

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 0.5 mg film-coated tablets
Mekinist 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mekinist 0.5 mg film-coated tablets

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib.

Mekinist 2 mg film-coated tablets

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Mekinist 0.5 mg film-coated tablets

Yellow, modified oval, biconvex, film-coated tablets, approximately 4.8 x 8.9 mm, with “GS” debossed on one face and “TFC” on the opposing face.

Mekinist 2 mg film-coated tablets

Pink, round, biconvex, film-coated tablets, approximately 7.5 mm, with “GS” debossed on one face and “HMJ” on the opposing face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

4.2 Posology and method of administration

Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.

Posology

The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily.

Missed doses

If a dose of trametinib is missed, only take the dose if it is more than 12 hours until the next scheduled dose.

If a dose of dabrafenib is missed, when trametinib is given in combination with dabrafenib, only take the dose of dabrafenib if it is more than 6 hours until the next scheduled dose.

Duration of treatment

It is recommended that patients continue treatment with trametinib until patients no longer derive benefit or the development of unacceptable toxicity.

Treatment adjustments

The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation (see Tables 1 and 2).

Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see dabrafenib SmPC for further details).

Table 1 Recommended dose level reductions

Dose level	Trametinib dose Used as monotherapy or in combination with dabrafenib	Dabrafenib dose* Only when used in combination with trametinib
Starting dose	2 mg once daily	150 mg twice daily
1st dose reduction	1.5 mg once daily	100 mg twice daily
2nd dose reduction	1 mg once daily	75 mg twice daily
3rd dose reduction (combination only)	1 mg once daily	50 mg twice daily
Dose adjustment for trametinib below 1 mg once daily is not recommended, whether used as monotherapy or in combination with dabrafenib. Dose adjustment for dabrafenib below 50 mg twice daily is not recommended when used in combination with trametinib.		
*Please refer to the dabrafenib SmPC, Posology and method of administration, for dosing instructions for treatment with dabrafenib monotherapy.		

Table 2 Dose modification schedule based on the grade of any Adverse Events (AE)

Grade (CTC-AE)*	Recommended trametinib dose modifications Used as monotherapy or in combination with dabrafenib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.
* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)	

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The trametinib dose should not exceed 2 mg once daily.

If treatment-related toxicities occur when trametinib is used in combination with dabrafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for pyrexia, uveitis, RAS mutation positive non-cutaneous malignancies and QT prolongation (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Pyrexia

When trametinib is used in combination with dabrafenib and the patient's temperature is $\geq 38.5^{\circ}\text{C}$ please refer to the dabrafenib SmPC (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.

Uveitis

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

RAS-mutation-positive non-cutaneous malignancies

Consider the benefits and risks before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the dabrafenib SmPC (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction

Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of $>10\%$ in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) (see section 4.4). No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring (see section 4.4).

With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued (see section 4.4).

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)

If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If RPED is diagnosed follow the dose modification schedule in Table 3 below for trametinib (see section 4.4).

Table 3 Recommended dose modifications for trametinib for RPED

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily.
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

Interstitial lung disease (ILD)/Pneumonitis

Withhold trametinib in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis.

Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment (see section 5.2). There are no data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with dabrafenib.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (see section 5.2). There are no clinical data in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with dabrafenib.

Non-Caucasian patients

The safety and efficacy of trametinib in non-Caucasian patients have not been established. No data are available.

Elderly

No initial dose adjustment is required in patients >65 years of age. More frequent dose adjustments (see Tables 1 and 2 above) may be required in patients >65 years of age (see section 4.8).

Paediatric population

The safety and efficacy of trametinib has not been established in children and adolescents (<18 years). No data are available. Studies in juvenile animals have shown adverse effects of trametinib which had not been observed in adult animals (see section 5.3).

Method of administration

Trametinib should be taken orally with a full glass of water. Trametinib tablets should not be chewed or crushed. Trametinib should be taken without food, at least 1 hour before or 2 hours after a meal.

It is recommended that the dose of trametinib is taken at a similar time every day. When trametinib and dabrafenib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

If a patient vomits after taking trametinib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to dabrafenib SmPC for information on method of administration when given in combination with trametinib.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When trametinib is given in combination with dabrafenib, the SmPC of dabrafenib must be consulted prior to initiation of treatment. For additional information on warnings and precautions associated with dabrafenib treatment, please refer to the dabrafenib SmPC.

BRAF V600 testing

The safety and efficacy of trametinib have not been evaluated in patients whose melanoma tested negative for the BRAF V600 mutation.

Trametinib monotherapy compared to BRAF inhibitors

Trametinib monotherapy has not been compared with a BRAF inhibitor in a clinical study in patients with BRAF V600 mutation positive unresectable or metastatic melanoma. Based on cross-study comparisons, overall survival and progression-free survival data appear to show similar effectiveness between trametinib and BRAF inhibitors; however, overall response rates were lower in patients treated with trametinib than those reported in patients treated with BRAF inhibitors.

Trametinib in combination with dabrafenib in patients who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of trametinib with dabrafenib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

Trametinib in combination with dabrafenib in patients with brain metastases

The safety and efficacy of the combination of trametinib and dabrafenib have not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain.

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib.

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with trametinib in combination with dabrafenib. Cases of cuSCC can be managed with excision and do not require treatment modification. Please refer to the dabrafenib SmPC (section 4.4).

New primary melanoma

New primary melanoma was reported in patients receiving trametinib in combination with dabrafenib. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Please refer to the dabrafenib SmPC (section 4.4).

Non-cutaneous malignancy

Based on its mechanism of action, dabrafenib may increase the risk of non-cutaneous malignancies when RAS mutations are present. When trametinib is used in combination with dabrafenib please refer to the dabrafenib SmPC (section 4.4). No dose modification of trametinib is required for RAS mutation positive malignancies when taken in combination with dabrafenib.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The majority of bleeding events were mild. Fatal intracranial haemorrhages have occurred for trametinib in combination with dabrafenib in 1% (3/209) of patients in study MEK115306 and in <1% (3/350) of patients in study MEK116513. In these clinical studies, the median time to onset of the first occurrence of haemorrhagic events was 94 days in both studies for the combination of trametinib and dabrafenib. The potential for these events in patients with unstable and/or symptomatic brain metastases or low platelets (<75,000) is not established as patients with these conditions were excluded from clinical trials. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF, when used as monotherapy or in combination with dabrafenib (see section 4.8). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 and 5 months.

Trametinib should be used with caution in patients with impaired left ventricular function. Patients with left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant uncontrolled arrhythmias, and uncontrolled hypertension were excluded from clinical trials; safety of use in this population is therefore unknown. LVEF should be evaluated in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3-monthly intervals while on treatment (see section 4.2 regarding dose modification).

In patients receiving trametinib in combination with dabrafenib, there have been occasional reports of acute, severe left ventricular dysfunction due to myocarditis. Full recovery was observed when stopping treatment. Physicians should be alert to the possibility of myocarditis in patients who develop new or worsening cardiac signs or symptoms.

Pyrexia

Fever has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The incidence and severity of pyrexia are increased with the combination therapy (see dabrafenib SmPC section 4.4). In patients receiving trametinib in combination with dabrafenib, pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency.

When trametinib is used in combination with dabrafenib and the patient's temperature is $\geq 38.5^{\circ}\text{C}$ please refer to the dabrafenib SmPC (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.

Hypertension

Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension (see section 4.8). Blood pressure should be measured at baseline and monitored during treatment with trametinib, with control of hypertension by standard therapy as appropriate.

Interstitial lung disease (ILD)/Pneumonitis

In a Phase III trial, 2.4% (5/211) of patients treated with trametinib monotherapy developed ILD or pneumonitis; all five patients required hospitalisation. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days). In studies MEK115306 and MEK116513 <1% (2/209) and 1 % (4/350), respectively, of patients treated with trametinib in combination with dabrafenib developed pneumonitis or ILD (see section 4.8).

Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib should be permanently discontinued for patients diagnosed with treatment-related ILD or pneumonitis (see section 4.2). If trametinib is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose.

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, may occur with trametinib as monotherapy and in combination with dabrafenib. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). In clinical trials uveitis and iridocyclitis have also been reported in patients treated with trametinib in combination with dabrafenib.

Trametinib is not recommended in patients with a history of RVO. The safety of trametinib in subjects with predisposing factors for RVO, including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes, has not been established.

If patients report new visual disturbances, such as diminished central vision, blurred vision or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. If RPED is diagnosed, follow the dose modification schedule in Table 3 (see section 4.2); if uveitis is diagnosed, please refer to dabrafenib SmPC section 4.4. In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Rash

Rash has been observed in about 60% of patients in trametinib monotherapy studies and in about 25% of patients in trametinib and dabrafenib combination studies MEK115306 and MEK116513 (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking trametinib as monotherapy or in combination with dabrafenib (see section 4.8). In some cases, patients were able to continue trametinib. In more severe cases hospitalisation, interruption or permanent discontinuation of trametinib or trametinib and dabrafenib combination was required. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated.

Renal failure

Renal failure has been identified in patients treated with trametinib in combination with dabrafenib in clinical studies. Please refer to the dabrafenib SmPC (section 4.4).

Pancreatitis

Pancreatitis has been reported in patients treated with trametinib in combination with dabrafenib in clinical studies. Please refer to the dabrafenib SmPC (section 4.4).

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the dabrafenib SmPC section 4.4.

Hepatic events

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). It is recommended that patients receiving treatment with trametinib monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued thereafter as clinically indicated.

Hepatic impairment

As metabolism and biliary excretion are the primary routes of elimination of trametinib, administration of trametinib should be undertaken with caution in patients with moderate to severe hepatic impairment (see sections 4.2 and 5.2).

Deep vein thrombosis (DVT)/Pulmonary embolism (PE)

Pulmonary embolism or deep vein thrombosis can occur when trametinib is used as monotherapy or in combination with dabrafenib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Gastrointestinal disorders

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8). Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognised risk of gastrointestinal perforation.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on trametinib

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (e.g. carboxyl-esterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions (see section 5.2). Drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.

Trametinib is an *in vitro* substrate of the efflux transporter P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

Effect of trametinib on other medicinal products

Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interaction with CYP enzymes or transporters (see section 5.2). Trametinib may result in transient inhibition of BCRP substrates (e.g. pitavastatin) in the gut, which may be minimised with staggered dosing (2 hours apart) of these agents and trametinib.

Combination with dabrafenib

When trametinib is used in combination with dabrafenib see sections 4.4 and 4.5 of the dabrafenib SmPC for interactions.

Effect of food on trametinib

Patients should take trametinib as monotherapy or in combination with dabrafenib at least one hour prior to or two hours after a meal due to the effect of food on trametinib absorption (see section 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Advise female patients of reproductive potential to use highly effective contraception during treatment with trametinib and for 4 months after treatment.

It is currently unknown if hormonal contraceptives are affected by trametinib. To prevent pregnancy, female patients using hormonal contraception are advised to use an additional or alternative method during treatment and for 4 months following discontinuation of trametinib.

Use with dabrafenib may render hormonal contraceptives less effective and therefore an alternative method of contraception, such as a barrier method, should be used when trametinib is used in combination with dabrafenib. Refer to the dabrafenib SmPC for further information.

Pregnancy

There are no adequate and well-controlled studies of trametinib in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Trametinib should not be administered to pregnant women or nursing mothers. If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is not known whether trametinib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding infant cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue trametinib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for trametinib as monotherapy or in combination with dabrafenib. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see section 5.3). Trametinib may impair fertility in humans.

Men taking trametinib in combination with dabrafenib

Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients taking trametinib in combination with dabrafenib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Refer to the dabrafenib SmPC for further information.

4.7 Effects on ability to drive and use machines

Trametinib has minor influence on the ability to drive or use machines. The clinical status of the patient and the adverse reaction profile should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills. Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect these activities.

4.8 Undesirable effects

Summary of the safety profile

The safety of trametinib monotherapy has been evaluated in the integrated safety population of 329 patients with metastatic melanoma treated with trametinib 2 mg once daily. Of these patients, 211 patients were treated with trametinib for BRAF V600 mutant melanoma in a randomised open label phase III study (see section 5.1). The most common adverse reactions ($\geq 20\%$) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform.

The safety of trametinib in combination with dabrafenib has been evaluated in 2 Phase III studies, MEK115306 and MEK116513, where an analysis of the safety of trametinib in combination with dabrafenib has been conducted in 209 and 350 patients, respectively, with BRAF V600 mutation positive unresectable or metastatic melanoma receiving trametinib (2 mg once daily) and dabrafenib (150 mg twice daily) combination therapy (see section 5.1 combination therapy). The most common adverse reactions ($\geq 20\%$) for trametinib and dabrafenib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting and cough.

Tabulated summary of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class.

The following convention has been utilised for the classification of frequency:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Not known (cannot be estimated from the available data)

Categories have been assigned based on absolute frequencies in the clinical trial data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Trametinib monotherapy

Table 4 Adverse reactions occurring in patients treated with trametinib in the integrated safety population (n=329)

System Organ Class	Frequency (all grades)	Adverse Reactions
Blood and lymphatic system disorders	Common	Anaemia
Immune system disorders	Common	Hypersensitivity ^a
Metabolism and nutrition disorders	Common	Dehydration
Eye disorders	Common	Vision blurred
		Periorbital oedema
		Visual impairment
	Uncommon	Chorioretinopathy
		Papilloedema
		Retinal detachment
		Retinal vein occlusion
Cardiac disorders	Common	Left ventricular dysfunction
		Ejection fraction decreased
		Bradycardia
Vascular disorders	Uncommon	Cardiac failure
	Very common	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Haemorrhage ^b
	Common	Lymphoedema
Gastrointestinal disorders	Very common	Cough
		Dyspnoea
		Pneumonitis
		Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
	Uncommon	Gastrointestinal perforation
		Colitis

Skin and subcutaneous disorders	Very common	Rash
		Dermatitis acneiform
		Dry skin
		Pruritus
		Alopecia
	Common	Erythema
		Palmar-plantar erythrodysaesthesia syndrome
		Skin fissures
Skin chapped		
Musculoskeletal and connective tissue disorders	Uncommon	Rhabdomyolysis
General disorders and administration site conditions	Very common	Fatigue
		Oedema peripheral
		Pyrexia
	Common	Face oedema
		Mucosal inflammation
		Asthenia
Infections and infestation	Common	Folliculitis
		Paronychia
		Cellulitis
		Rash pustular
Investigations	Very common	Aspartate aminotransferase increased
	Common	Alanine aminotransferase increased
		Blood alkaline phosphatase increased
		Blood creatine phosphokinase increased
		Heart rate decreased
^a May present with symptoms such as fever, rash, increased liver transaminases, and visual disturbances		
^b Events include but are not limited to: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, intracranial and post procedural haemorrhage.		

Trametinib and dabrafenib combination therapy

Table 5 Adverse reactions occurring in the two randomised phase III combination studies MEK115306 (n = 209) and MEK116513^a (n = 350)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and Infestations	Very common	Urinary tract infection
		Nasopharyngitis
	Common	Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma ^b
		Papilloma ^c
		Seborrheic keratosis
		Acrochordon (skin tags)
	Uncommon	New primary melanoma
Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Anaemia
		Thrombocytopenia
		Leukopenia

Immune system disorders	Uncommon	Drug hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
	Uncommon	Chorioretinopathy
		Uveitis
		Retinal detachment
		Periorbital oedema
Cardiac disorder	Common	Ejection fraction decreased
		Bradycardia
	Unknown	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage ^d
	Common	Hypotension
	Uncommon	Lymphoedema ^a
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
	Uncommon	Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Gastrointestinal perforation
		Colitis

Hepatobiliary disorder	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Dermatitis acneiform
	Common	Erythema
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
	Common	Muscle spasms ^a
		Blood creatine phosphokinase increased
Renal and urinary disorders	Uncommon	Renal failure ^a
		Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
	Common	Mucosal inflammation
		Influenza-like illness
		Face oedema
Investigations	Common	Heart rate decreased
^a The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease, rhabdomyolysis (uncommon). ^b cu SCC: SCC of the skin, SCC <i>in situ</i> (Bowen's disease) and keratoacanthoma ^c Papilloma, skin papilloma ^d Bleeding from various sites, including intracranial bleeding and fatal bleeding		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

Description of selected adverse reactions

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib. Please refer to the dabrafenib SmPC.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. The majority of bleeding events were mild. Fatal intracranial haemorrhages have occurred for trametinib in combination with dabrafenib in 1% (3/209) of patients in study MEK115306 and in <1% (3/350) of patients in study MEK116513. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, treat as clinically indicated (see section 4.4).

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF when used as monotherapy or in combination with dabrafenib. In clinical trials, the median time to first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 to 5 months. In 2 phase III clinical trials decreased LVEF has been reported in 6 to 8% of patients treated with trametinib in combination with dabrafenib, with most cases being asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with trametinib. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Pyrexia

Pyrexia has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy. Please refer to sections 4.4 and 4.8 of the dabrafenib SmPC.

Hepatic events

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Liver events were detected in clinical trials with monitoring every four weeks. It is recommended that patients receiving treatment with trametinib monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

Hypertension

Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate (see section 4.4).

Interstitial lung disease (ILD)/Pneumonitis

Patients treated with trametinib or combination with dabrafenib may develop ILD or pneumonitis. Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. For patients diagnosed with treatment-related ILD or pneumonitis trametinib should be permanently discontinued (see sections 4.2 and 4.4).

Visual impairment

Disorders associated with visual disturbances, including RPED and RVO, have been observed with trametinib. Symptoms such as blurred vision, decreased acuity, and other visual disturbances have been reported in the clinical trials with trametinib (see sections 4.2 and 4.4).

Rash

Rash has been observed in about 60% of patients when given as monotherapy and in about 25% of patients in trametinib and dabrafenib combination studies MEK115306 and MEK116513. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions (see sections 4.2 and 4.4).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking trametinib alone or in combination with dabrafenib. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated (see section 4.4).

Pancreatitis

Pancreatitis has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib SmPC.

Renal failure

Renal failure has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib SmPC.

Special populations

Elderly population

In the phase III study with trametinib in patients with unresectable or metastatic melanoma (n = 211), 49 patients (23%) were ≥ 65 years of age, and 9 patients (4%) were ≥ 75 years of age. The proportion of subjects experiencing adverse events (AE) and serious adverse events (SAE) was similar in the subjects aged < 65 years and those aged ≥ 65 years. Patients ≥ 65 years were more likely to experience AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those < 65 years.

In the phase III studies MEK115306 (n = 209) and MEK116513 (n = 350) with trametinib in combination with dabrafenib in patients with unresectable or metastatic melanoma, 56 patients (27%) and 77 patients (22%) respectively were ≥ 65 years of age; 11 patients (5%) and 21 patients (6%) respectively were ≥ 75 years of age. The proportion of patients experiencing AEs was similar in those aged < 65 years and those aged ≥ 65 years in both studies. Patients ≥ 65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those < 65 years.

Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Trametinib should be used with caution in patients with severe renal impairment (see sections 4.2 and 4.4).

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (see section 5.2). Trametinib should be used with caution in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4)

4.9 Overdose

In clinical trials with trametinib monotherapy one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose. In clinical trials with the combination of trametinib and dabrafenib 11 patients reported trametinib overdose (4 mg); no SAEs were reported. There is no specific treatment for overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01XE25

Mechanism of action

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

Combination with dabrafenib

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of trametinib with dabrafenib has shown anti-tumour activity in BRAF V600 mutation positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

Determination of BRAF mutation status

Before taking trametinib or the combination with dabrafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.

In clinical trials, central testing for BRAF V600 mutation using a BRAF mutation assay was conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with a validated polymerase chain reaction (PCR) assay developed by Response Genetics Inc. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only patients with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the CE-marked bioMerieux (bMx) THxID BRAF validated assay. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical studies with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical studies (n = 876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Pharmacodynamic effects

Trametinib suppressed levels of phosphorylated ERK in BRAF mutant melanoma tumour cell lines and melanoma xenograft models.

In patients with BRAF and NRAS mutation positive melanoma, administration of trametinib resulted in dose-dependent changes in tumour biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). The mean trametinib concentrations observed following repeat dose administration of 2 mg once daily exceeds the preclinical target concentration over the 24-hr dosing interval, thereby providing sustained inhibition of the MEK pathway.

Clinical efficacy and safety

In the clinical studies only patients with cutaneous melanoma were studied. Efficacy in patients with ocular or mucosal melanoma has not been assessed.

Trametinib in combination with dabrafenib

Treatment naïve patients

The safety and efficacy of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two Phase III studies and one supportive Phase I/II study.

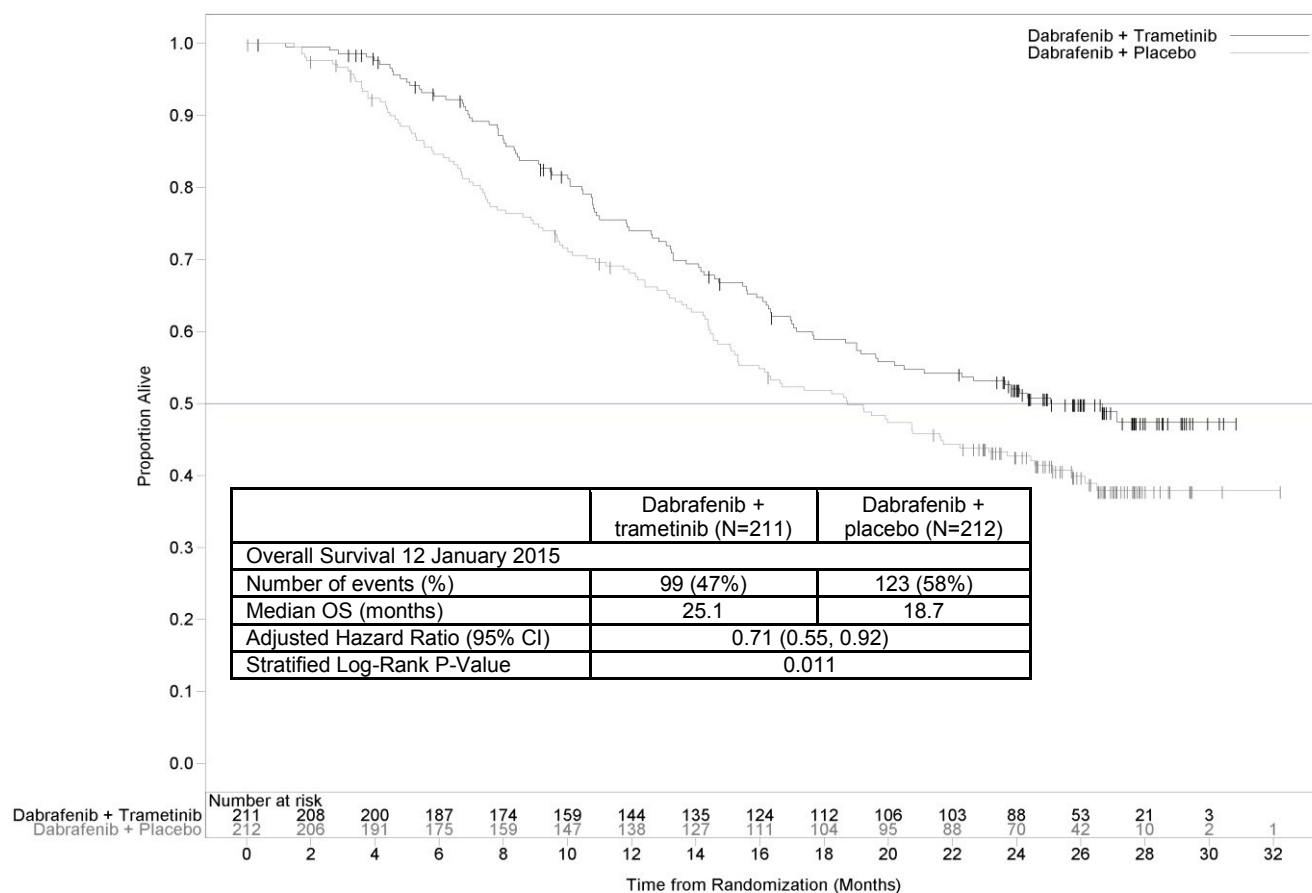
MEK115306 (COMBI-d):

MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 423 subjects were randomised 1:1 to either combination (N = 211) or dabrafenib (N = 212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), ECOG performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the trial.

The final OS analysis (12 January 2015) demonstrated a statistically significant improvement in OS for the combination compared with dabrafenib monotherapy (Figure 1). The 1-year (74%) and 2-year (51%) OS estimates for the combination arm were greater than those for dabrafenib monotherapy (68% and 42% respectively).

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)



Statistically significant improvements were observed for the primary endpoint of PFS and secondary endpoint of ORR. A longer duration of response is also observed (Table 6).

Table 6 Efficacy results for Study MEK115306 (COMBI-d)

Endpoint	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Data cut-off date	26 August 2013		12 January 2015	
PFS ^a				
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)
Median PFS (months) (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)	
P value	0.035		<0.001	
ORR ^b (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)
ORR difference (95% CI)	15 ^e (5.9, 24.5)		15 ^e (6.0, 24.5)	
P value	0.0015		0.0014	
DoR ^c (months)				
Median (95% CI)	9.2 ^d (7.4, NR)	10.2 ^d (7.5, NR)	12.9 (9.4, 19.5)	10.6 (9.1, 13.8)
a – Progression-free survival (investigator assessed) b – Overall Response Rate = Complete Response + Partial Response c – Duration of response d - At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing e – ORR difference calculated based on the ORR result not rounded NR = Not reached				

MEK116513 (COMBI-v):

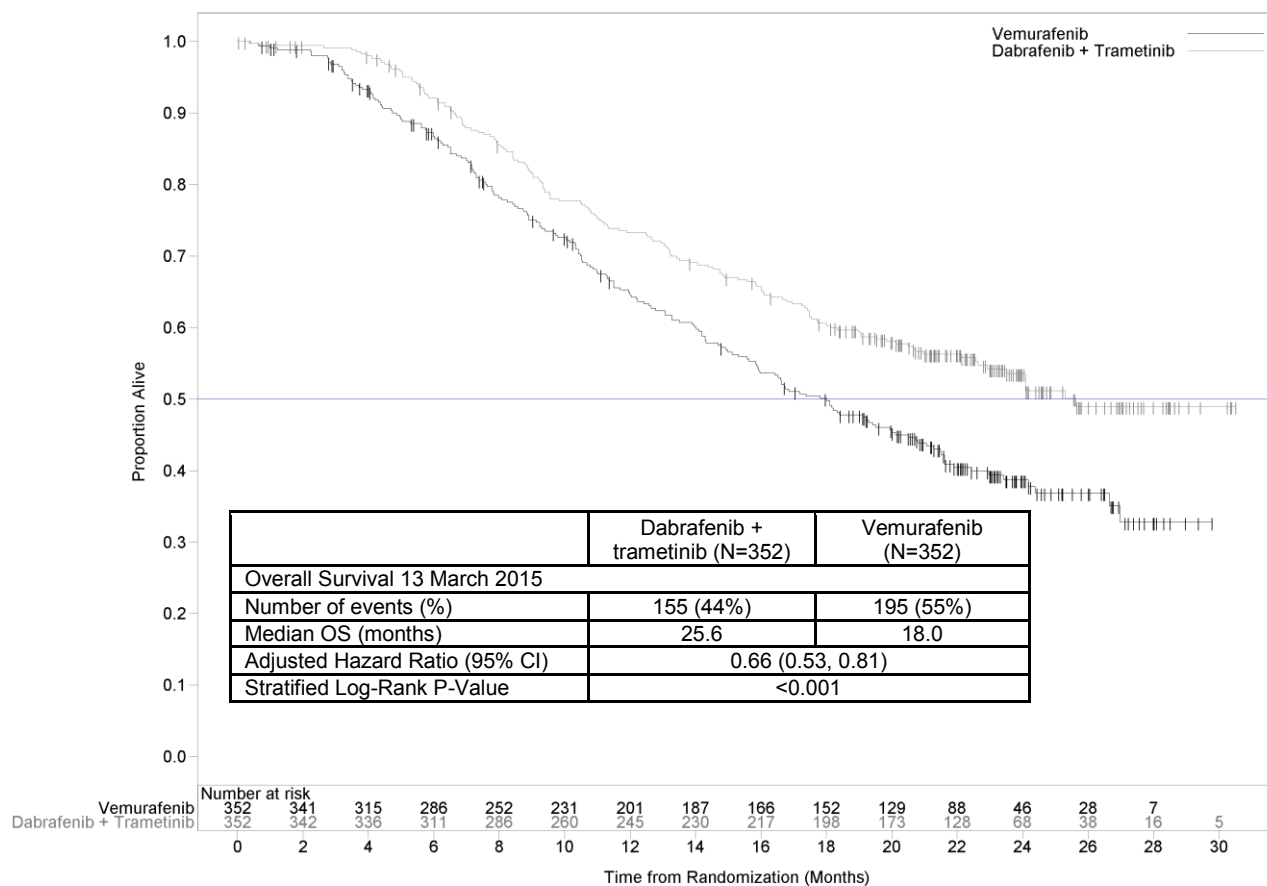
Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. The primary endpoint of the study was overall survival with a key secondary endpoint of PFS. Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

The updated OS analysis (13 March 2015) demonstrated a statistically significant improvement in OS for the combination compared with vemurafenib monotherapy (Figure 2). The 12-month OS estimate was 72% for combination therapy and 65% for vemurafenib.

Figure 2 Kaplan-Meier curves Updated OS analysis for Study MEK116513

Page 1 of 1



Statistically significant improvements are observed for the secondary endpoints of PFS and ORR. A longer duration of response is also observed (Table 7).

Table 7 Efficacy results for Study MEK116513 (COMBI-v)

Endpoint	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)
PFS		
Progressive disease or death, n (%)	166 (47)	217 (62)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)	
P value	<0.001	
ORR (95% CI)	226 (64) (59.1, 69.4)	180 (51) (46.1, 56.8)
ORR difference (95% CI)	13 (5.7, 20.2)	
P value	0.0005	
DoR (months) Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

Prior BRAF inhibitor therapy

There are limited data in patients taking the combination of trametinib with dabrafenib who have progressed on a prior BRAF inhibitor.

Part B of study BR113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor (see section 4.4). The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95% CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

Trametinib monotherapy

Treatment naïve patients

The efficacy and safety of trametinib in patients with BRAF mutant melanoma (V600E and V600K) were evaluated in a randomised open-label Phase III study (MEK114267). Measurement of patients' BRAF V600 mutation status was required.

Patients (N = 322) who were treatment naïve or may have received one prior chemotherapy treatment in the metastatic setting [Intent to Treat (ITT) population] were randomised 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m² every 3 weeks or paclitaxel 175 mg/m² every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to progression-free survival (PFS) in patients with advanced/metastatic BRAF V600E mutation-positive melanoma without a prior history of brain metastases (N = 273) which is considered the primary efficacy population. The secondary endpoints were progression-free survival in the ITT population and overall survival (OS), overall response rate (ORR), and duration of response in the primary efficacy population and ITT population. Patients in the chemotherapy arm were allowed to cross-over to the trametinib arm after independent confirmation of progression. Of the patients with confirmed disease progression in the chemotherapy arm, a total of 51 (47%) crossed over to receive trametinib.

Baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population. In the ITT population, 54% of patients were male and all were Caucasian. The median age was 54 years (22% were ≥ 65 years); all patients had an ECOG performance score of 0 or 1; and 3 % had history of brain metastases. Most patients (87%) in the ITT population had BRAF V600E mutation and 12% of patients had BRAF V600K. Most patients (66%) received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 8. Kaplan-Meier curves of investigator assessed overall survival (post-hoc analysis 20 May 2013) is presented in Figure 3.

Table 8 Investigator assessed efficacy results (ITT population)

Endpoint	Trametinib	Chemotherapy ^a
Progression-Free Survival	(N = 214)	(N = 108)
Median PFS (months) (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95% CI) <i>P</i> value	0.45 (0.33, 0.63) <0.0001	
Overall Response Rate (%)	22	8
ITT = Intent to Treat; PFS = Progression-free survival; CI = confidence interval. ^a Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m ² every 3 weeks or paclitaxel 175 mg/m ² every 3 weeks.		

The PFS result was consistent in the subgroup of patients with V600K mutation positive melanoma (HR = 0.50; [95% CI: 0.18, 1.35], *p*=0.0788).

An additional overall survival analysis was undertaken based upon the 20 May 2013 data cut, see Table 9.

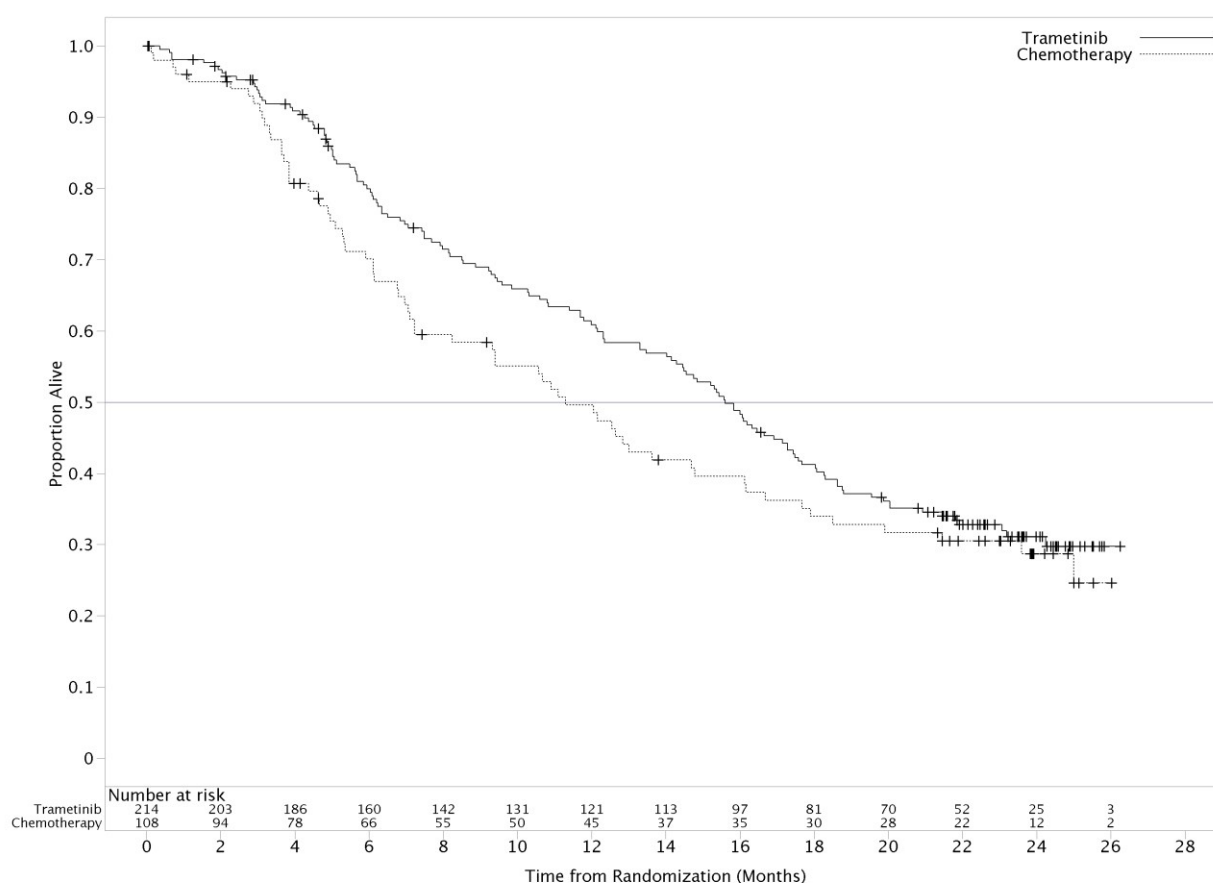
For October 2011, 47% of subjects had crossed over, while for May 2013, 65% of subjects had crossed over.

Table 9 Survival data from the primary and post-hoc analyses

Cut-off dates	Treatment	Number of deaths (%)	Median months OS (95% CI)	Hazard ratio (95% CI)	Percent survival at 12 months (95% CI)
October 26, 2011	Chemotherapy (n=108)	29 (27)	NR	0.54 (0.32, 0.92)	NR
	Trametinib (n=214)	35 (16)	NR		NR
May 20, 2013	Chemotherapy (n=108)	67 (62)	11.3 (7.2, 14.8)	0.78 (0.57, 1.06)	50 (39,59)
	Trametinib (n=214)	137 (64)	15.6 (14.0, 17.4)		61(54, 67)

NR=not reached

Figure 3 Kaplan-Meier curves of overall survival (OS –ad hoc analysis 20 May 2013)



Prior BRAF inhibitor therapy

In a single-arm Phase II study, designed to evaluate the objective response rate, safety, and pharmacokinetics following dosing of trametinib at 2 mg once daily in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma (MEK113583), two separate cohorts were enrolled: Cohort A: patients with prior treatment with a BRAF inhibitor either with or without other prior therapy, Cohort B: patients with at least 1 prior chemotherapy or immunotherapy, without prior treatment with a BRAF inhibitor.

In Cohort A of this study, trametinib did not demonstrate clinical activity in patients who had progressed on a prior BRAF inhibitor therapy.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with trametinib in all subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72% relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, steady-state geometric mean C_{max} , $AUC_{(0-\tau)}$ and predose concentration were 22.2 ng/ml, 370 ng*hr/ml and 12.1 ng/ml, respectively with a low peak:trough ratio (1.8). Inter-subject variability at steady state was low (<28%).

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 at 2 mg once daily dose. Steady-state was achieved by Day 15.

Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70% and 10% decrease in C_{max} and AUC, respectively compared to fasted conditions (see sections 4.2 and 4.5).

Distribution

Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of approximately 1200 L determined following administration of a 5 µg intravenous microdose.

Biotransformation

In vitro studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. CYP3A4 oxidation is considered a minor pathway of metabolism. The deacetylation is mediated by carboxyl-esterases (i.e. carboxylesterase 1b/c and 2) and may also be mediated by other hydrolytic enzymes.

Following single and repeated doses of trametinib, trametinib as parent is the main circulating component in plasma.

Elimination

Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery is low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long elimination half-life. Faecal excretion is the major route of elimination after [14C]-trametinib oral dose, accounting for >80% of excreted radioactivity recovered while urinary excretion accounted for <19% of excreted radioactivity recovered. Less than 0.1% of the excreted dose was recovered as parent in urine.

Special patient populations

Hepatic impairment

A population pharmacokinetic analysis indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect trametinib oral clearance. No data are available in patients with moderate or severe hepatic impairment. As metabolism and biliary excretion are the primary routes of elimination of trametinib, administration of trametinib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2).

Renal impairment

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib were characterised in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (<6% for either group). No data are available in patients with severe renal impairment (see section 4.2).

Elderly

Based on the population pharmacokinetics analysis (range 19 to 92 years), age had no relevant clinical effect on trametinib pharmacokinetics. Safety data in patients ≥ 75 years is limited (see section 4.8).

Race

There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics as clinical experience is limited to Caucasians.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of trametinib in paediatric patients.

Gender / Weight

Based on a population pharmacokinetic analysis, gender and body weight were found to influence trametinib oral clearance. Although smaller female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dosage adjustment is warranted.

Medicinal product interactions

Effects of trametinib on drug-metabolising enzymes and transporters: *In vitro* and *in vivo* data suggest that trametinib is unlikely to affect the pharmacokinetics of other medicinal products. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the *in vitro* potency of inhibition or induction values, trametinib is not considered to be an *in vivo* inhibitor or inducer of these enzymes or transporters, although transient inhibition of BCRP substrates in the gut may occur (see section 4.5).

Effects of other drugs on trametinib: *In vivo* and *in vitro* data suggest that the pharmacokinetics of trametinib are unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the transporters BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2, and MATE1. Trametinib is an *in vitro* substrate of BSEP and the efflux transporter P-gp. Although trametinib exposure is unlikely to be affected by inhibition of BSEP, increased levels of trametinib upon strong inhibition of hepatic P-gp cannot be excluded (see section 4.5).

5.3 Preclinical safety data

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC.

Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues.

In reproductive toxicity studies in rats and rabbits, trametinib induced maternal and developmental toxicity. In rats decreased foetal weights and increased post-implantation loss were seen at exposures below or slightly above the clinical exposures based on AUC. In pregnant rabbits, decreased foetal body weight, increased abortions, increased incidence of incomplete ossification and skeletal malformations were seen at sub-clinical exposures based on AUC).

In repeat-dose studies the effects seen after trametinib exposure are found mainly in the skin, gastrointestinal tract, haematological system, bone and liver. Most of the findings are reversible after drug-free recovery. In rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥ 0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥ 0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks. In adult rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver and kidney and haemorrhage in the lung at exposures comparable to the human clinical exposure. In rats, hypertrophy of the physis and increased bone turnover were observed, but the physal hypertrophy is not expected to be clinically relevant for adult humans. In rats and dogs given trametinib at or below clinical exposures, bone marrow necrosis, lymphoid atrophy in thymus and GALT and lymphoid necrosis in lymph nodes, spleen and thymus were observed, which have the potential to impair immune function. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately 2 times adult human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC_{50} at 2.92 μ g/ml, ≥ 130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

Combination with dabrafenib

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastro-intestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mekinist 0.5 mg film-coated tablets

Tablet core

Mannitol (E421)
Microcrystalline cellulose (E460)
Hypromellose (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Sodium laurilsulfate
Colloidal silicon dioxide(E551)

Tablet film-coat

Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Iron oxide yellow(E172)

Mekinist 2 mg film-coated tablets

Tablet core

Mannitol (E421)
Microcrystalline cellulose (E460)
Hypromellose (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Sodium laurilsulfate
Colloidal silicon dioxide(E551)

Tablet film-coat

Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Polysorbate 80 (E433)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 18 months

Opened bottle: 30 days

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Store in the original package in order to protect from light and moisture.

Keep the bottle tightly closed.

Once opened, the bottle may be stored for 30 days at not more than 30°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with child resistant polypropylene closure. The bottle contains a desiccant.

Pack sizes: One bottle contains either 7 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Mekinist 0.5 mg film-coated tablets

EU/1/14/931/001

EU/1/14/931/002

Mekinist 2 mg film-coated tablets

EU/1/14/931/005

EU/1/14/931/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Glaxo Wellcome, S.A.
Avda. Extremadura, 3
09400, Aranda de Duero
Burgos
Spain

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Mekinist 0.5 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg trametinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

7 film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C to 8°C).
Store in the original package to protect from light and moisture. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/001	7 film-coated tablets
EU/1/14/931/002	30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 0.5 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Mekinist 0.5 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg trametinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

7 tablets

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C to 8°C) in the original bottle. Keep the bottle closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/001	7 film-coated tablets
EU/1/14/931/002	30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Mekinist 2 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 2 mg trametinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

7 film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C to 8°C).
Store in the original package to protect from light and moisture. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/14/931/005	7 film-coated tablets
EU/1/14/931/006	30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 2 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Mekinist 2 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 2 mg trametinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

7 tablets

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C to 8°C) in the original bottle. Keep the bottle closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/005	7 film-coated tablets
EU/1/14/931/006	30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mekinist 0.5 mg film-coated tablets

Mekinist 2 mg film-coated tablets

trametinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mekinist is and what it is used for
2. What you need to know before you take Mekinist
3. How to take Mekinist
4. Possible side effects
5. How to store Mekinist
6. Contents of the pack and other information

1. What Mekinist is and what it is used for

Mekinist is a medicine that contains the active substance trametinib. It is used either on its own or in combination with another medicine containing dabrafenib to treat a type of skin cancer called melanoma

- that has a particular change (mutation) in a gene called BRAF, and
- that has spread to other parts of the body, or cannot be removed by surgery.

This mutation in the gene may have caused the melanoma to develop. Your medicine targets proteins made from this modified gene and slows down or stops the development of your cancer.

2. What you need to know before you take Mekinist

Mekinist should only be used to treat melanomas with the BRAF mutation. Therefore, before starting treatment your doctor will test for this mutation.

If your doctor decides that you will receive treatment with the combination of Mekinist and dabrafenib, **read the dabrafenib leaflet carefully as well as this leaflet.**

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

Do not take Mekinist:

- if you are allergic to trametinib or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking your medicine. Your doctor needs to know:

- if you have any **liver problems**. Your doctor may take blood samples to monitor your liver function while you are taking this medicine.
- if you have or have ever had **kidney problems**.
- if you have or have ever had **lung or breathing problems**.
- if you have heart problems such as heart failure or problems with the way your heart beats.
- if you have eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid blockage (chorioretinopathy).

Before you take Mekinist in combination with dabrafenib your doctor needs to know:

- **if you have had a different type of cancer other than melanoma**, as you may be at greater risk of developing non-skin cancers when taking Mekinist.

Check with your doctor if you think this may apply to you.

Conditions you need to look out for

Some people taking Mekinist develop other conditions which can be serious. You need to know about important symptoms to look out for.

Bleeding

Taking Mekinist or the combination of Mekinist and dabrafenib can cause serious bleeding including in your brain, the digestive system (such as stomach, rectum or intestine), lungs, and other organs, and can lead to death. Symptoms may include:

- headaches, dizziness, or feeling weak
- passing blood in the stools or passing black stools
- passing blood in the urine
- stomach pain
- coughing / vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Heart disorder

Mekinist can cause heart problems, or make existing heart problems worse (see also “Heart conditions” in section 4).

Tell your doctor if you have a heart disorder. Your doctor will run tests to check that your heart is working properly before and during your treatment with this medicine. Tell your doctor immediately if it feels like your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, lightheadedness, shortness of breath or swelling in the legs. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Fever (high temperature)

Taking Mekinist or the combination of Mekinist and dabrafenib may cause fever, although it is more likely if you are taking the combination treatment. In some cases, people with fever may develop low blood pressure, dizziness or other symptoms.

Tell your doctor immediately if you get a temperature above 38.5°C while you are taking your medicine.

Changes in your skin which may indicate new skin cancer

Taking the combination of Mekinist and dabrafenib may cause a different type of skin cancer called *cutaneous squamous cell carcinoma (cuSCC)*. Usually, this lesion remains local and can be removed with surgery and people can continue treatment.

Some people taking Mekinist in combination with dabrafenib also may notice that new melanomas have appeared. These lesions are usually removed by surgery and people can continue treatment.

Your doctor will check your skin before you start treatment, and periodically thereafter. **Tell your doctor immediately** if you notice any changes to your skin while taking this medicine or after treatment (see also section 4).

Liver problems

Mekinist, or the combination with dabrafenib, can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:

- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Tell your doctor as soon as possible if you get any of these symptoms.

Eye problems

You should have your eyes examined by your doctor while you are taking your medicine.

Mekinist can cause eye problems including blindness. Mekinist is not recommended if you have ever had blockage of the vein draining the eye (retinal vein occlusion). Tell your doctor immediately if you get the following symptoms of eye problems: blurred vision, loss of vision or other vision changes, coloured dots in your vision or halos (seeing blurred outline around objects) during your treatment. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Lung or breathing problems

Tell your doctor if you have any lung or breathing problems, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue. Your doctor may arrange to check your lung function before you start taking your medicine.

Muscle pain

Mekinist can result in the breakdown of muscle (rhabdomyolysis), **Tell your doctor** as soon as possible if you get any of these symptoms:

- muscle pain
- dark urine due to kidney damage

If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

➔ **Read the information “Possible serious side effects” in section 4 of this leaflet.**

Hole in the stomach or intestine (perforation)

Taking Mekinist or the combination of Mekinist and dabrafenib may increase the risk of developing holes in the gut wall. Tell your doctor as soon as possible if you have severe abdominal pain.

Children and adolescents

Mekinist is not recommended for children and adolescents since the effects of Mekinist in people younger than 18 years old are not known.

Other medicines and Mekinist

Before starting treatment, tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. Keep a list of the medicines you take, so you can show it to your doctor, nurse or pharmacist when you get a new medicine.

Mekinist with food and drink

It is important to take Mekinist on an empty stomach because food affects the way the medicine is absorbed into your body (see section 3).

Pregnancy, breast-feeding and fertility

Mekinist is not recommended for use during pregnancy.

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Mekinist can harm the unborn baby.
- If you are a woman who could become pregnant, you must use reliable birth control (contraception) while you are taking Mekinist and for 4 months after you stop taking it.
- Birth control using hormones (such as pills, injections or patches) may not work as well if you are taking Mekinist or combination treatment (Mekinist as well as dabrafenib). You need to use another reliable method of birth control such as a barrier method (e.g. condom) so you do not become pregnant while you are taking this medicine. Ask your doctor, nurse or pharmacist for advice.
- If you do become pregnant while you are taking Mekinist, tell your doctor immediately.

Mekinist is not recommended while breast-feeding

It is not known whether the ingredients of Mekinist can pass into breast milk.

If you are breast-feeding, or planning to breast-feed, you must tell your doctor. It is recommended that you do not breast-feed while you are taking Mekinist. You and your doctor will decide whether you will take Mekinist or breast-feed.

Fertility – both men and women

Mekinist may impair fertility in both men and women.

Taking Mekinist with dabrafenib: Dabrafenib may permanently reduce male fertility. In addition, men who are taking dabrafenib may have a reduced sperm count, and their sperm count may not return to normal levels after they stop taking this medicine.

Prior to starting treatment with dabrafenib, talk to your doctor about options to improve your chances to have children in the future.

If you have any further questions on the effect of this medicine on fertility, ask your doctor, nurse or pharmacist.

Driving and using machines

Mekinist can have side effects that may affect your ability to drive or use machines. Avoid driving or using machines if you feel tired or weak, if you have problems with your vision or if your energy levels are low.

Descriptions of these effects can be found in other sections (see sections 2 and 4). Read all the information in this leaflet for guidance.

Discuss with your doctor, nurse or pharmacist if you are unsure about anything. Even your disease, symptoms and treatment situation may affect your ability to drive or use machines.

3. How to take Mekinist

Always take Mekinist exactly as your doctor, nurse or pharmacist has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How much to take

The usual dose of Mekinist either used alone or in combination with dabrafenib is one 2 mg tablet once a day. The recommended dose of dabrafenib, when used in combination with Mekinist, is 150 mg twice daily.

Your doctor may decide to lower the dose if you get side effects.

Don't take more Mekinist than your doctor has recommended.

How to take it

Swallow the tablet whole, with a full glass of water.

Take Mekinist once a day, on an empty stomach (at least 1 hour before a meal or 2 hours after a meal).

This means that:

- after taking Mekinist, you must wait at least 1 hour before eating, or
- after eating, you must wait at least 2 hours before taking Mekinist.

Take Mekinist at about the same time each day.

If you take more Mekinist than you should

If you take too many tablets of Mekinist, contact your doctor, nurse or pharmacist for advice. If possible, show them the Mekinist pack and this leaflet.

If you forget to take Mekinist

If the missed dose is less than 12 hours late, take it as soon as you remember.

If the missed dose is more than 12 hours late, skip that dose and take your next dose at the usual time.

Then carry on taking your tablets at regular times as usual.

Do not take a double dose to make up for a missed dose.

If you stop taking Mekinist

Take Mekinist for as long as your doctor recommends. Do not stop unless your doctor advises you to.

If you have any further questions on how to take Mekinist, ask your doctor, nurse or pharmacist.

How should you take Mekinist in combination with dabrafenib

- Take Mekinist in combination with dabrafenib exactly as your doctor, nurse or pharmacist tells you. Do not change your dose or stop Mekinist or dabrafenib unless your doctor, nurse or pharmacist tells you to.
- Take **Mekinist once daily** and take **dabrafenib twice daily**. It may be good for you to get into the habit of taking both medicines at the same times each day. Mekinist should be taken with **either** the morning dose of dabrafenib **or** the evening dose of dabrafenib. The dabrafenib doses should be about 12 hours apart.
- Take Mekinist and dabrafenib on an empty stomach, at least one hour before or two hours after a meal. Take whole with a full glass of water.
- If you miss a dose of Mekinist or dabrafenib, take it as soon as you remember: Do not make up for missed doses and just take your next dose at your regular time:
 - If it is less than 12 hours to your next scheduled dose of Mekinist, which is taken once daily.
 - If it is less than 6 hours to your next scheduled dose of dabrafenib, which is taken twice daily.
- If you take too much Mekinist or dabrafenib, immediately contact your doctor, nurse or pharmacist. Take Mekinist tablets and dabrafenib capsules with you when possible. If possible, show them the Mekinist and dabrafenib pack with each leaflet.
- If you get side effects your doctor may decide that you should take lower doses of Mekinist and dabrafenib. Take the doses of Mekinist and dabrafenib exactly as your doctor, nurse or pharmacist tells you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects

Heart conditions

Mekinist can affect how well your heart pumps blood. It is more likely to affect people who have an existing heart problem. You will be checked for any heart problems while you are taking Mekinist. Signs and symptoms of heart problems include:

- feeling like your heart is pounding, racing, or beating irregularly
- dizziness
- tiredness
- feeling lightheaded
- shortness of breath
- swelling in the legs

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

High blood pressure

Mekinist can cause new or worsening high blood pressure (hypertension). Your doctor or nurse should check your blood pressure during treatment with Mekinist. Call your doctor or nurse right away if you develop high blood pressure, your blood pressure worsens, or you have severe headache, light-headedness, or dizziness.

Bleeding problems

Mekinist can cause serious bleeding problems, especially in your brain or stomach. Call your doctor or nurse and get medical help right away if you have any unusual signs of bleeding, including:

- headaches, dizziness, or weakness
- coughing up of blood or blood clots
- vomit containing blood or that looks like “coffee grounds”
- red or black stools that look like tar

Eye (vision) problems

Mekinist can cause eye problems. Mekinist is not recommended if you have ever had a blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye examination before you take Mekinist and while you are taking it. Your doctor may ask you to stop taking Mekinist or refer you to a specialist, if you develop signs and symptoms in your vision that include:

- loss of vision
- eye redness and irritation
- coloured dots in your vision
- halo (seeing a blurred outline around objects)
- blurred vision

Skin problems

If you notice any changes in your skin while taking this medicine, please talk to your doctor, pharmacist or nurse as soon as possible.

Up to 3 in 100 people taking Mekinist in combination with dabrafenib may develop a different type of skin cancer called *cutaneous squamous cell carcinoma (cuSCC)*. Others may develop a type of skin cancer called *basal cell carcinoma (BCC)*. Usually, these skin changes remain local and can be removed with surgery and treatment with Mekinist and dabrafenib can be continued without interruption.

Some people taking Mekinist in combination with dabrafenib may also notice that new melanomas have appeared. These melanomas are usually removed by surgery and treatment with Mekinist and dabrafenib can be continued without interruption.

Your doctor will check your skin before you start taking dabrafenib, then check it again every month while you are taking this medicine and for 6 months after you stop taking it. This is to look for any new skin cancers.

Your doctor will also check your head, neck, mouth and lymph glands and you will have scans of your chest and stomach area (called CT scans) regularly. You may also have blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

Check your skin regularly whilst taking dabrafenib.

If you notice any of the following:

- new wart
 - skin sore or reddish bump that bleeds or does not heal
 - change of a mole in size or colour
- ➔ **Tell your doctor, pharmacist or nurse as soon as possible** if you get any of these symptoms - either for the first time or if they get worse.

Mekinist as monotherapy or in combination with dabrafenib can cause rash or acne-like rash. Follow your doctor's instructions for what to do to help prevent rash. Tell your doctor or nurse as soon as possible if you get any of these symptoms for the first time or if they get worse.

Contact your doctor immediately if you get a severe skin rash with any of the following symptoms: blisters on your skin, blisters or sores in your mouth, peeling of your skin, fever, redness or swelling of your face, or soles of your feet.

Tell your doctor or nurse as soon as possible if you get any skin rash, or if you have a rash that gets worse.

Muscle pain

Mekinist can result in the breakdown of muscle (rhabdomyolysis). Tell your doctor or nurse if you have any new or worsening symptoms, including:

- muscle pain
- dark urine due to kidney damage

Lung or breathing problems

Mekinist can cause inflammation of the lung (pneumonitis or interstitial lung disease). Tell your doctor or nurse if you have any new or worsening symptoms of lung or breathing problems, including:

- shortness of breath
- cough
- fatigue

The other side effects that you may see when you take Mekinist alone are as follows:

Very common side effects (may affect more than 1 in 10 people):

- Skin rash, acne-like rash, redness of the face, dry or itching skin (see also "Skin problems" earlier in section 4)
- Diarrhoea
- Feeling sick (nausea), being sick (vomiting)
- Constipation
- Stomach ache
- Dry mouth
- Lack of energy or feeling weak or tired

- Swelling of the hands or feet
- Unusual hair loss or thinning
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious
- Fever (high temperature)
- Cough
- Shortness of breath

Common side effects (may affect up to 1 in 10 people):

- Inflammation of hair follicles in the skin
- Skin rash with pus-filled blisters (see also “Skin problems” earlier in section 4)
- Redness, chapping or cracking of the skin
- Infection of the skin (cellulitis)
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Red, painful hands and feet
- Nose bleeds
- Dehydration (low levels of water or fluid)
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Inflammation of the lung (pneumonitis or interstitial lung disease)
- Swelling of the face, localised tissue swelling
- Swelling around the eyes
- Blurred vision
- Eyesight problems (see also “Eye (vision) problems” earlier in section 4)
- Changes in how the heart pumps blood (left ventricular dysfunction) (see also “Heart conditions” earlier in section 4)
- Heart rate that is lower than the normal range and/or a decrease in heart rate
- Abnormal blood test results related to the liver, decreased red blood cells (anaemia), abnormal test related to creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Allergic reaction (hypersensitivity)

Uncommon side effects (may affect up to 1 in 100 people):

- Blockage of the vein draining the eye (retinal vein occlusion) (see also “Eye (vision) problems” earlier in section 4)
- Swelling in the eye caused by fluid leakage (chorioretinopathy) (see also “Eye (vision) problems” earlier in section 4)
- Breakdown of muscle which can cause muscle pain and kidney damage (rhabdomyolysis)
- Swelling of nerves at the back of the eye (papilloedema) (see also “Eye (vision) problems” earlier in section 4)
- Separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) (see also “Eye (vision) problems” earlier in section 4).
- Heart pumping less efficiently, causing shortness of breath, extreme tiredness and swelling in ankles and legs (heart failure)
- A hole (perforation) in the stomach or intestines
- Inflammation of the intestines (colitis)

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

Side effects when Mekinist and dabrafenib are taken together

When you take Mekinist and dabrafenib together you may get any of the side effects given in the lists above, although the frequency may change (increase or decrease).

You may also get **additional side effects due to taking dabrafenib** at the same time as Mekinist in the list below.

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Please read the dabrafenib Package Leaflet for details of the side effects you may get when taking this medicine.

The side effects that you may see when you take Mekinist in combination with dabrafenib are as follows:

Very common side effects (may affect more than 1 in 10 people):

- Dizziness
- Chills
- High temperature
- Rash, dry skin, itching, acne-like problems
- Decreased appetite
- Headache
- High blood pressure
- Cough
- Stomach ache
- Feeling sick (nausea), being sick (vomiting)
- Diarrhoea
- Constipation
- Joint pain, muscle pain, or pain in the hands or feet
- Lack of energy, feeling weak
- Swelling of the hands or feet
- Nasal and throat inflammation
- Bleeding (haemorrhage)
- Infection of the urinary system

Very common side effects that may show up in your blood tests

- Low levels of white blood cells
- Abnormal blood test results related to the liver

Common side effects (may affect up to 1 in 10 people):

- Low blood pressure
- Excessive sweating
- Skin effects including rough scaly patches of skin, skin rash with pus-filled blisters, brown or yellowish thickening of the skin, skin tags, skin cracking, wart-like growths or redness and swelling of the palms, fingers and soles of the feet, cutaneous squamous cell carcinoma (a type of skin cancer), inflammation of the fatty layer underneath the skin, papilloma (a type of skin tumour which is usually not harmful), infection of the skin (cellulitis), inflammation of hair follicles in the skin
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Unusual hair loss or thinning
- Dehydration (low levels of water or fluid)
- Blurred vision, eyesight problems
- Shortness of breath
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Dry mouth
- Flu-like illness
- Muscle spasms
- Swelling of face

- Night sweats
- Heart pumping less efficiently
- Heart rate that is lower than the normal range and/or a decrease in heart rate

Common side effects that may show up in your blood tests

- Decrease in number of blood platelets (cells that help blood to clot)
- Decrease in number of red blood cells (anaemia) and a type of white blood cells (leukopenia)
- Low levels of sodium in the blood
- Increase in some substances (enzymes) produced by the liver
- Increase in creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Increase in blood sugar level
- Low levels of phosphate in the blood

Uncommon side effects (may affect up to 1 in 100 people):

- Allergic reactions
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), inflammation of the eye (uveitis), separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) and swelling around the eyes
- Swelling of the face, localised tissue swelling
- Inflammation of pancreas
- Kidney failure, inflammation of kidneys
- Inflammation of the lung (pneumonitis)
- New primary melanoma
- A hole (perforation) in the stomach or intestines
- Inflammation of the intestines (colitis)

Not known (frequency cannot be estimated from the available data):

- Inflammation of the heart muscle (myocarditis) which can result in breathlessness, fever, palpitations and chest pain.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mekinist

Keep this medicine out of the sight and reach of children.

Do not take Mekinist after the expiry date (EXP) shown on the bottle and carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Store in the original package in order to protect from light and moisture.

Keep the bottle tightly closed. The bottle contains a desiccant in a small cylinder shaped container. Do not remove or eat the desiccant.

The bottle should not be removed from refrigerated conditions for more than 30 days.

Do not throw away medicines in wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mekinist contains

- The active substance is trametinib. Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg or 2 mg of trametinib.
- The other ingredients are
 - Tablet: mannitol (E421), microcrystalline cellulose (E460), hypromellose (E464), croscarmellose sodium (E468), magnesium stearate (E470b), sodium laurilsulfate and colloidal silicon dioxide (E551).
 - Film-coat: hypromellose (E464), titanium dioxide (E171), polyethylene glycol, iron oxide yellow (E172) (for 0.5 mg tablets), polysorbate 80 (E433) and iron oxide red (E172) (for 2 mg tablets).

What Mekinist looks like and contents of the pack

The Mekinist 0.5 mg film-coated tablets are yellow, modified oval, biconvex, with “GS” debossed on one face and “TFC” on the opposing face.

The Mekinist 2 mg film-coated tablets are pink, round, biconvex, with “GS” debossed on one face and “HMJ” on the opposing face.

The film-coated tablets are supplied in opaque white plastic bottles with threaded plastic closures.

The bottles also include a silica gel desiccant in a small cylinder shaped container. The desiccant must be kept inside the bottle and must not be eaten.

One bottle contains either 7 or 30 tablets.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for trametinib, the scientific conclusions of CHMP are as follows:

Cumulatively, there are three reported cases of myocarditis in patients receiving trametinib in combination with dabrafenib. All three cases are reported as causally related to the trametinib/dabrafenib combination and were categorised as serious. One case was fatal and in the two non-fatal cases there was recovery after stopping the trametinib/dabrafenib combination. Based on the evidence presented the PRAC considered that causal relationship between myocarditis and the trametinib/dabrafenib combination is likely in each of the two non-fatal cases based on temporal relationship, positive de-challenge and the absence of compelling alternative causes.

In addition, in the context of myocarditis being a potentially life-threatening event that can be misdiagnosed, the PRAC recommended that the existing warning on left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction should be updated to include specific reference to these cases of myocarditis in order to raise awareness of the possibility of this adverse reaction amongst prescribers, and highlight that stopping treatment resolved the myocarditis.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing trametinib were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for trametinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing trametinib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.