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 “BRAFTOVI” 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 “BRAFTOVI” 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 “BRAFTOVI”.
Part VI: Summary of the risk management plan

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

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

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

This summary of the RMP for BRAFTOVI when administered in combination with MEKTOVI 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 when administered in combination with MEKTOVI.

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 is not authorised for use as monotherapy.

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


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

Important risks of BRAFTOVI in combination with MEKTOVI, together with measures to minimise such risks and the proposed studies for learning more about the risks of BRAFTOVI in combination MEKTOVI, 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 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 in combination with MEKTOVI 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 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.

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

The following important risks are those specific to encorafenib with additional important risks for encorafenib when used in combination with binimetinib:

<table>
<thead>
<tr>
<th>Safety concerns for encorafenib</th>
<th>Additional safety concerns for encorafenib in combination with binimetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
</tr>
<tr>
<td>- Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma</td>
<td>- Haemorrhage</td>
</tr>
<tr>
<td>- Palmar-plantar erythrodysaesthesia syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
<td></td>
</tr>
<tr>
<td>- QT prolongation</td>
<td>- Hepatotoxicity</td>
</tr>
<tr>
<td>- Non-cutaneous malignancies with RAS mutation</td>
<td></td>
</tr>
<tr>
<td>- Over-exposure due to concomitant use with strong and moderate Cytochrome P450 3A4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>- Embryo-foetal toxicity</td>
<td></td>
</tr>
<tr>
<td>- Over-exposure in patients with moderate to severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>- Potential for renal dysfunction due to overdose</td>
<td></td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
<td></td>
</tr>
<tr>
<td>- Use in patients with severe renal impairment</td>
<td>None</td>
</tr>
</tbody>
</table>
### II.B Summary of important risks and missing information

<table>
<thead>
<tr>
<th>Important identified risk for encorafenib: Secondary skin neoplasms: cutaneous squamous cell carcinoma (cuSCC) and new primary melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence linking the risk to the medicine</strong></td>
</tr>
<tr>
<td><strong>Risk factors and risk groups</strong></td>
</tr>
</tbody>
</table>
| **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 Package Insert Leaflet (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 |

<table>
<thead>
<tr>
<th>Important identified risk for encorafenib: Palmar-plantar erythrodysaesthesia syndrome (PPES)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence linking the risk to the medicine</strong></td>
</tr>
<tr>
<td><strong>Risk factors and risk groups</strong></td>
</tr>
</tbody>
</table>
| **Risk minimisation measures** | Routine risk minimisation measures:  
Dose modification recommendations in section 4.2 of the SmPC  
Listed in section 4.8 of SmPC and relevant PIL section  
Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.  
Additional risk minimisation measures: None |

<table>
<thead>
<tr>
<th>Additional important identified risk for encorafenib in combination with binimetinib: Haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence linking the risk to the medicine</strong></td>
</tr>
</tbody>
</table>
Patients receiving anti-platelet and anti-coagulant 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 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: QT prolongation**

- QT interval prolongation is a class effect for BRAF inhibitors. For encorafenib, the determined IC<sub>50</sub> for hERG inhibition indicates an unlikely effect of encorafenib on QTc prolongation and no clinical risk is predicted for QTc prolongation. Safety pharmacology results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in heart rate 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 QTc prolongation, QT prolongation class-effect is considered as potential risk.

**Important potential risk for encorafenib: Non-cutaneous malignancies with RAS mutation**

- 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.

<table>
<thead>
<tr>
<th>Risk factors and risk groups</th>
<th>None identified</th>
</tr>
</thead>
</table>
| 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 cytochrome 450 (CYP 450) 3A4 inhibitors**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Encorafenib is primarily metabolised by CYP3A4. Based on the pharmacokinetic 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>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.</td>
</tr>
</tbody>
</table>
| 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: Embryo-foetal toxicity**

| Evidence linking the risk to the medicine | No data are available regarding the use of encorafenib in pregnant women.  
Embryo-foetal toxicity in animals was observed with encorafenib exposure during organogenesis. Hence, there is a potential for human embryo-foetal toxicity due to encorafenib. |
|-----------------------------|-----------------|
| Risk factors and risk groups | Women of child-bearing potential (i.e. pre- or peri-menopausal) without an effective method of contraception, with exposure during pregnancy.  
Encorafenib may decrease the efficacy of hormonal contraceptives. Concomitant use with hormonal contraceptives that are substrates of CYP3A4 may result in loss of efficacy of these agents. |
| Risk minimisation measures | Routine risk minimisation measures:  
Warning in section 4.6 and preclinical information in section 5.3 of the SmPC and relevant PIL section  
Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer |
### 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 physiology-based pharmacokinetic 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 |

### Important potential risk for encorafenib: Potential for renal dysfunction due to overdose

| Evidence linking the risk to the medicine | Non-clinical sub-acute and sub-chronic toxicity studies were not predictive of tubular and interstitial damage for encorafenib. In early phase studies, at high doses of encorafenib from 600 to 800 mg once daily, renal dysfunction (grade 3 hypercreatininaemia) was observed in 3 out of 14 patients. All were reversible and suspected to be related to encorafenib. |
| Risk factors and risk groups | Risk factors other than drug overdose are well known risks for renal impairment in routine practice including patients with baseline 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:**
- Listed in section 4.9 of SmPC
- Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer

**Additional risk minimisation measures:** None

## Additional important potential risk for encorafenib in combination with binimetinib: Hepatotoxicity

### Evidence linking the risk to the medicine

Liver laboratory abnormalities represent a class-effect risk for both MEK inhibitors and BRAF inhibitors, as single-agents or in combination and is considered as an important potential risk for the combination encorafenib and binimetinib. Increased Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) are identified as adverse reactions for the combination.

### Risk factors and risk groups

Risk factors for hepatotoxicity include history of hepatic injuries, hepatotoxic agents and drug combinations at high risk of hepatotoxic interactions, alcohol intake, viral hepatitis (Hepatitis B, C, E, cytomegalovirus, Epstein Barr virus hepatitis) and auto-immune hepatitis.

### 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 SmPC and relevant PIL 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 pharmacokinetics 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.