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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Mekinist 0.5 mg tablet
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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Trametinib 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 is 2 mg once daily (QD).

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.

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 Table 1 and Table 2).

Table 1: Dose level reductions

Dose level	**Trametinib dose**
Starting dose	2 mg QD
1st dose reduction	1.5 mg QD
2nd dose reduction	1 mg QD
Dose adjustment for trametinib below 1 mg QD is not recommended.	

Table 2: Dose modification schedule

Grade (CTC-AE)*	**Recommended trametinib dose modification**
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 0-1and 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 QD.

Detailed dosing modifications for selected adverse reactions

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). 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, blurry 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 should be permanently discontinued. 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, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related 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.

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.

Non-Caucasian patients

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

Elderly patients

No initial dose adjustment is required in patients > 65 years of age.
More frequent dose adjustments (see Table 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.

Method of administration

It is recommended that the dose of trametinib is taken at a similar time every day.

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.

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

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

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 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.

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF (see section 4.8). In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 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).

Hypertension

Elevations in blood pressure have been reported in association with trametinib 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 3 trial, 2.4 % (5/211) of patients treated with trametinib 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).

Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib should be permanently discontinued for patients diagnosed with treatment-related ILD or pneumonitis (see sections 4.2 and 4.8).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. The potential for these events in patients with brain metastases or low platelets (< 100,000) 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 (see section 4.8).

Rhabdomyolysis

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

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, have been observed with trametinib . Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). 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, blurry 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). In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued.

Rash

In clinical studies with trametinib, rash has been observed in about 60 % of patients (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Hepatic Events

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

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).

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, 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.

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.

Effect of food on trametinib

Patients should take trametinib 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.

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. 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.

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 judgment, 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 has been evaluated in the integrated safety population of 329 patients with metastatic melanoma treated with trametinib 2 mg QD. 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 (≥ 20 %) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform.

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	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥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.

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
	Uncommon	Cardiac failure
Vascular disorders	Very common	Hypertension
		Haemorrhage[b]
	Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
		Dyspnoea

	Common	Pneumonitis
	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
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

[a] May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances

[b]Events include: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, and post procedural haemorrhage.

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 Annex V.

Description of selected adverse reactions

LVEF Reduction/Left Ventricular Dysfunction
Trametinib has been reported to decrease LVEF. In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 months. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Hypertension
Elevations in blood pressure have been reported in association with trametinib 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 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, dyspnea, 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
In clinical studies with trametinib, rash has been observed in about 60 % of patients. 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).

Haemorrhage
Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. 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).

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

Hepatic Events
Hepatic adverse events have been reported in clinical trials with trametinib. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib therapy, 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 have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

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.

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 one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose. 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.

Determination of BRAF mutation status

Before taking trametinib 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 tumors 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 xenografts 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 QD 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.

BRAF inhibitor 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 QD or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 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 5. Kaplan-Meier curves of investigator assessed overall survival (post-hoc analysis 20 May 2013) is presented in Figure 1.

Table 5: 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) *P* 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).

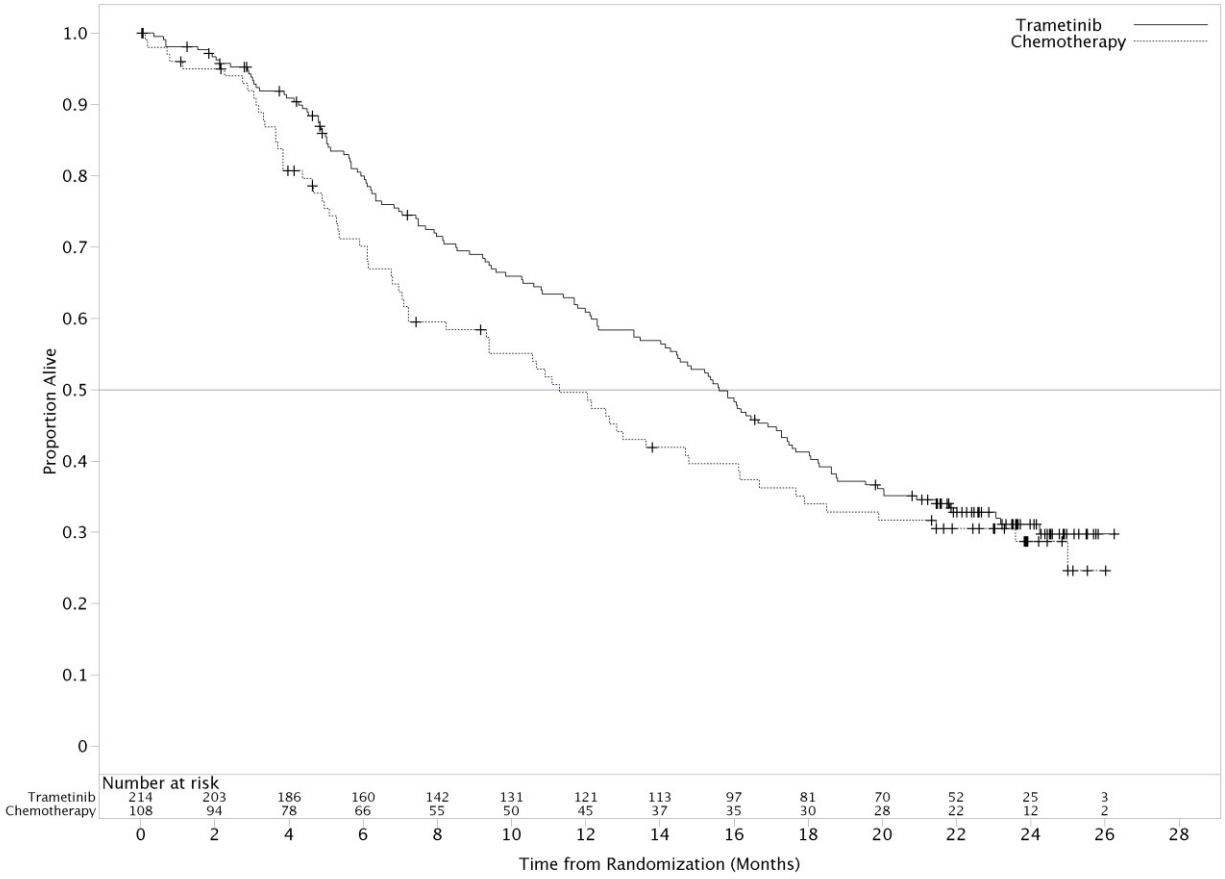
An additional overall survival analysis was undertaken based upon the 20 May 2013 data cut, see Table 6 For October 2011, 47 % of subjects had crossed over, while for May 2013, 65 % of subjects had crossed over.

Table 6: 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 1: Kaplan-Meier curves of overall survival (OS –ad hoc analysis 20 May 2013)



BRAF pre-treated treatment

In a single arm Phase II study, designed to evaluate the objective response rate, safety, and pharmacokinetics following dosing of trametinib at 2.0 mg QD 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 QD 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 hydrolytic enzymes, such as carboxyl-esterases or amidases. However, the enymes(s) involved in the metabolism of trametinib is yet unknown.

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 radiolabeled 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 was 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 Whites.

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 Metabolizing 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 OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low clinical trametinib systemic exposure (0.04 μM) relative to the *in vitro* inhibition or induction values (> 0.34 μM), trametinib is not considered to be a *in vivo* inhibitor of these enzymes/transporters although transient inhibition of BCRP substrates in the gut may occur.

Effects of Other Drugs on Trametinib: *In vivo* and *in vitro* data suggest that the PK of trametinib is unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the efflux transporters P-gp nor BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk.

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. 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 rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver, 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 physeal 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.

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 μg/ml, ≥ 130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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)

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° 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)

EU/1/14/931/01
EU/1/14/931/02

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2014

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.

▼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 1.0 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 1.0 mg of trametinib

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Mekinist 1 mg tablets
White, round, biconvex, film-coated tablets, approximately 7.0 mm, with 'GS' debossed on one face and 'LHE' on the opposing face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Trametinib 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 is 2 mg once daily (QD).

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.

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 Table 1 and Table 2).

Table 1: Dose level reductions

Dose level	**Trametinib dose**
Starting dose	2 mg QD
1st dose reduction	1.5 mg QD
2nd dose reduction	1 mg QD
Dose adjustment for trametinib below 1 mg QD is not recommended.	

Table 2: Dose modification schedule

Grade (CTC-AE)*	**Recommended trametinib dose modification**
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 0-1and 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 QD.

Detailed dosing modifications for selected adverse reactions

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). 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, blurry 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 should be permanently discontinued. 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, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related 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.

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.

Non-Caucasian patients

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

Elderly patients

No initial dose adjustment is required in patients > 65 years of age.
More frequent dose adjustments (see Table 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.

Method of administration

It is recommended that the dose of trametinib is taken at a similar time every day.

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.

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

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

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 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.

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF (see section 4.8). In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 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).

Hypertension

Elevations in blood pressure have been reported in association with trametinib 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 3 trial, 2.4 % (5/211) of patients treated with trametinib 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).

Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib should be permanently discontinued for patients diagnosed with treatment-related ILD or pneumonitis (see sections 4.2 and 4.8).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. The potential for these events in patients with brain metastases or low platelets (< 100,000) 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 (see section 4.8).

Rhabdomyolysis

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

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, have been observed with trametinib . Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). 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, blurry 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). In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued.

Rash

In clinical studies with trametinib, rash has been observed in about 60 % of patients (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Hepatic Events

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

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).

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, 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.

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.

Effect of food on trametinib

Patients should take trametinib 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.

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. 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.

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 judgment, 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 has been evaluated in the integrated safety population of 329 patients with metastatic melanoma treated with trametinib 2 mg QD. 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 (≥ 20 %) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform.

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	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥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.

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
	Uncommon	Cardiac failure
Vascular disorders	Very common	Hypertension
		Haemorrhage[b]
	Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
		Dyspnoea

	Common	Pneumonitis
	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
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

[a] May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances

[b]Events include: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, and post procedural haemorrhage.

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 Annex V.

Description of selected adverse reactions

LVEF Reduction/Left Ventricular Dysfunction

Trametinib has been reported to decrease LVEF. In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 months. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Hypertension
Elevations in blood pressure have been reported in association with trametinib 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 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, dyspnea, 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
In clinical studies with trametinib, rash has been observed in about 60 % of patients. 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).

Haemorrhage
Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. 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).

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

Hepatic Events
Hepatic adverse events have been reported in clinical trials with trametinib. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib therapy, 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 have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

<u>Special populations</u>

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.

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 one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose. 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.

Determination of BRAF mutation status

Before taking trametinib 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 tumors 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 xenografts 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 QD 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.

BRAF inhibitor 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 QD or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 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 5. Kaplan-Meier curves of investigator assessed overall survival (post-hoc analysis 20 May 2013) is presented in Figure 1.

Table 5: 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) *P* 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).

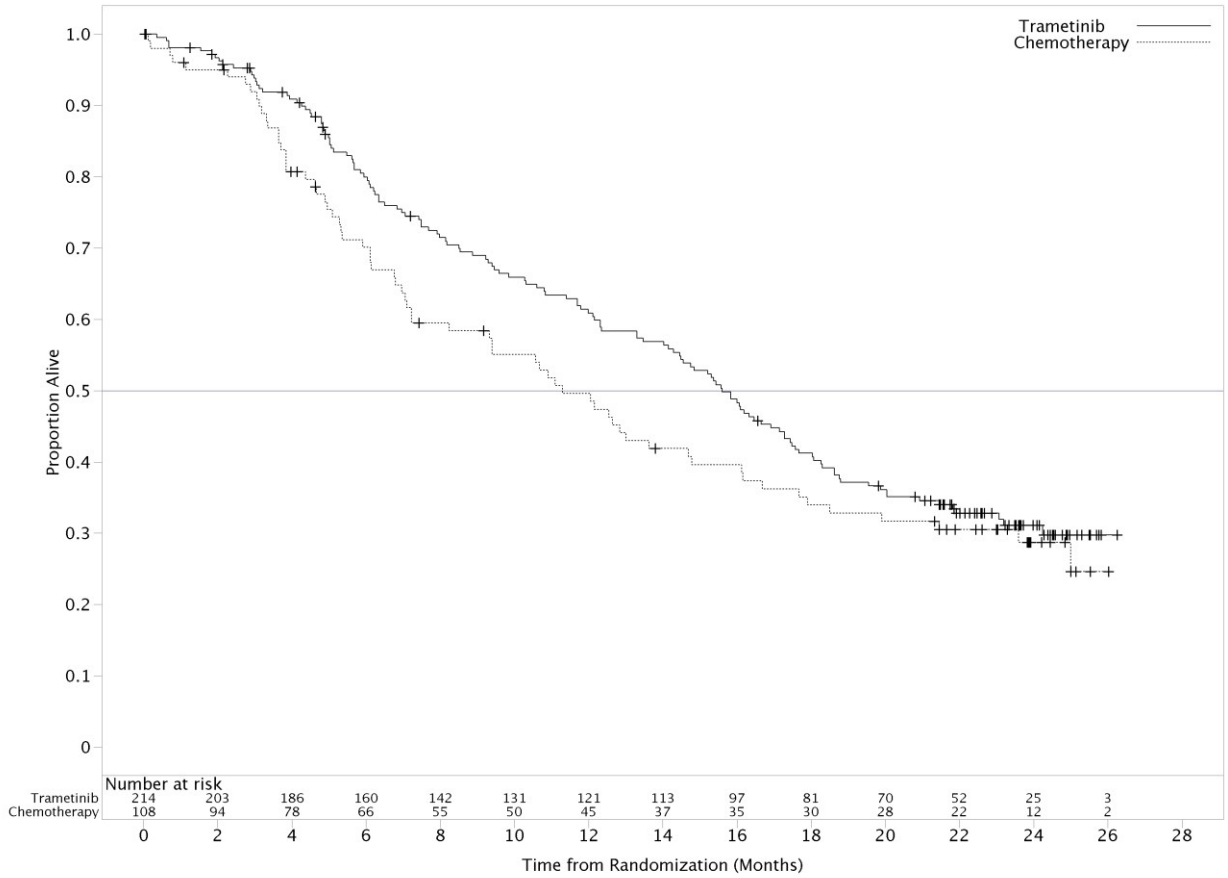
An additional overall survival analysis was undertaken based upon the 20 May 2013 data cut, see Table 6 For October 2011, 47 % of subjects had crossed over, while for May 2013, 65 % of subjects had crossed over.

Table 6: 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 1: Kaplan-Meier curves of overall survival (OS –ad hoc analysis 20 May 2013)



BRAF pre-treated treatment

In a single arm Phase II study, designed to evaluate the objective response rate, safety, and pharmacokinetics following dosing of trametinib at 2.0 mg QD 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 QD 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 hydrolytic enzymes, such as carboxyl-esterases or amidases. However, the enymes(s) involved in the metabolism of trametinib is yet unknown.

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 radiolabeled 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 was 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 Whites.

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 Metabolizing 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 OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low clinical trametinib systemic exposure (0.04 μM) relative to the *in vitro* inhibition or induction values (> 0.34 μM), trametinib is not considered to be a *in vivo* inhibitor of these enzymes/transporters although transient inhibition of BCRP substrates in the gut may occur.

Effects of Other Drugs on Trametinib: *In vivo* and *in vitro* data suggest that the PK of trametinib is unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the efflux transporters P-gp nor BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk.

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. 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 rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver, 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 physeal 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.

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 μg/ml, ≥ 130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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° 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)

EU/1/14/931/03
EU/1/14/931/04

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2014

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.

▼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 2.0 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 2.0 mg of trametinib

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Mekinist 2 mg 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 is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Trametinib 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 is 2 mg once daily (QD).

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.

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 Table 1 and Table 2).

Table 1: Dose level reductions

Dose level	**Trametinib dose**
Starting dose	2 mg QD
1st dose reduction	1.5 mg QD
2nd dose reduction	1 mg QD
Dose adjustment for trametinib below 1 mg QD is not recommended.	

Table 2: Dose modification schedule

Grade (CTC-AE)*	**Recommended trametinib dose modification**
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 0-1and 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 QD.

Detailed dosing modifications for selected adverse reactions

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). 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, blurry 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 should be permanently discontinued. 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, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related 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.

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.

Non-Caucasian patients

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

Elderly patients

No initial dose adjustment is required in patients > 65 years of age.
More frequent dose adjustments (see Table 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.

Method of administration

It is recommended that the dose of trametinib is taken at a similar time every day.

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.

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

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

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 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.

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF (see section 4.8). In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 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).

Hypertension

Elevations in blood pressure have been reported in association with trametinib 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 3 trial, 2.4 % (5/211) of patients treated with trametinib 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).

Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib should be permanently discontinued for patients diagnosed with treatment-related ILD or pneumonitis (see sections 4.2 and 4.8).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. The potential for these events in patients with brain metastases or low platelets (< 100,000) 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 (see section 4.8).

Rhabdomyolysis

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

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, have been observed with trametinib . Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). 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, blurry 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). In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued.

Rash

In clinical studies with trametinib, rash has been observed in about 60 % of patients (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Hepatic Events

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

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).

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, 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.

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.

Effect of food on trametinib

Patients should take trametinib 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.

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. 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.

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 judgment, 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 has been evaluated in the integrated safety population of 329 patients with metastatic melanoma treated with trametinib 2 mg QD. 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 (≥ 20 %) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform.

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	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥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.

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
	Uncommon	Cardiac failure
Vascular disorders	Very common	Hypertension
		Haemorrhage[b]
	Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
		Dyspnoea

	Common	Pneumonitis
	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
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

[a] May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances

[b]Events include: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, and post procedural haemorrhage.

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 Annex V.

Description of selected adverse reactions

LVEF Reduction/Left Ventricular Dysfunction

Trametinib has been reported to decrease LVEF. In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 months. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Hypertension
Elevations in blood pressure have been reported in association with trametinib 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 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, dyspnea, 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
In clinical studies with trametinib, rash has been observed in about 60 % of patients. 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).

Haemorrhage
Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ), have occurred in patients taking trametinib. 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).

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

Hepatic Events
Hepatic adverse events have been reported in clinical trials with trametinib. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib therapy, 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 have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

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.

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 one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose. 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.

Determination of BRAF mutation status

Before taking trametinib 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 tumors 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 xenografts 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 QD 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.

BRAF inhibitor 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 QD or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 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 5. Kaplan-Meier curves of investigator assessed overall survival (post-hoc analysis 20 May 2013) is presented in Figure 1.

Table 5: 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) *P* 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).

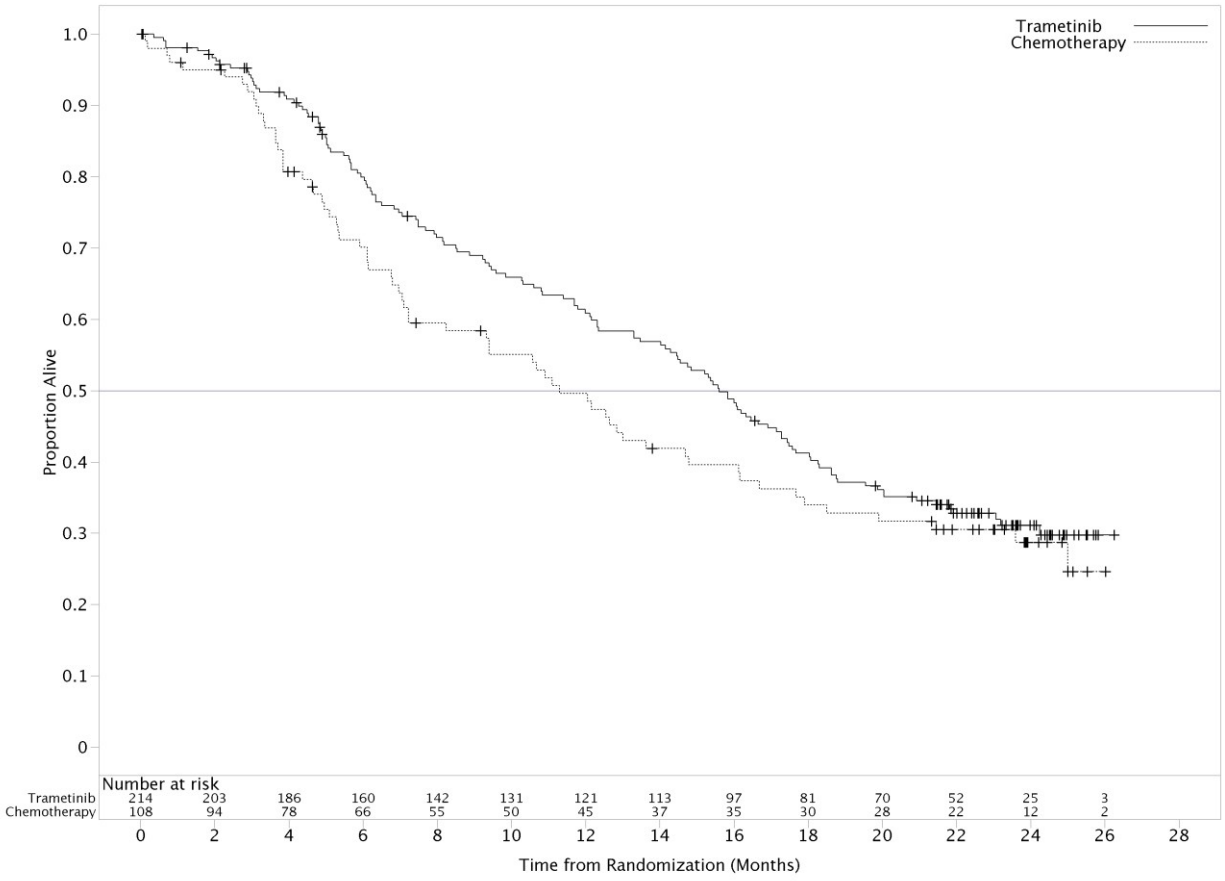
An additional overall survival analysis was undertaken based upon the 20 May 2013 data cut, see Table 6 For October 2011, 47 % of subjects had crossed over, while for May 2013, 65 % of subjects had crossed over.

Table 6: 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 1: Kaplan-Meier curves of overall survival (OS –ad hoc analysis 20 May 2013)



BRAF pre-treated treatment

In a single arm Phase II study, designed to evaluate the objective response rate, safety, and pharmacokinetics following dosing of trametinib at 2.0 mg QD 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 QD 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 hydrolytic enzymes, such as carboxyl-esterases or amidases. However, the enymes(s) involved in the metabolism of trametinib is yet unknown.

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 radiolabeled 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 was 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 Whites.

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 Metabolizing 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 OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low clinical trametinib systemic exposure (0.04 μM) relative to the *in vitro* inhibition or induction values (> 0.34 μM), trametinib is not considered to be a *in vivo* inhibitor of these enzymes/transporters although transient inhibition of BCRP substrates in the gut may occur.

Effects of Other Drugs on Trametinib: *In vivo* and *in vitro* data suggest that the PK of trametinib is unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the efflux transporters P-gp nor BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk.

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. 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 rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver, 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 physeal 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.

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 μg/ml, ≥ 130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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° 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)

EU/1/14/931/05
EU/1/14/931/06

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2014

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON- 0.5mg film-coated tablets

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

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° 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/1/14/931/01
EU/1/14/931/02

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 0.5 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL- 0.5 mg film-coated tablets

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

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° 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/1/14/931/01
EU/1/14/931/02

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON- 1 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 1 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 1 mg trametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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° 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/1/14/931/03
EU/1/14/931/04

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 1 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL- 1 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 1 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 1 mg trametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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° 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/1/14/931/03
EU/1/14/931/04

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON- 2 mg film-coated tablets

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

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° 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/1/14/931/05
EU/1/14/931/06

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 2 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL- 2 mg film-coated tablets

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

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° 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/1/14/931/05
EU/1/14/931/06

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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 1 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.

What is in this leaflet

1. What Mekinist is and what it is used for

Mekinist is a medicine that contains the active substance *trametinib*. It is used 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.
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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 of this package leaflet).

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**.

Check with your doctor if you think these 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.

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, lightheaded, shortness of breath or swelling in the legs. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

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.

→ **Read the information 'Possible serious side effects' in Section 4 of this leaflet.**

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 How to take Mekinist).*

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 your 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.
- If you do become pregnant while you're taking Mekinist, tell your doctor immediately.

- Birth control using hormones (such as pills, injections or patches) may not work as well if you are taking Mekinist. You need to use another reliable method of birth control (such as barrier methods) while you are taking Mekinist. Ask your doctor, nurse or pharmacist for advice.

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.

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 Section 2 and Section 4. Posible side effects*).
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

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

The usual dose of Mekinist is one 2 mg tablet once a day.
Your doctor may decide to lower the dose if you get side effects.

Don’t take any 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 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 than12 hours late, skip that dose and take your next dose at the usual time. Then carry on taking your tablet at regular times as usual.
Do not take a double dose to make up for a missed dose.

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.

Don’t stop taking Mekinist without advice
Take Mekinist for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

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

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

Rash or other skin problems
Mekinist 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), which can lead to 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

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 'Rash or other 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 'Rash and other 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 problems', earlier in Section 4*)
- Changes in how the heart pumps blood (left ventricular dysfunction) (*see also 'Heart conditions', earlier in Section 4)*
- 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 problems', earlier in Section 4)*
- Swelling in the eye caused by fluid leakage (chorioretinopathy) (*see also 'Eye 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 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 problems', earlier in Section 4)*.
- Heart pumping less efficiently, causing shortness of breath, extreme tiredness and swelling in ankles and legs (heart failure)

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

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, 1 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 1 mg film-coated tablets are white, round, biconvex, with ‘GS’ debossed on one face and ‘LHE’ 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 high density polyethylene (HDPE) bottles with threaded polypropylene 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 web site: http://www.ema.europa.eu.

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