Summary of the risk management plan for MEKTOVI

This is a summary of the risk management plan (RMP) for MEKTOVI in combination with BRAFTOVI. The RMP details important risks of MEKTOVI in combination with BRAFTOVI, how these risks can be minimised, and how more information will be obtained about MEKTOVI in combination with BRAFTOVI risks and uncertainties (missing information).

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

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

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

I. The Medicine and what it is used for

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

MEKTOVI is not authorised for use as a single agent.

Further information about the evaluation of MEKTOVI in combination with BRAFTOVI can be found in the MEKTOVI and BRAFTOVI EPARs, including a plain-language summary, available on the EMA website, under the medicine's webpage

https://www.ema.europa.eu/en/medicines/human/EPAR/mektovi

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

Important risks of MEKTOVI in combination with BRAFTOVI, together with measures to minimise such risks and the proposed studies for learning more about MEKTOVI in combination with BRAFTOVI, 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 packaging of the medicine;
- The authorised pack size - the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The legal status of the medicine- the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises 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 assessments, so that immediate action can be taken and updates made as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of MEKTOVI in combination with BRAFTOVI 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 MEKTOVI in combination with BRAFTOVI. Potential risks are concerns for which an association with the use of these medicines 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 MEKTOVI as a single agent or in combination with BRAFTOVI that is currently missing and needs to be collected.

Table Part VI.1: Safety concerns for binimetinib in combination with encorafenib

Important identified risks	- Left ventricular dysfunction - Haemorrhage - Hepatotoxicity
Important potential risks	- Pneumonitis/Interstitial lung disease
Missing information	- None

II.B Summary of important risks and missing information

Important identified risk: Left ventricular dysfunction	
Description of the risk title	Heart problems, e.g. a drop in the amount of blood pumped by the heart.
Evidence for linking the risk to the medicine	Left ventricular dysfunction is an identified ADR for binimetinib. Left ventricular dysfunction is a known effect of MEK inhibitors, a class of drugs to which binimetinib belongs. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. Left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction, can occur with binimetinib. Left ventricular dysfunction, including ejection fraction decreased, was reported in 11.9% (51/427) of patients in the Bini 45 P population, and was Grade 3/4 in 4.4% (19/427) of patients. It was the most frequent cause of dose discontinuation, which was required in 4.2% of patients.
Risk factors and risk groups	Patients with significant heart problems were excluded from the binimetinib clinical trials. Among the patients who were included in the binimetinib clinical studies, no risk groups or factors have been identified. LVEF shift data were assessed in patients with or without baseline cardiovascular risk factors (defined as current/ex-smoker and/or history of hypertension, diabetes, hyperlipidaemia [raised cholesterol], cardiac disorders, arteriosclerosis [thickening of the walls of

	arteries] and ischemic heart disease [coronary heart disease]) with most patients having baseline risk factors. These data showed no difference in the percent of patients LVEF shifts for patients with worst post-baseline LVEF by baseline cardiac risk factor category 'yes' or 'no'.
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. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional risk minimisation measures: None
Important identified risk: Haemorrhage	
Description of the risk title	A large flow of blood from a damaged blood vessel
Evidence for linking the risk to the medicine	Haemorrhage is a known class effect of MEK inhibitors. ADRs in the grouped term of haemorrhage were reported as common for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. In melanoma patients in the Bini 45 P population, Grade 3/4 haemorrhage occurred in 2.3% (10/427) of patients.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Patients receiving antiplatelet and anticoagulant medications in combination with any other treatment which may cause bleeding are at greater risk of haemorrhage.
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. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional risk minimisation measures: None.
Important identified risk: Hepatotoxicity	
Description of the risk title	Liver problems
Evidence for linking the risk to the medicine	There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk and abnormal liver enzymes. ALT and AST increased are class effects related to MEK inhibitors and elevation of liver enzymes is an identified ADR for binimetinib. In melanoma patients in the Bini 45 P population, the incidence of adverse events reported as Grade 3 or 4 increases in liver laboratory tests among patients receiving binimetinib were: 2.3% (10/427) for ALT and 2.1% (9/427) for AST. No case fulfilling the criteria of Hy's law was identified.

	One case of liver failure with fatal outcome was reported in a patient receiving binimetinib at a high dose of 60 mg BID (dose-escalation study CMEK162X2201), assessed as related to binimetinib.
Risk factors and risk groups	In the binimetinib clinical studies, hepatic events were reported more frequently in patients with liver metastasis when compared to the overall patient population. In the Bini 45 P, an increase of ALT >3 × ULN (a measure of hepatic toxicity) was reported more frequently in patients with liver metastasis when compared to the overall patient population and to patients with no liver metastasis (12/131 [9.2%], 28/414 [6.8%], and 16/283 [5.7%] patients, respectively). There were no other remarkable differences in liver parameters according to the presence of baseline metastases.
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. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional risk minimisation measures: None
Important potential risk: Pneumonitis/Interstitial Lung Disease	
Description of the risk title	Inflammation inside the lungs
Evidence for linking the risk to the medicine	Pneumonitis is a known class effect of MEK inhibitors. There may be a causal association of binimetinib for this potential risk. In melanoma patients in the Bini 45 P population, pneumonitis events were reported in 1.4% (6/427) of patients; while 0.7% (3/427) of patients reported Grade 3/4 pneumonitis events.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Pneumonitis was reported in 3 patients in Study CMEK162A2301 and was associated with lung metastases in 2 patients, and history of pneumonitis was reported in the third patient. Drug-induced interstitial lung disease is reported to occur with higher frequency in the Asian population (Peerzada 2011).
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. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional risk minimisation measures: None.
Missing Information	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.