded that, vemurafenib may have the potential for BCRP mediated DDI when co-administered with other BCRP substrates or

Important potential risk: Drug-drug Interaction	
	inhibitors. An in vitro assessment of the substrate potential for human MRP2 transport protein was also performed. Experiments with MRP2 single and MRP2 / OATP1B1 double transfected cells revealed that vemurafenib is not a substrate of human MRP2 in vitro. Therefore, in vivo DDIs are not expected when co-medicating vemurafenib with inhibitors of MRP2 (Report 1054797).
Risk factors and risk groups	Patients receiving concomitant medications primarily metabolized by CYP1A2 or CYP3A4 or receiving warfarin or other narrow therapeutic index drugs metabolized by CYP2C9
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Exercise caution and consider additional INR (International Normalised Ratio) monitoring when vemurafenib is used concomitantly with warfarin. 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 products are used concomitantly with vemurafenib. This has been adequately captured in Section 4.4 and 4.5 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Zelboraf subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study GO29475

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Zelboraf.

II.C.2 Other studies in post-authorization development plan

Study GO29475: A steady-state interaction study with itraconazole (CYP3A4 inhibitor) (MEA 011) is completed.

Study short name: GO29475

Purpose of the study: To evaluate the effect of a strong CYP3A4 inhibitor (i.e., itraconazole) and a strong CYP3A4 inducer (i.e., rifampin) on vemurafenib steady-state PK in adult cancer patients with BRAF V600 mutation.