NOVARTIS

Regulatory Affairs

# Drug generic name

## Summary of the EU Safety Risk Management Plan

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| Active substance(s) (INN or common name): | *Dabrafenib* |
| Product(s) concerned (brand name(s)): | *Tafinlar* |
| Document status: | *Final* |
| Version number of the RMP Public Summary: | *11.1* |
| Date of final sign off of the RMP Public Summary | *30-10-2023* |

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 minimise 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 / 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 “Tafinlar” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Tafinlar”.

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# Summary of the risk management plan for Tafinlar (dabrafenib)

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

Tafinlar and Finlee's summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Tafinlar and Finlee should be used.

This summary of the RMP for Tafinlar and Finlee should be read in the context of all this information including the assessment reports of the evaluation and their plain-language summaries, all which are part of the European Public Assessment Reports (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tafinlar and Finlee's RMP.

## I. The medicine and what it is used for

Tafinlar capsules contain dabrafenib as the active substance and are used 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 Tafinlar capsules is 150 mg twice daily.

Finlee dispersible tablets contain dabrafenib as active substance, and are used in the following indications:

- Dabrafenib in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.
- Dabrafenib in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

The recommended dose of Finlee dispersible tablets is body weight based and should be administered twice daily.

Further information about the evaluation of Tafinlar and Finlee's benefits can be found in Tafinlar and Finlee's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpages:

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

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

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

Important risks of Tafinlar and Finlee, together with measures to minimize such risks and the proposed studies for learning more about Tafinlar and Finlee'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 Tafinlar and Finlee 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 Tafinlar and Finlee. 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**

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| Important identified risks for dabrafenib (including combination therapy) | ●Pre-renal and Intrinsic Renal failure<br>●Uveitis<br>●Severe Photosensitivity |
| Important potential risks for dabrafenib (including combination therapy) | ●Non-specific cardiac toxicity<br>●Testicular Toxicity<br>●Developmental toxicity<br>●Pregnancy and risks in breast feeding<br>●Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation) |
| 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**

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| **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**<br>SmPC Sections 4.2 and 4.8.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 3 Important identified risk: Uveitis**

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| **Evidence for linking the risk to the medicine** | In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated |

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| | 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**<br>SmPC Sections 4.2 and 4.8<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 4 Important identified risk: Severe Photosensitivity**

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| **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**<br>SmPC Section 4.8.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 5 Important potential risk: Non-specific Cardiac Toxicity**

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| **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. |

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| **Risk minimization measures** | **Routine risk minimization measures**<br>None<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 6 Important potential risk: Testicular toxicity**

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| **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**<br>SmPC Section 5.3.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 7 Important potential risk: Developmental toxicity**

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| **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** | Women of child-bearing potential. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Sections 4.6 and 5.3.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

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

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| **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. |

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| **Risk factors and risk groups** | Women of child-bearing potential and breast feeding mothers. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.6.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures. |

**Table 9 Important potential risk: Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)**

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| **Evidence for linking the risk to the medicine** | Studies in juvenile animals have shown reproductive, developmental toxicity and testicular toxicity in rats. The testicular toxicity findings observed in non-clinical studies with dabrafenib + trametinib in combination indicate a risk for impaired spermatogenesis in males.<br>The effects on bone growth are likely relevant for paediatric population, and growth will be monitored in clinical trials with paediatric patients during treatment. |
| **Risk factors and risk groups** | Patients under 18 years of age. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 5.3.<br>**Additional risk minimization measures**<br>There are no additional risk minimization measures.<br>**Additional pharmacovigilance activities**<br>CDRB436G2401 (EudraCT number 2018-004459-19) |

**Table 10 Important potential risk only for combination of dabrafenib with trametinib: Pulmonary embolism, deep vein thrombosis**

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| **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**<br>SmPC Sections 4.2 and 4.4. |

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| | **Additional risk minimization measures**<br>There are no additional risk minimization measures. |

## II C: Post-authorization development plan

### II.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

CDRB436G2401 study is a post-authorization development plan for dabrafenib.

**Table 11 Other studies in the post-authorization development plan**

| Study Short name | Rationale and study objectives |
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| CDRB436G2401 | This study will facilitate data collection of the long-term outcomes of pediatric subjects who have been treated in clinical trials with dabrafenib, trametinib or the combination, to assess the long-term effect on growth, development and general health of these subjects. Further, for those subjects currently on treatment in the parent protocol and would benefit from continued treatment (per investigator determination), this study will offer a mechanism to continue treatment outside the parent protocols.<br><br>The primary objective is to assess the long-term safety of treatment with dabrafenib, trametinib or the combination. The secondary objectives are to assess the long-term effect of treatment with dabrafenib, trametinib or the combination on general health, growth and development; and to assess efficacy as determined by institutional standard of care procedures. |