NOVARTIS

Regulatory Affairs

Drug generic name

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Trametinib*
Product(s) concerned (brand name(s)):	*Mekinist*
Document status:	*Final*
Version number of the RMP Public Summary:	*19.2*
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 “Mekinist” 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 “Mekinist” 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 “Mekinist”.

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Summary of the risk management plan for Mekinist (trametinib)

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

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

This summary of the RMP for Mekinist and Spexotras 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 Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Mekinist and Spexotras' RMP.

I. The medicine and what it is used for

Mekinist film-coated tablets contain trametinib as active substance and are authorized in the following indications:

- Trametinib as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation;
    - Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.
- Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation;
- Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

The recommended dose of Mekinist tablets is 2 mg once daily.

Spexotras powder for oral solution contains trametinib as active substance and it is used in the following indications:

- Trametinib in combination with dabrafenib 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.
- Trametinib in combination with dabrafenib 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 Spexotras powder for oral solution is body weight based and should be administered once daily.

Further information about the evaluation of Mekinist and Spexotras' benefits can be found in Mekinist and Spexotras' 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/mekinist

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

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

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

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

II.A: List of important risks and missing information

Important risks of Mekinist and Spexotras 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 Mekinist and Spexotras. 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

List of important risks and missing information	
Important identified risks for trametinib	• Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment), • Pneumonitis/Interstitial lung disease, • Hepatic events (e.g., AST, ALT increased**,** and hepatic failure), • Gastrointestinal disorders (diarrhea, colitis, and GI perforation).
Important potential risks for trametinib	• Impaired female fertility, • Developmental toxicity, • Long-term safety in patients < 18 years old (including potential adverse effects on skeletal maturation and sexual maturation), • Pregnancy and risks in breast-feeding.
Important potential risks related to trametinib+dabrafenib combination therapy only	• Pulmonary embolism, deep vein thrombosis.
Missing information for trametinib	• Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system), • Safety in patients with severe renal impairment, • Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic > 140 mmHg and/or diastolic > 90 mmHg which cannot be controlled by anti-hypertensive therapy).

II.B: Summary of important risks

Important identified risks for trametinib

Table 2 Important identified risk – ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachement)

Evidence for linking the risk to the medicine	Blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib. In clinical trials uveitis and iridocyclitis have also been reported in patients treated with trametinib in combination with dabrafenib.
Risk factors and risk groups	None identified yet for trametinib.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.8. **Additional risk minimization measures** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None.

Table 3 Important identified risk – pneumonitis/Interstitial lung disease

Evidence for linking the risk to the medicine	Patients treated with trametinib or combination with dabrafenib may develop ILD or pneumonitis. In a Phase III trial, 2.4% (5/211) of patients treated with trametinib monotherapy developed ILD or pneumonitis. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days).
Risk factors and risk groups	Specific risks for trametinib treated patients have not been identified. Pneumonitis with some chemotherapeutic agents (associated with the event) such as gemcitabine may be seen with higher frequency in pancreatic cancer patients with prior irradiation. It is unclear if this holds for trametinib.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.8. **Additional risk minimization measures** No risk minimization measures.

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None.

Table 4 Important identified risk – hepatic events (e.g., AST ALT increased, and hepatic failure)

Evidence for linking the risk to the medicine	Hepatic adverse events have been reported in clinical trials with trametinib. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. Liver events were detected in clinical trials with monitoring every four weeks. It is recommended that patients receiving treatment with trametinib monotherapy have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated.
Risk factors and risk groups	Specific risk factors that predict possible hepatic enzyme elevations have not been identified for trametinib treated patients. Patients with liver metastases are considered to be at higher risk for events of hepatic failure.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.8. **Additional risk minimization measures** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None.

Table 5 Important identified risk – gastrointestinal disorder (diarrhea, colitis, and GI perforation)

Evidence for linking the risk to the medicine	Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking trametinib.
Risk factors and risk groups	None identified yet for trametinib.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.4, section 4.8, and section 5.3. **Additional risk minimization measures**

	No risk minimization measures.
Additional pharmacovigilance activities	None.

Important Potential Risks for trametinib

Table 6 Important potential risk – impaired female fertility

Evidence for linking the risk to the medicine	Early studies in animals have shown that trametinib may affect the fertility both when taking the medication and after it has been stopped. It is not known whether these effects will also be seen in humans, as there have been no human studies to look at whether trametinib can affect a woman's ability to have children.
Risk factors and risk groups	Women of child-bearing potential.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.6. **Additional risk minimization measures** No 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	Women of child-bearing potential
Risk minimization measures	**Routine risk minimization measures** SmPC section 5.3. **Additional risk minimization measures** No risk minimization measures.

Table 8 Important potential risk – Long-term safety in patients <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)

Evidence for linking the risk to the medicine	Studies in juvenile animals have shown adverse effects of trametinib which had not been observed in adult animals. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately twice the adult human clinical exposure based on AUC).
Risk factors and risk groups	Children under 18 years of age.
Risk minimization measures	**Routine risk minimization measures** SmPC section 4.2. **Additional risk minimization measures** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** CDRB436G2401 (EudraCT number 2018-004459-19)

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** SmPC section 4.6. **Additional risk minimization measures** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None

Important Potential Risks related to trametinib + dabrafenib combination therapy only

Table 10 Important potential risk – pulmonary embolism, deep vein thrombosis

Evidence for linking the risk to the medicine	In clinical trials, 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), those on oestrogen-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 4.4. **Additional risk minimization measures** No risk minimization measures.

Missing information for trametinib

Table 11 Missing information – Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)

Risk minimization measures	**Routine risk minimization measures** SmPC section 4.4 **Additional risk minimization measures** No risk minimization measures.

Table 12 Missing information – Safety in patients with severe renal impairment

Risk minimization measures	**Routine risk minimization measures** SmPC section 4.2. **Additional risk minimization measures** No risk minimization measures

Table 13 Missing information – Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic >140mmhg and/or diastolic >90mmHg which cannot be controlled by anti-hypertensive therapy)

Risk minimization measures	**Routine risk minimization measures** SmPC section 4.4. **Additional risk minimization measures** No 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 trametinib.

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

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

Table 14 Other studies in the post-authorization development plan

Study Short name	Rationale and study objectives
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. 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.