Summary of the risk management plan for Tafinlar (dabrafenib)

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

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

This summary of the RMP for dabrafenib 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 the current ones will be included in updates of dabrafenib RMP.

I. The medicine and what it is used for

Tafinlar contains dabrafenib as the active substance and it is used for in the following indications:

- Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) with BRAF V600 mutation.
- Adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily.

Further information about the evaluation of dabrafenib's benefits can be found in dabrafenib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage: link to the EPAR summary landing page https://www.ema.europa.eu/en/medicines/human/EPAR/tafinlar

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of dabrafenib, together with measures to minimize such risks and the proposed studies for learning more about dabrafenib' 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 authorised 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 reactions is collected continuously and regularly analysed, including 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 dabrafenib 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 dabrafenib. 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).

Table 1 List of important risks and missing information

Important identified risks for dabrafenib (including combination therapy)	• Pre-renal and Intrinsic Renal failure • Uveitis • Severe Photosensitivity
Important potential risks for dabrafenib (including combination therapy)	• Non-specific cardiac toxicity • Testicular Toxicity • Developmental toxicity • Pregnancy and risks in breast feeding
Important potential risks related to dabrafenib+ trametinib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing Information for dabrafenib	• None

II B: Summary of important risks

Table 2 Important identified risk: Pre-renal and Intrinsic Renal Failure

Evidence for linking the risk to the medicine	In juvenile toxicity studies in rats, renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) was observed (≥0.2 times adult human clinical exposure based on AUC). Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib.
Risk factors and risk groups	No specific risk groups were identified during clinical trials. Risk factors may include pyrexia, dehydration with pre-renal azotemia and/or hypotension.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 3 Important identified risk: Uveitis

Evidence for linking the risk to the medicine	In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib.
Risk factors and risk groups	No risk groups or risk factors have been identified.

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 **Additional risk minimization measures** There are no additional risk minimization measures.

Table 4 Important identified risk: Severe Photosensitivity

Evidence for linking the risk to the medicine	Dabrafenib was phototoxic in an in vitro mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and in vivo at doses ≥100 mg/kg (>44 times clinical exposure based on Cmax) in an oral phototoxicity study in hairless mice. Post marketing data identified a serious/severe case with positive de- and re-challenge to dabrafenib/trametinib combination therapy
Risk factors and risk groups	No risk groups have been identified, sun exposure is a risk factor for photosensitivity.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 5 Important potential risk: Non-specific Cardiac Toxicity

Evidence for linking the risk to the medicine	Cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation were seen in dogs (≥2 times clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5 and 0.6 times clinical exposure for rats and mice respectively).
Risk factors and risk groups	Risk factors identified for potential cardiac toxicity typically include patients with a previous diagnosis of cardiovascular disease, including structural heart disease and prior arrhythmias.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 6 Important potential risk: Testicular toxicity

Evidence for linking the risk to the medicine	In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Non clinical data See Part II Module SII: Developmental toxicity.
Risk factors and risk groups	None
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 7 Important potential risk: Developmental toxicity

Evidence for linking the risk to the medicine	In rats and rabbits given trametinib monotherapy, maternal and developmental toxicity (decreased fetal body weights and increased ossification variations) were observed at exposures below the exposures achieved at the recommended clinical dose of 2 mg per day. Additionally, decreased corpora lutea were observed in rats given trametinib, which may impact female fertility. It is not known whether these effects will also be seen in humans.
Risk factors and risk groups	Children of women of child-bearing potential
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 8 Important potential risk: Pregnancy and risks in breast-feeding

Evidence for linking the risk to the medicine	Animal studies with trametinib have shown reproductive toxicity. It is not known whether these effects will also be seen in humans.
Risk factors and risk groups	Women of child-bearing potential and breast feeding mothers.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 2 Important potential risks only for combination of dabrafenib with trametinib: Pulmonary embolism, deep vein thrombosis

Evidence for linking the risk to the medicine	In clinical trial pulmonary embolism and deep vein thrombosis (PE/DVT) events were reported in 3% of the subjects (6/209) on trametinib and dabrafenib combination therapy.
Risk factors and risk groups	Risk factors include history or family history of VTE, immobilization, increased age (>60 years), those on estrogen-based compounds, recent surgery and cancer. Therefore, patients with metastatic melanoma are at risk from the nature of their disease.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

II C: Post-authorization development planII.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 dabrafenib.

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

There are no other studies in post-authorization development plan for dabrafenib.