NOVARTIS

Drug Regulatory Affairs

Mekinist®

0.5 mg, 2 mg film-coated tablets

Summary of the Risk Management Plan (RMP) for Mekinist® (trametinib)

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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 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“ 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“ (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 Mekinist®.

Overview of disease epidemiology

Mekinist is used to treat melanoma (a type of skin cancer) that has metastasised (spread to other parts of the body) or cannot be surgically removed. The number of people with this cancer is increasing worldwide. In 2012, around 82’000 new melanomas occurred in the 27 European countries (EU-27). In about 6 out of 100 newly-diagnosed cases (5.9%), the melanoma is inoperable or has spread to other sited in the body (metastatic melanoma). This suggests that newly-diagnosed inoperable or metastatic melanomas in the EU-27 number almost 5’000 per year.

About 50% of patients have a mutation (a change) in the “BRAF” gene, which may have caused the melanoma to develop. Mekinist is specifically for patients whose melanoma cells have a mutation (change) in the ‘BRAF’ gene called 'BRAF V600', which may have caused the melanoma to develop. Around one third of the total melanoma patients in the UK, Germany, France, Spain and Italy in 2012 had a BRAF gene mutation and these patients may be suited to treatments that target BRAF activity.

Summary of treatment benefits

Trametinib monotherapy
In the main study involving 322 patients, patients were treated with either Mekinist or chemotherapy (treatment with cancer medicines dacarbazine or paclitaxel). The study’s main measure of effectiveness was how long patients lived until their disease got worse (progression-free survival) and Mekinist was shown to be more effective than chemotherapy: patients taking Mekinist lived on average for 4.8 months without their disease getting worse compared with 1.5 months for those on chemotherapy.

Trametinib + dabrafenib combination
The main patient study (MEK115306 compared trametinib in combination with dabrafenib (called 'combination therapy') to dabrafenib as monotherapy. This study involved a total of 423 patients with BRAF gene mutation melanoma which has spread to other places in the body, and is not operable. The effectiveness of combination therapy compared with dabrafenib was assessed by measuring the length of time during and after treatment that a patient lives with the disease. Results showed that one-half of the patients in the combination therapy group lived for at least 25 months, compared with about 19 months in the dabrafenib-treated group. More of the patients taking combination therapy (69%) were reported to have a reduction in their tumour, versus 53% of patients receiving dabrafenib.

Unknowns relating to treatment benefits

Most patients in studies with Mekinist alone or Mekinist taken together with Tafinlar were white Caucasian adults less than 65 years of age. However, there is no evidence to suggest that results would differ in non-white patients or those aged over 65 years. Neither Mekinist nor Mekinist taken together with Tafinlar have been studied in patients with severe liver or kidney problems or in patients under 18 years.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
(Skin toxicities e.g., rash, dermatitis acneiform)	About 9 in 10 patients treated with trametinib alone and 5 in 10 patients treated with trametinib taken together with dabrafenib experienced skin problems such as rash, acne-type rash or redness. In about one-half of patients with skin-related problems these skin problems first appeared within about 1 month of starting treatment with trametinib alone or when taken together with dabrafenib. These side effects were generally mild to moderate and in the majority of cases did not lead to an interruption or reduction of the treatment dose.	The package leaflet informs the patient that severe skin reactions (rash) may occur when taking trametinib alone or together with dabrafenib and that patients developing a severe rash, and blisters or sores, should seek immediate help from their doctor. There are no known factors identified to prevent rash but it can generally be managed by standard medical care. Skin problems can be treated with medicines, in most cases without reducing the dose or stopping treatment with trametinib alone or trametinib and dabrafenib together.
Diarrhoea	About 5 in 10 patients treated with trametinib alone	There is no known way of preventing diarrhoea resulting

	and 3 in 10 patients treated with trametinib taken together with dabrafenib, experienced diarrhoea (loose and watery stools). Most of the reported cases of diarrhoea were mild to moderate and in about half of the patients with diarrhoea, diarrhoea first started within 14 days of starting treatment with trametinib alone and within 2 months after starting treatment with trametinib taken together with dabrafenib.	from treatment with trametinib alone, or when taken together with dabrafenib. However, diarrhoea can usually be treated with medicines.
Heart problems (e.g. a drop in the amount of blood pumped to the body by the heart, general problems with how the heart pumps blood) (Left ventricular systolic dysfunction e.g., LVEF decreased and left ventricular dysfunction)	In patient studies, about 7 in 100 patients treated with trametinib alone, or when taken together with dabrafenib experienced heart problems linked to the pumping of blood to the rest of the body. Most of the cases were mild to moderate in nature and in about half of the patients with heart problems, the heart problems first occurred within the first 3 months of starting treatment with trametinib alone and within about 5 months of starting treatment together with dabrafenib.	The prescriber's guide advises doctors to temporarily stop treatment with trametinib if the patient is showing symptoms of heart problems. If trametinib is taken together with dabrafenib, then treatment with dabrafenib alone may be continued. If the patient recovers, treatment with trametinib may be restarted, but at a reduced dose and the patient should be carefully monitored.
Eye problems (e.g. blood clot in a vein in the eye, damage to the retina – the light sensitive back of the eye [leading to blurry vision, distorted vision such as halo effects and coloured dots, abnormal colour vision and blindspots]), swelling and redness of the iris and other parts of the eye) (Ocular events (e.g., retinal	About 1 in 10 of patients treated with trametinib alone or when taken together with dabrafenib may experience any eye problems. Most of the eye problems in study patients were mild to moderate, for example, blurred vision, dry eye and some disturbance to vision. Some problems may be	Patients experiencing mild to moderate eye problems while receiving trametinib alone or when taken together with dabrafenib may have their trametinib dose lowered or stopped for a short time. If the eye problems persist at the lower dose or after treatment is restarted, then trametinib treatment may be stopped

vein occlusion, retinal pigment epithelial detachment, and uveitis)	more severe, including blood clots in a vein in the eye or damage to the retina that, may cause a decrease in vision; overall, these events occur in less than 1 in 100 patients treated with trametinib and vision may improve after stopping treatment. The patient studies indicate that eye problems may first occur at any time from 2 days after starting treatment with trametinib alone and within about 3 months when taken together with dabrafenib.	completely. A thorough examination of the eyes should be carried out before and treatment and for patients that have eye problems while taking the medicine. There is a possibility that some patients with severe eye problems may not recover completely from these eye problems after the treatment is stopped.
Inflammation (swelling/irritation) inside the lungs (Pneumonitis/interstitial lung disease)	Patient studies show that about 2 in 100 patients treated with trametinib alone and up to 1 in 100 patients treated with trametinib taken together with dabrafenib may experience swelling/irritation in the lungs which can be severe.	Lung inflammation following treatment with trametinib may require the dose to be adjusted, or treatment temporarily stopped or completely discontinued (depending on the severity of the lung inflammation). In most cases, following changes to their treatment, patients recover from the lung problems, or experience an improvement in the symptoms linked to the lung inflammation.
Liver problems (liver tests indicate inflammation due to injury or damage to the liver) (Hepatic events - AST, ALT increased)	Increased levels of 2 naturally occurring enzymes in the body, ALT and AST, may sometimes indicate inflammation of the liver, due to injury or damage. In patient studies about 1 in 10 patients taking trametinib alone and 2 in 10 patients taking trametinib together with dabrafenib had increased levels of the 2 enzymes, ALT or AST, when tested. Most of the cases were mild or moderate, involving small	Lowering the dose of the medicine or stopping treatment for a short time, will help enzyme levels to improve or return to normal in most cases.

	increases in the levels of the enzymes ALT or AST; they first occurred about 1 month after starting treatment with trametinib alone, and about 2 months after treatment with trametinib and dabrafenib together.	
Raised blood pressure (Hypertension)	In patient studies about 15 in 100 patients treated with trametinib alone and about 25 in 100 patients treated with trametinib taken together with dabrafenib had increased blood pressure. All of the reported cases were mild to moderate increases in blood pressure and in about half of the patients with increased blood pressure, it first occurred around 2 weeks after starting starting treatment with trametinib alone, and about 2 months after starting to take trametinib together with dabrafenib. In the majority of cases, the raised blood pressure was managed without requiring changes to the patient's treatment.	Doctors are advised that they should monitor their patient's blood pressure routinely. Appropriate treatment to lower blood pressure should be given based on the doctor's judgement, taking into account the possibility that the patient may have an existing medical condition, or may be taking medication for other medical conditions.
Swelling and puffiness (e.g. swelling and puffiness of around the feet and ankles) (Oedema events [e.g., oedema peripheral])	Swelling and puffiness of the skin due to a build-up of fluid can occur in most parts of the body; it is most common around the feet and ankles. Swelling and puffiness under the skin was a common side effect in studies involving patients treated with trametinib alone and occurred in. about 4 in 10 patients. Swelling and puffiness was noted in about	Patient studies indicate that the majority of the cases of swelling or puffiness can be managed with standard medical care, and a change to the dose levels of the medicine is typically not required.

	1 in 4 treated with trametinib taken together with dabrafenib. In about one-half of patients with swelling or puffiness, it first occurred around 4 months after the combined trametinib and dabrafenib treatment was started. In almost all cases , the swelling or puffiness was mild to moderate, and treatment with trametinib alone or when taken together with dabrafenib was continued without interruption or the need to lower the dose level.	
Allergic reaction (Hypersensitivity)	Allergic reaction can occur in less than 1 in 100 people treated with trametinib alone or when taken together with dabrafenib. Symptoms that may be associated with an allergic reaction (eczema, hives, face swelling) can occur in up to 17 in 100 people treated with these medications.	Although allergic reactions are rare, information in the package leaflet informs the patient that they should seek medical advice (from a doctor, nurse or pharmacist) if they experience symptoms of an allergic reaction.
Breakdown of muscle fibres which leads to the release of the contents (called myoglobin) into the bloodstream (Rhabdoymyolysis)	Trametinib alone or when taken together with dabrafenib can increase the risk of rhabdomyolysis, a condition in which muscle breakdown causes pain, vomiting, and possibly kidney failure. Patients taking trametinib should report these symptoms to their doctor.	Patients taking trametinib should report any muscle tenderness (pain), weakness or stiffness to their doctor.
Bleeding events (Haemorrhagic events)	Trametinib alone or when taken together with dabrafenib can increase the risk of bleeding. Bleeding can occur at different sites in the body. In patient studies about 1 in 5 patients treated	Patients taking trametinib alone or when taken together with dabrafenib should report any unusual (not due to injury) or excessive (more than would be expected) events of bleeding to their doctor.

	with trametinib alone and when taken together with dabrafenib had bleeding. Most cases of bleeding are minor, but they can be serious/severe requiring treatment in the hospital or blood transfusion. About 1 in 100 patients experienced events of bleeding in the brain which have been fatal.	
Related to trametinib+dabrafenib together		
Fever (Pyrexia)	About 6 in 10 patients treated with trametinib taken together with dabrafenib experienced fever. Whilst most of the fever events were mild to moderate, about 1 in 7 patients treated with trametinib taken together with dabrafenib experienced severe fever-related symptoms, including high temperature, thirst/feeling dry, shivering, low blood pressure, and symptoms indicating kidney problems. Fever symptoms usually first occurred within a month after treatment started.	Patients with fever responded well when the dabrafenib dose was reduced, or treatment was temporarily stopped. Fever symptoms should be treated with appropriate medication (e.g., paracetamol or ibuprofen), and treatment with dabrafenib can be restarted when fever symptoms clear.
Different skin cancers (Cutaneous SCC (cuSCC)	About 3 in 100 patients treated with trametinib taken together with dabrafenib developed a different type of skin cancer, called squamous cell carcinoma. This type of cancer is generally confined to one part of the body and can be surgically removed. In about one-half of the patients with squamous cell carcinoma, it was generally first seen after the first 4 months of starting treatment with trametinib taken together with dabrafenib.	Most squamous cell carcinoma can be cured by surgery and patients are able to continue treatment without any dose adjustment. Patients are advised to inform their doctor right away if they notice changes in how their skin looks (colour of texture), or feels to the touch. The doctors' prescribing information advises doctors about the risk of squamous cell carcinoma and recommends that a skin examination is performed prior to giving treatment and

		at regular intervals during and after treatment.
New non-skin cancers/recurring cancers (Non-cutaneous secondary/recurrent malignancies)	Less than 1 in 100 people treated with trametinib taken together with dabrafenib had new non-skin cancers or experienced recurrence of previous, non-skin related cancers in patient studies. Cancer types included lung cancer, acute myeloid leukaemia, prostate cancer, thyroid cancer and a tumor of adrenal gland tissue. The relationship between treatment with trametinib taken together with dabrafenib and these cancers is not known. There is limited data on the number of cases of secondary cancer (cancer which has spread beyond the original site in the body), or recurring cancers, in patients taking trametinib together with dabrafenib. However, the limited data suggests that the number of cases is similar to the number of cases of secondary/recurring cancers seen in the general population.	No specific measures have been identified to prevent new cancers. Patients who may be at risk, for example if they have had other types of cancers in the past, should be monitored during and following treatment for possible cancers as a result of taking trametinib together with trametinib.
New melanoma skin cancers (New primary melanoma)	Less than 1 in 100 people treated with trametinib taken together with dabrafenib in patient studies developed new melanoma skin cancers.	New melanoma skin cancers can be managed with surgery and patients can continue treatment without any dose adjustment. Patients are advised to tell their doctor if they notice any changes in the look (e.g. colour and texture) or feel of the skin.The doctors' prescribing information advises doctors about the risk of new melanoma skin cancers and recommends that a skin examination is performed prior to starting treatment and

		at regular intervals during and after treatment.
Kidney failure (Renal failure)	Kidney failure has been reported in up to 1 in 100 people treated with trametinib taken together with dabrafenib. Overall, problems associated with the kidney (including kidney failure) have been seen in up to 7 in 100 patients treated with trametinib and dabrafenib taken together. In about one-half of patients with renal failure, it generally first occurs within about 3-5 months after starting treatment.	Kidney failure may be irreversible. Some cases of kidney failure are thought to be related to severe cases of fever.
Inflammation of the pancreas (a gland that controls blood sugar levels and helps digest food) (Pancreatitis)	Less than 1 in 100 people treated with trametinib taken together with dabrafenib had inflammation (swelling that may lead to damage) of the pancreas. None of the reported cases in patients taking trametinib and dabrafenib together were serious, patients continued treatment and recovered.	Patients experiencing strong abdominal pain should seek medical help.
Low number of white blood cells (Neutropenia)	About 14 of 100 patients receiving trametinib together with dabrafenib developed low white blood cell counts (neutropenia). An abnormally low number of white blood cells (in particular neutrophils) increases the risk of infections. However, in most cases of neutropenia reported in patients receiving trametinib together with dabrafenib, significant changes in treatment, or a change in the dose level of the medicines received, were not required. In about one-half of patients with low white blood cells, the	A drop in the number of white blood cells, particularly neutrophils (which will show up in a blood test) can happen in patients taking trametinib together with dabrafenib and can lead to an increased risk of infection.

	first occurrence was within about 5 months after the combined trametinib and dabrafenib treatment was started.	
A blood clot that forms in a vein deep in the body (deep vein thrombosis) that can break off and travel through the bloodstream, possibly to an artery in the lungs which can block blood flow (pulmonary embolism) (Pulmonary embolism, deep vein thrombosis)	There is a risk of venous thromboembolism, a condition in which a blood clot forms in a vein deep in the body (deep vein thrombosis), which can break off and travel to an artery in the lungs (pulmonary embolism) when trametinib is taken together with dabrafenib. In patient studies about 3 in 100 patients treated with trametinib taken together with dabrafenib had venous thromboembolism. Most cases were severe, but did not always require a dose change and none were fatal. In about one-half of patients with venous thromboembolism, the first occurrence was within about 9 months after the combined trametinib and dabrafenib treatment was started.	Patients should report any swelling, pain, or tenderness accompanied by warmth or redness of the leg to their doctor. This can be a sign of a blood clot in the leg. Patients should report any unexplained shortness of breath or pain when breathing deeply to their doctor. This can be a sign of a blood clot that has travelled to an artery in the lungs.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Related to both trametinib alone and trametinib+dabrafenib together:	
Use to treat cancers for which trametinib is not approved (Off-label use: in resectable/resected melanoma (adjuvant therapy), in nonmelanoma tumours harbouring a BRAF V600-mutation, melanoma tumours negative for BRAF V600 mutation, in patients with tumour progression during prior treatment with BRAF inhibitor therapy (trametinib monotherapy only), in combination with other anti-cancer agents, or when non-validated tests are used)	Trametinib has been developed to treat melanomas with the BRAF gene mutation. Trametinib alone or taken together with dabrafenib is specifically for use, in the treatment of melanomas which cannot be removed surgically or which have spread to other sites in the body (metastatic melanoma). There may be a risk that some doctors may consider using trametinib to treat patients with cancers for which it has not been widely tested, or approved. This napproved, or off-label use,

	may include: treating melanomas which can be surgically removed or which have not spread to other sites in the body, or skin cancers which are not of the BRAF gene mutation kind or in untested combinations with other medicine to treat cancer. Information on the appropriate patients for treatment will be provided in the prescriber's information.
Liver failure (Hepatic failure)	There may be a risk that trametinib taken alone or together with dabrafenib can cause damage to the liver. This damage can be permanent liver damage or liver failure. Patients are advised to tell their doctor if they have liver problems. Their doctor will also do some blood tests to monitor how well a patient's liver is working before and during treatment with trametinib.
Problems with the ability to have children in women (Impaired female fertility)	Early studies in animals have shown that trametinib may affect the ability to have children 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. As the effects of trametinib when taken alone or together with dabrafenib on human's reproductive organs is unknown, patients are advised to speak to their doctor about options to improve the chances of having children, before starting treatment with trametinib alone or when taken together with dabrafenib.
Problems with the development of the unborn child (Developmental toxicity)	Early studies in animals have shown that trametinib may cause problems in the development of the foetus in pregnant animals (problems seen include smaller than average foetus weight and poor development of bones or the skeleton). It is not known whether these effects will also be seen in humans, as there have been no human studies to look at the effect of trametinib when used during pregnancy. Women who have the potential to become pregnant should use appropriate contraception to avoid becoming pregnant whilst being treated with trametinib, and for 4 months after

	stopping treatment with trametinib. Female patients should also be aware that the contraceptive pill (or other hormone-based contraceptive methods), may not be as effective when taken with dabrafenib. herefore, an alternative method of contraception (such as a condom) should be used if a patient is being treated with trametinib and dabrafenib together.
Increased risk for dose adjustments, permanent treatment discontinuations in elderly population (≥65 years), as well as SAEs and Grade 3 AEs (combination only) in this population	In studies, elderly patients (≥65 years) treated with trametinib alone or when taken together with dabrafenib required more frequent dose adjustments (interruptions and/or reductions of dose) and discontinuations of their medication compared with patients <65 years. In addition, patients ≥65 years treated with trametinib taken together with dabrafenib had more frequent serious and severe unwanted side effects compared with younger patients.
Related to trametinib + dabrafenib together	
Testicular problems (Testicular toxicity)	Currently, there is no information on the likelihood of testicular or reproductive problems (such as poor sperm production; or faulty sperm) in patients taking trametinib together with dabrafenib. Although no reported cases of testicular or reproductive problems in human patients have emerged, early studies, based on animals, reported some cases of animals with faulty sperm production following treatment with dabrafenib. Male patients receiving treatment with trametinib taken together with dabrafenib should be made aware of the possible risk of testicular problems and faulty sperm production, which may be irreversible.
Drug combination effects (Drug-drug interaction)	When taken in combination with dabrafenib, some medicines may affect how dabrafenib works; or make unwanted side effects more likely. Dabrafenib can also affect how some other medicines work.
Electrical abnormality in the heart (QT prolongation)	QT prolongation (an electrical abnormality in the heart) may occur in patients taking dabrafenib. The doctors' prescribing information will contain advice on monitoring higher-risk groups (e.g. with pre-existing heart conditions, or severe liver problems) when trametinib is taken together with dabrafenib.
Effects in children	Studies of trametinib given alone to patients

(Paediatric effects)	aged under 18 years have started but no information is available from them yet. Studies of trametinib given together with dabrafenib have not included patients aged under 18 years. Animal studies have identified some differences in the effects of dabrafenib between young and adult animals (e.g. in bone growth, development of the kidneys, ovaries and testes). These animal studies may indicate potential risks in the use of dabrafenib in children.

Summary of Safety Concerns – Missing Information

Risk	What is known
Related to trametinib alone	
Use in children and adolescents (patients less than 18 years) Use in paediatric population (children less than 18 years)	Trametinib is not tested or approved for use in children and adolescents. Trametinib is not recommended for children and adolescents younger than 18 years as the effects in this patient group are not known**.**
Related to both trametinib alone and trametinib + dabrafenib together	
Use in patients with heart failure (Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure – (NYHA functional classification system))	Patients with current or a previous history of heart failure have not been included in patient studies with trametinib alone, or trametinib given together with dabrafenib. There are no ongoing or planned patient studies that would include this patient group. The package leaflet warns patients that trametinib can affect how well the heart pumps blood and that this side effect may be more likely in patients with an existing heart problem. Patients taking trametinib alone or when given together with dabrafenib will be checked for any heart problems while taking the medicine.
Use in patients with severe kidney problems (Safety in patients with severe renal impairment)	Patients with severe kidney problems were not included in patient studies; therefore results on the effect of trametinib alone or when taken together with dabrafenib in this patient group are not available. Trametinib taken alone or together with dabrafenib should be used with caution in patients with severe kidney problems. Patients are advised to tell their doctor if they have kidney problems, as this may affect the way taking trametinib alone or together with

	dabrafenib may work in the body.
Use in patients with moderate to severe liver problems (Safety in patients with moderate to severe hepatic impairment)	There is no information from patient studies about the effect of trametinib when taken alone or together with dabrafenib in patients with moderate or severe liver problems. The prescriber's guide informs doctors that trametinib should be used with caution in patients with moderate or severe liver problems when taken alone or together with dabrafenib. Liver problems may affect the way trametinib when taken alone or together with dabrafenib works in the body. The Package Leaflet advises patients to inform their doctor if they have liver problems. Their doctor will also do some blood tests to monitor how well a patient's liver is working before and during treatment with trametinib alone or together with dabrafenib.
Use in non-white population (Use in non-white population)	Almost all the patients in studies with trametinib taken alone or together with dabrafenib were white. As melanoma occurs mostly in white Caucasians, the patient studies largely reflect the expected patients for this medical condition. However, there is no evidence to suggest that results would be any different in non-white patients.
Limited information on pregnancy and in breastfeeding women	There is no information from studies on the effect of trametinib taken alone or together with dabrafenib in unborn children or in breast feeding infants. The product labelling and package leaflet contains information on use in pregnancy or during breastfeeding.
Use in patients with moderate to severe physical disability (ECOG 2-4) (Risks in patients with ECOG 2-4)	The ECOG (Eastern Cooperative Oncology Group) scale is a method for assessing the performance and physical ability of cancer patients. ECOG 2 - 4 denotes patients that have moderate to severe health and physical issues. A status of 2 indicates a patient is mobile and capable of self-care, but is not able to carry out work or strenuous activity. A status of 4 applies to a patient who is completely disabled, bed- or chair- bound and not able to care for themselves. There is no information on whether trametinib taken alone or together with dabrafenib is appropriate for use in patients with an ECOG of between 2 to 4.
Safety in patients with abnormal heart rate,	The effect of trametinib taken alone or together

recent problems with blood supply to the heart including: poor blood supply (unstable angina), problems following treatment for narrowing of the blood vessels supplying the heart (coronary angioplasty, stenting), irregular heartbeat/heart pumping action and high blood pressure which cannot be controlled by medicine and abnormal heart valve. (Safety in patients with baseline QTc ≥480 msec QT prolongation, recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia), treatment refractory hypertension (blood pressure of systolic > 140 mmHg and/or diastolic > 90 mmHg which cannot be controlled by anti-hypertensive therapy) and abnormal cardiac valve morphology (combination only)	with dabrafenib is not known in patients with a history of heart problems, including: poor supply of blood to the heart, problems following treatment for narrowing of the blood vessels to the heart, irregular heartbeat and blood pressure which cannot be controlled by medicines. Information on the effect of treatment with trametinib taken alone or together with dabrafenib in patients with a history of these heart problems will be collected over time from patient studies and use in the general population. The leaflet included in the medicine's packaging informs patients that they are more likely to develop heart problems if they have an existing heart problem. Patients should tell their doctor as soon as possible if they have signs of heart problems (pounding or racing heart, dizziness, shortness of breath, tiredness, feeling light-headed or swelling in the legs). Patients will be checked for any heart problems whilst taking trametinib alone or together with dabrafenib.
Safety in patients with a history of eye problems (blood clot in a vein in the eye, or fluid beneath the retina, the light-sensitive back of the eye) (Safety in patients with history of retinal vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED))	Trametinib taken alone or together with dabrafenib has not been tested in patients with a history of retinal vein occlusion or retinal pigment epithelial detachment. It is not known whether the risk of experiencing eye problems is greater in patients who have a history of serious eye problems. However, trametinib is not recommended for patients who have ever had a clot in a vein in the eye. The leaflet included in the medicine's packaging informs patients that they should tell their doctor if they experience any eye problems (blurred vision, loss of vision, seeing coloured dots or seeing halos – a blurred outline around objects). Patients will be checked for any eye problems whilst taking trametinib alone or together with dabrafenib.
Safety in patients with inflammation (swelling/irritation) inside the lungs or conditions causing inflammation of the tissue around the lungs	It is not known whether patients with a history of inflammation of the lung are at an increased risk of experiencing lung problems when treated with trametinib alone or when taken

(Safety in patients with history of pneumonitis or interstitial lung disease)	together with dabrafenib.
Drug interaction effects (Drug-drug interactions i.e., enzymes responsible for the hydrolytic cleavage of trametinib, potential for saturation of P-gp and BCRP, whether Mekinist is a substrate of OATP1B1 and OATP1B3 and whether Mekinist is an inhibitor of OCT2, OAT1, or OAT3)	It is unknown if some medicines may affect levels of trametinib in the body, or if trametinib may affect levels of other medicines.

Summary of risk minimisation measures by safety concern

All medicines have a Product Information which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. A shortened version of this information in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measure.

This medicine has no additional risk minimization measures like educational materials.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
A study sponsored by the National Cancer Institute that will help determine the correct dose of trametinib in patients who have moderate to severe liver problems [MEK116354]	The main objective is to determine the proper dose of trametinib to be taken in patients who have moderate to severe liver problems	Dose adjustments potentially needed in patients who have moderate to severe liver problems	Study start planned 2Q2014	Final report completion 4Q2017
Annual reports/analyses will be available about heart problems (e.g. a drop in the amount of blood pumped to the body by the heart,	To identify and characterise the risk of heart problems in patients taking trametinib alone or in combination with other anti-cancer medicines	Heart problems (e.g. a drop in the amount of blood pumped around the body by the heart, general	Ongoing – Interim reports will be submitted annually	Final report completion 4Q2020

general problems with how the heart pumps blood to the body) that are reported in patients who are enrolled in certain clinical trials using trametinib alone or together with other medicines [201711]		problems with how the heart pumps blood around the body)		
A study conducted in a lab (not in humans or animals (*in vitro*)) to determine the risk of sensitivity to sunlight in patients taking trametinib	To identify and characterise the risk of sensitivity to sunlight in patients taking trametinib alone or in combination with other anti-cancer medicines	Sensitivity to sunlight	Study start planned 2Q2014	Final report completion 1Q2015
A study to investigate the possibility of drug-drug interaction with certain enzymes involved in the breakdown of trametinib [GSK1120212B]	To help predict drug-drug interactions	Drug-drug interactions	Start start planned 2Q2014	Final report completion 1Q2015
Studies to determine the potential for drug-drug interactions with certain (transporter) proteins involved in the breakdown of trametinib	To better characterise the risk of drug-drug interactions	Drug-drug interactions	Start planned 2Q2014	Final report completion 1Q2015
Studies to determine whether certain (transporter) proteins affect trametinib and whether trametinib affects certain (transporter) proteins	To better characterise the risk of drug-drug interactions	Drug-drug interactions	Start planned 2Q2014	Final report completion 1Q2015
A study to evaluate the possibility of an electrical abnormality in the heart in patients taking trametinib [MEK114655]	To evaluate the effect of repeat oral dosing of trametinib on electrical activity of the heart in subjects with solid tumours.	Characterisation of the potential risk of a type of electrical abnormality in the heart (QT	Ongoing	4Q2015

		prolongation)		
A study comparing the combination of dabrafenib and trametinib versus two placebos in the treatment of patients who have a certain type of melanoma (BRAF V600 mutation-positive) who have already undergone surgery to remove the cancer [BRF115532]	The main objective is to evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K highrisk, stage III cutaneous melanoma	The effectiveness of dabrafenib and trametinib combination will be compared with taking two placebos in patients who have had their melanoma surgically removed.	Ongoing	1Q2016
A study to determine whether there is a potential for drug interaction between trametinib and certain types of hormonal birth control (contraceptives) [MEK113707]	Assess the effect of repeat-dose trametinib on the repeat-dose pharmacokinetics of certain types of hormonal birth control (ethinyl estradiol and norethindrone).	Drug-drug interaction	Planned	2Q2018
Annual reports/analyses will be submitted about eye problems (e.g. blurred vision, loss of vision, seeing coloured dots or seeing halos – a blurred outline around objects) that are reported in patients who are enrolled in certain clinical trials using trametinib [201712]	To identify and characterise the risk of eye problems in patients taking trametinib alone or in combination with other anti-cancer medicines	Eye problems (e.g. blurred vision, loss of vision, seeing coloured dots or seeing halos – a blurred outline around objects)	Ongoing – Interim reports will be submitted annually	Final report completion 4Q2020

Studies which are a condition of the marketing authorization

None of the above studies is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in January 2016.