Summary of the risk management plan

Summary of the risk management plan for BRAFTOVI

This is a summary of the risk management plan (RMP) for BRAFTOVI when administered in combination with MEKTOVI or cetuximab. The RMP details important risks of BRAFTOVI in combination with MEKTOVI or cetuximab, how these risks can be minimised, and how more information will be obtained about BRAFTOVI in combination with MEKTOVI or cetuximab risks and uncertainties (missing information). Summary of product characteristics (SmPC) for BRAFTOVI and its package leaflets give essential information to healthcare professionals and patients on how BRAFTOVI should be used.

This summary of the RMP for BRAFTOVI when administered in combination with MEKTOVI or cetuximab should be read in the context of all this information including the assessment reports of the evaluation and the plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to current concerns will be included in future updates of the RMP for BRAFTOVI.

I. The medicine and what it is used for

BRAFTOVI is authorised in combination with MEKTOVI for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see SmPC for the full indication). The active substance of BRAFTOVI is encorafenib and of MEKTOVI is binimetinib and both are given by the oral route of administration.

BRAFTOVI in combination with cetuximab is authorised for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy. Cetuximab is given by intravenous infusion.

BRAFTOVI is not authorised for use as monotherapy.

Further information about the evaluation of BRAFTOVI in combination with MEKTOVI or cetuximab can be found in the BRAFTOVI EPAR, including in the plain-language summaries, available on the EMA website, under the medicine's webpage

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004580/human_med_002298.jsp.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BRAFTOVI in combination with MEKTOVI or cetuximab, together with measures to minimise such risks and the proposed studies if any, for learning more about the risks of BRAFTOVI in combination with MEKTOVI or cetuximab, are outlined below.

Measures to minimise the risks identified for medicinal products include:

- 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 authorised pack size - the amount of medicine in a pack is chosen so, as to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR/PBRER assessments, so that immediate action and updates can be implemented as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BRAFTOVI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BRAFTOVI in combination with MEKTOVI or cetuximab are risks that need risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely.

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 BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab.

Potential risks are concerns for which an association with the use of BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab is possible based on available data, but this association has not yet been established and needs further evaluation.

Missing information refers to information on the safety of BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab that is currently missing and needs to be collected.

The following important risks are those specific to encorafenib regardless of the indication for use:

Table Part VI.1: Safety concerns for encorafenib

Important identified risks	- Secondary skin neoplasms: cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma
Important potential risks	- QT prolongation - Non-cutaneous malignancies with RAS mutation - Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors - Over-exposure in patients with moderate to severe hepatic impairment
Missing information	- Use in patients with severe renal impairment

II.B Summary of important risks and missing information

Important identified risk for encorafenib: Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	
Evidence linking the risk to the medicine	Secondary skin neoplasms including cuSCC and new primary melanoma represent a known class-effect with the use of BRAF inhibitors. CuSCC and new primary melanoma have been identified as ADRs for encorafenib single agent, based on the clinical trial data.
Risk factors and risk groups	Associations have been reported with older age (≥65 years) for vemurafenib and dabrafenib-treated patients, and with prior skin cancer, and chronic sun exposure for vemurafenib-treated patients.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in Section 4.2 of the SmPC Warning in section 4.4 of the SmPC and PIL relevant section Listed in section 4.8 of SmPC and PIL relevant section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None
Important potential risk for encorafenib: QT prolongation	
Evidence linking the risk to the medicine	QT prolongation is a class effect for BRAF inhibitors. For encorafenib, the determined IC_{50} for hERG inhibition indicates an unlikely effect of encorafenib on QT prolongation and no clinical risk is predicted for QT prolongation. Safety pharmacology results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in HR at a clinically relevant dose. Small increases in QTc interval and mild increases in heart rate were apparent in the Enco 300 population. Due to the theoretical risk of clinical complications (torsades de pointes, ventricular arrhythmia) due to sustained QT prolongation, QT prolongation class-effect is considered as potential.
Risk factors and risk groups	Risk factors for torsade de pointes other than QTc interval >500 ms or >60 ms increase from baseline value include uncorrected hypokalaemia, hypomagnesemia and hypocalcaemia, long QT syndrome, concomitant therapy with multiple QTc interval–prolonging drugs. Other risk factors for torsade de pointes include acute myocardial infarction, heart failure with reduced ejection fraction, diuretic therapy, age ≥65 years, female sex, family history of sudden cardiac death at <50 years, cardiac disease and history of arrhythmia or bradycardia.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None

Important potential risk for encorafenib: Non-cutaneous malignancies with RAS mutation	
Evidence linking the risk to the medicine	As for other BRAF inhibitors and based on its mechanism of action, encorafenib may promote malignancies associated with RAS mutation associated with activation of RAS through mutation or other mechanisms. No cases of non-cutaneous malignancy with RAS mutation possibly related to encorafenib were identified from the pooled safety data of the clinical development programme, however due to the seriousness of this class-effect risk, non-cutaneous carcinoma is considered an important potential risk.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendation in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and PIL relevant section Additional risk minimisation measures: None
Important potential risk for encorafenib: Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	
Evidence for linking the risk to the medicine	Encorafenib is primarily metabolised by CYP3A4. Based on the PK data, the use of strong CYP3A4 inhibitors was not allowed during clinical trials. Concomitant administration of encorafenib and strong or moderate CYP3A4 inhibitors may lead to increased encorafenib exposure and potential increase in toxicity.
Risk factors and risk groups	Risk factors include any medical condition requiring the use of strong (ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice, etc.) or moderate CYP3A4 inhibitors (amiodarone, erythromycin, fluconazole, diltiazem, delavirdine, amprenavir and imatinib) with no possibility for an alternate therapy.
Risk minimisation measures	Routine risk minimisation measures: Warning in section 4.4 of the SmPC and PIL Discussion in section 4.5 of the SmPC Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None
Important potential risk for encorafenib: Over-exposure in patients with moderate to severe hepatic impairment	
Evidence linking the risk to the medicine	Results from a dedicated clinical trial indicate a 25 % higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55 % increase of the unbound encorafenib exposure. The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver and based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in moderate or severe hepatic impairment.

Risk factors and risk groups	Risk factors are those well known for hepatic dysfunction in routine practice including patients with baseline hepatic impairment regardless of aetiology, concurrent hepatobiliary disease/disorders and concomitant use of hepatotoxic agents. Patients with massive liver metastatic disease with consequent associated moderate to severe liver dysfunction are unlikely to be candidates for the combination treatment as first-line therapy.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in section 4.2 of the SmPC and relevant PIL section Warning in section 4.4 of the SmPC and PIL relevant section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional risk minimisation measures: None
Missing information for encorafenib: Use in patients with severe renal impairment	
Evidence linking the risk to the medicine	Patients with severe renal impairment were excluded from the pivotal trials and there are insufficient data to evaluate PK in these patients.
Risk factors and risk groups	Presence of renal impairment regardless of aetiology, dehydration or poor oral intake, severe and untreated gastrointestinal disorders leading to dehydration and concomitant use of nephrotoxic agents. In addition, advanced cancer is a known risk factor for renal dysfunction.
Risk minimisation measures	Routine risk minimisation measures: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

None

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

None.