NOVARTIS

Drug Regulatory Affairs

TAFINLAR®

50 and 75 mg hard capsules

Public Summary of the EU Risk Management Plan (RMP) v9.1 for Tafinlar® (dabrafenib)

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Summary of the Risk Management Plan (RMP) for Tafinlar® (dabrafenib)

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 Tafinlar ® 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“ 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 Tafinlar in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Tafinlar®.

What is Tafinlar and what is it 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.
- Dabrafenib in combination with trametinib is indicated for adjuvant treatment of 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.

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 „Arzneimittelinformation“ 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 analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

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)	– New Primary/Secondary malignancy – Pre-renal and Intrinsic Renal failure – Uveitis – Medicinal Products that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters. – 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	– Safety in patients with severe renal impairment – Safety in patients with moderate to severe hepatic impairment

Summary of important risks

Table 2. Important identified risk: New Primary/Secondary malignancy

Evidence for linking the risk to the medicine	Cases of cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma have been reported in patients treated with dabrafenib alone and in combination with trametinib (see "Fachinformation", section "Unerwünschte Wirkungen"). In the Phase III studies MEK115306 and MEK116513 in patients with unresectable or metastatic melanoma, cuSCC occurred in 10% (22/211) of patients receiving dabrafenib as a single agent and in 18% (63/349) of patients receiving vemurafenib as a single agent, respectively. In the integrated safety population of patients with melanoma and advanced NSCLC, cuSCC occurred in 2% (19/1076) of patients receiving dabrafenib in combination with trametinib. The median time to diagnosis of the first occurrence of cuSCC in study MEK115306 was 223 days (range 56 to 510 days) in the combination therapy arm and 60 days (range 9 to 653 days) in the dabrafenib monotherapy arm. In the Phase III study BFR115532 in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving dabrafenib in combination with trametinib as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm of the adjuvant

	treatment study was approximately 18 weeks. In the see "Fachinformation" cuSCC is reported as an ADR with frequency of 'Common' have been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib in melanoma studies. In the see "Fachinformation" new primary melanomas is reported as an ADR with frequency of 'Uncommon'. RAS-associated malignancies have been reported in clinical trials, both with another BRAF inhibitor (chronic myelomonocytic leukemia and non-cutaneous SCC of the head and neck) as well as with dabrafenib monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with dabrafenib in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer). In the Phase III study in the adjuvant treatment of melanoma comparing combination of dabrafenib and trametinib to placebo, non-cutaneous secondary malignancies or recurrent malignancies were observed in 1% (5/435) of patients receiving active therapy compared to 1% (3/432) of patients receiving placebo. In the dabrafenib integrated safety population, five subjects (<1%) with new primary melanoma were identified. These were identified within the first five months of therapy and did not require treatment modification other than excision. In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non –cutaneous malignancies in patients treated with Tafinlar. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. In one patient (1%) who received dabrafenib in combination with trametinib therapy for NSCLC, grade 3 non-cutaneous secondary/recurrent malignancy of hepatocellular carcinoma was observed.
Risk factors and risk groups	No risk groups or risk factors were identified in the integrated safety population (ISP). In general, cuSCC is primarily associated with exposure to ultraviolet radiation. Recurrence and the risk of metastases are associated with a number of risk factors, predominantly primary cuSCC location and size. Large

	lesions and primary lesions of the lip and ear are more likely to recur and metastasize. Previous history of cuSCC is also a risk factor (Alam 2001). Cutaneous SCC was reported in the dabrafenib ISP for 3% of subjects > 65 and 1% of subject's ≤ 65 years old. Whether a direct relationship exists between the increased incidence seen for cuSCC in the elderly population over the last 20 to 30 years, and the known increased mortality from cuSCC in this population, remains unclear (Alam 2001). A number of other risk factors have been reported in the literature (Alam 2001). Subjects with the underlying disease of unresectable or metastatic melanoma are at an increased risk of developing another new primary melanoma within the first year after diagnosis. The increased risk within the first and second year after initial diagnosis has been reported to be as high as 6% and 8%, respectively (Titus-Ernstoff 2006). Activating RAS mutations is a potential risk factor.
Risk minimization measures	**Routine risk minimization measures** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 3. 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** "Fachinformation", section "Unerwünschte Wirkungen".

	Additional risk minimization measures There are no additional risk minimization measures.

Table 4. 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** "Fachinformation", section "Dosierung/Anwendung". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 5. 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 rechallenge 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 6. 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 7. 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 8. 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 9. 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 10. 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** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 11. Missing information: Safety in patients with severe renal impairment

Risk minimization measures	**Routine risk minimization measures** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Table 12. Missing information: Safety in patients with moderate to severe hepatic impairment

Risk minimization measures	**Routine risk minimization measures** "Fachinformation", section "Unerwünschte Wirkungen". **Additional risk minimization measures** There are no additional risk minimization measures.

Post-authorization development plan

Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of dabrafenib.

Other studies in post-authorization development plan

Table 13. Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
PASS Study BRF115532	To evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival

(CDRB436F2301, COMBI-AD)	(RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, Stage III cutaneous melanoma.
Study 201710	Evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials
PASS Study CDRB436A2106	To evaluate the pharmacokinetics of a single oral dose of dabrafenib (and metabolites) in subjects with renal impairment as compared to healthy subjects with normal renal function.
PASS Study CDRB436A2107	To evaluate the pharmacokinetics of dabrafenib and metabolites after a single oral dose of dabrafenib in subjects with hepatic impairment as compared to healthy subjects with normal hepatic function (Child-Pugh classification).