RMP SUMMARY

MEKTOVI
(Binimetinib)

RMP Version number	0.7
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of MEKTOVI is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of MEKTOVI in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Pierre Fabre Pharma is fully responsible for the accuracy and correctness of the content of the published summary RMP of MEKTOVI.

PART VI: Summary of the risk management plan

Section VI.1: Binimetinib in the proposed indication

Summary of the risk management plan for MEKTOVI in combination with BRAFTOVI (binimetinib and encorafenib)

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).

Summaries of product characteristics (SmPC) for MEKTOVI in combination with BRAFTOVI and their package leaflets give essential information to healthcare professionals and patients on how MEKTOVI in combination with BRAFTOVI 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 in combination with BRAFTOVI.

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

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 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*.

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

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.

Safety concerns of binimetinib in combination with encorafenib
Important identified risks
- Left ventricular dysfunction - Hypertension - Rhabdomyolysis - Retinal pigment epithelial detachment - Venous thromboembolism - Haemorrhage
Important potential risks
- Hepatotoxicity - Pneumonitis/Interstitial lung disease - Retinal vein occlusion - Embryo-foetal toxicity - Over-exposure in patients with moderate to severe hepatic impairment
Missing information
- Use in patients with reduced cardiac function (Left ventricular ejection fraction [LVEF] <50%) or symptomatic chronic heart failure

II.B Summary of important risks

Important identified and potential risks for binimetinib in combination with encorafenib

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 adverse reaction 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 binimetinib 45 mg pooled 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. Left ventricular ejection fraction (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 (Patient information leaflet) 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: Hypertension	
Description of the risk title	High blood pressure.
Evidence for linking the risk to the medicine	Hypertension is an identified adverse reaction for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. Hypertension events were reported in 15.9% (68/427) of patients in the binimetinib 45 mg pooled population and was reported as Grade 3/4, including hypertensive crisis, in 8.7% (37/427) of patients.
Risk factors and risk groups	Clinical trials excluded patients with uncontrolled arterial hypertension despite appropriate medical therapy. All patients who had a history of hypertension and were receiving antihypertensive drugs before onset of study treatment, and/or had a screening systolic blood pressure ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, were to perform home monitoring of blood pressure on Days 10 and 30. Hypertension gained special interest with the use of newer-generation drugs in cancer patients due to the higher incidence observed, especially in patients treated with targeted therapies such as inhibitors of the VEGF signalling pathway. The primary at-risk patient groups, however, are those with pre-existing hypertension, advanced age (≥60 to 65 years), history of smoking, hypercholesterolemia, or obesity (*Wicki 2014, Hamnvik 2015*). However, there is variation among the different cancer types (potentially higher in patients who have renal cell carcinoma) and certain ethnic populations (e.g., in Japanese patients) (*Tomita 2011*). Hypertension risk at baseline is a risk factor for the adverse reaction of hypertension.
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: Rhabdomyolysis	
Description of the risk title	Breakdown of muscle fibres which leads to the release of a protein called myoglobin into the bloodstream.
Evidence for linking the risk to the medicine	Rhabdomyolysis and elevations of blood creatinine kinase (CK) are class effects related to MEK inhibitors and an identified adverse reaction for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. Asymptomatic CK elevations can occur in patients treated with binimetinib. Across clinical trials of binimetinib, rhabdomyolysis was uncommonly reported. In melanoma patients in the binimetinib 45 mg pooled population, Grade 3/4 rhabdomyolysis was reported in 0.5% (2/427) of patients.
Risk factors and risk groups	Patients at risk of rhabdomyolysis include those patients using certain drugs (statins, fibrates and neuroleptics), including illicit drugs or toxins (cocaine, heroin, methadone, drug abuse of barbiturates and benzodiazepine), as well as cases of alcohol abuse, trauma, excessive muscular activity, prolonged immobilisation, infection (sepsis), electrolyte and endocrine abnormalities and genetic disorders connective tissue disorders *(Melli 2005, Khan 2009).*

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: Retinal pigment epithelium detachment	
Description of the risk title	Eye problems (damage to the retina).
Evidence for linking the risk to the medicine	Ocular events associated with MEK inhibition include detachment of the retinal pigment epithelium and identified ADRs for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. In melanoma patients in the binimetinib 45 mg pooled population, Grade 3/4 events were reported in 2.1% (9/427) of patients.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Based on the performed pharmacokinetics and exposure analysis, the incidence of retinal events of any grade tended to increase with area under the curve (AUC) and maximum concentration ($C_{max)}$. The probability of retinal events increased significantly with higher model predicted $C_{max,ss}$ ($p = 0.00476$). Other exposure metrics, including $AUC_{tau,ss}$ and $C_{min,ss}$ did not significantly correlate with increased prevalence of retinal events. This finding suggests that retinal events may be related to the binimetinib peak concentrations. Epidemiological studies have identified several risk factors. Systemic steroid use, Cushing syndrome and stress are some of the reported factors *(Liew et al 2013).*
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: Venous thromboembolism	
Description of the risk title	Blood clot formation.
Evidence for linking the risk to the medicine	Venous thromboembolism (VTE) is a class effect of MEK inhibition and was reported with binimetinib as a commonadverse reaction. 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 thrombotic and embolic events occurred in 1.4% (6/427) of patients.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Prevalence of VTE in stage IV melanoma was reported at 25.2% with similar high levels in lung and gastrointestinal cancers. All patients suffered thrombotic events when they were treated with chemotherapy and at home when they stopped heparin prophylaxis *(Sparsa 2011).* While the risk of VTE appears to vary by cancer site, cancer stage and grade, nonetheless chemotherapy use and patient-related characteristics, cancer site, cancer stage ≥2, liver metastasis, chemotherapy, progesterone, being underweight or obese, hospitalisation/nursing home confinement, central vein catheter, and infection were independent risk factors for incident VTE in active cancer patients in a population-based retrospective case-control study *(Ashrani 2016).* In a risk assessment study, patient-related risk factors include prior history of VTE, hypercoagulability, recent major surgery, age ≥65 years, obesity (BMI ≥35 kg/m^2), poor performance status, bed rest and active hormonal therapy *(Dutia 2012).*
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. Adverse reactions 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 binimetinib 45 mg pooled 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 potential 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. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased are class effects related to MEK inhibitors and elevation of liver enzymes is an identified adverse reaction for binimetinib. In melanoma patients in the binimetinib 45 mg pooled 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 twice daily (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 binimetinib 45 mg pooled population, an increase of ALT >3 × upper limit of normal (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 binimetinib 45 mg pooled 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 et al 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.
Important potential risk: Retinal vein occlusion	
Description of the risk title	Eye problems (blood clot in a vein in the eye).
Evidence for linking the risk to the medicine	Retinal vein occlusion (RVO) is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk. In melanoma patients in the Bini 45 mg pooled population, Grade 3/4 retinal vein occlusion was reported in 1.2% of patients.
Risk factors and risk groups	The binimetinib clinical studies did not include patients with a history or current evidence of RVO or current risk factors of RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes). Additional risk factors for RVO include hypertension, diabetes mellitus, dyslipidaemia, smoking and renal disease *(Wong et al 2010).*
Risk minimisation measures	Routine risk minimisation measures: Treatment discontinuation is recommended 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: Embryo-foetal toxicity	
Description of the risk title	Effect in pregnant women
Evidence for linking the risk to the medicine	There are no data regarding the use of binimetinb in pregnant women. Non-clinical studies conducted in rats and rabbits showed evidence of embryo toxicity (increased post-implantation loss and resorptions) and teratogenicity in rabbits only (ventricular septal defects and pulmonary trunk alterations). In rats, only decreased ossification was observed and considered to be secondary to decreased foetal body weight at maternally toxic doses.
Risk factors and risk groups	The group at risk is women of childbearing potential (i.e. pre- or peri-menopausal) without an effective method of contraception, with exposure during pregnancy. The following can be risk factors among the target population of childbearing women at risk: • Foeto-toxic products: concomitant medicines, substances • Family and personal history of reproductive toxicity • Specific infectious disease during pregnancy
Risk minimisation measures	Routine risk minimisation measures: Warning in Section 4.6 of the SmPC and relevant PIL section. Information provided in Section 5.3 of the SmPC. 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: Over-exposure in patients with moderate to severe hepatic impairment	
Description of the risk title	Over-exposure to the drug in patients with moderate to severe liver impairment
Evidence for linking the risk to the medicine	As binimetinib is primarily metabolised and eliminated via the liver, patients with moderate to severe hepatic impairment may have increased exposure. Results from a dedicated clinical trial indicate similar exposures in patients with mild impairment (Child-Pugh A) and subjects with normal liver function. A two-fold increase in exposure (AUC) was observed in patients with moderate (Child-Pugh B) or severe (Child-Pugh B) hepatic impairment (Study CMEK162A2104).
Risk factors and risk groups	Hepatic impairment can affect exposure to binimetinib. Patients with moderate to severe hepatic impairment are at risk of over-exposure to binimetinib if the dose is not adjusted accordingly.
Risk minimisation measures	Routine risk minimisation measures: Dose recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Information in Section 5.2 of the SmPC. 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.

Summary of Missing Information

Missing Information: Use in patients with reduced cardiac function (left ventricular ejection fraction (LVEF) <50%) or symptomatic chronic heart failure	
Description of the missing information title	Use in patients with heart problems.
Evidence for linking the risk to the medicine	Cardiac function, especially left ventricular function can be impaired due to binimetinib. This is a known and generally reversible adverse class effect due to MEK inhibitors.
Risk factors and risk groups	Patients with reduced cardiac function (LVEF<50%) are at higher risk for cardiac failure. Close monitoring is required during treatment with binimetinib and permanent treatment discontinuation for any symptomatic cardiac dysfunction or drop in LVEF as detected by specific cardiac imaging (ECHO/MUGA scans).
Risk minimisation measures	Routine risk minimisation measures: Warning in Section 4.4 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.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or a specific obligation of MEKTOVI.

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

None.