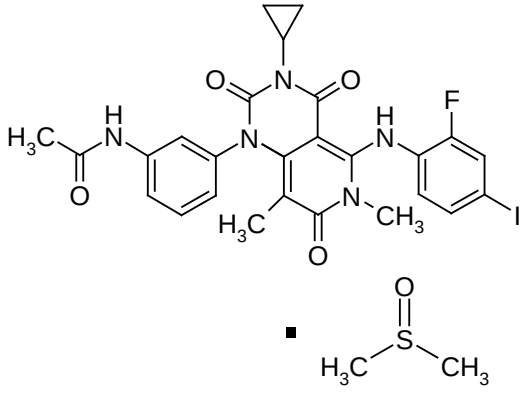
MEKINIST® TABLETS

PRODUCT INFORMATION

NAME OF THE MEDICINE

Trametinib dimethyl sulfoxide



It has the molecular formula $C_{26}H_{23}FIN_5O_4.C_2H_6OS$ and a molecular weight of 693.5.

CAS Registry Number: 1187431-43-1

DESCRIPTION

Trametinib dimethyl sulfoxide is a polycyclic, nitrogen containing heterocycle also possessing aromatic halide and amide functionality, and is a dimethyl sulfoxide solvate. The calculated partition coefficient of trametinib dimethyl sulfoxide is 4.99.

The chemical name for trametinib dimethyl sulfoxide is N-(3- {3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2 ,4,7-trioxo-3,4,6,7 -tetrahydropyrido[4,3-d]pyrimidin-1 (2H)-yl } phenyl)acetamide.

Trametinib dimethyl sulfoxide is a white to almost white powder. It is almost insoluble in water.

The MEKINIST tablets contain trametinib dimethyl sulfoxide equivalent to 0.5, 1 or 2 mg of trametinib as the active ingredient. The tablets also contain mannitol, cellulose - microcrystalline, hypromellose, croscarmellose sodium, magnesium stearate, sodium lauryl sulphate, silica -colloidal anhydrous and Opadry 03B120006 Yellow (0.5 mg tablet only), Opadry OY-S-28876 White (1 mg tablet only) and Opadry YS-1-14762-A Pink (2 mg tablet only).

PHARMACOLOGY

Monotherapy:

Trametinib is a reversible allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are critical 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 and stimulates tumour cell growth. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of $BRAF^{V600}$ mutant melanoma cell lines and demonstrates anti-tumour effects in $BRAF^{V600}$ mutant melanoma animal models.

Combination with dabrafenib:

Dabrafenib is an ATP-competitive inhibitor of BRAF V600 mutant kinases and wild type BRAF and CRAF kinases. Mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. Dabrafenib and trametinib inhibit two critical kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. Combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation positive melanoma cell lines in vitro and delays the emergence of resistance in vivo in BRAF V600 mutation positive melanoma xenografts.

Pharmacodynamic Effects

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

QT Prolongation

The QT prolongation potential of trametinib was assessed as part of the first time in human study to determine the relationship between the independently manually-read QTc interval and plasma concentrations of trametinib using a nonlinear mixed effects model. Data were available in 50 subjects with a total of 498 matched QTc values. Based on the concentration-QTc analysis, trametinib showed no apparent potential to alter the QTc interval. At the mean C_{max} value observed at the recommended dose of 2 mg once daily, the median increase in QTc is 2.2 msec (90% CI: 0.2, 4.0).

Determination of BRAF mutation status

In the Phase II and III clinical trials, screening for eligibility required central testing for $BRAF^{V600}$ mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO) developed by Response Genetics Inc. (RGI). The RGI IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with $BRAF^{V600E \text{ or } V600K}$ mutation positive tumours were eligible for study participation.

Pharmacokinetics:

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, geometric mean C_{max}, $AUC_{(0-t)}$ 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 was low (<28%).

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 DOSAGE AND ADMINISTRATION)*.

Distribution

Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of 1060 L determined following administration of a 5μg IV microdose.

Metabolism

In vitro studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. The deacetylation is mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases.

Following a single dose of [^{14}C]-trametinib, about 50% of circulating radioactivity is represented as parent. However, based on metabolite profiling after repeat dosing of trametinib, ≥75% of drug related material in plasma is parent.

Excretion

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 5.3 days (range 3.4-9.0) after single dose administration. Steady-state is generally achieved by Day 15. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery is low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long half-life. Faecal excretion is the major route of elimination after [^{14}C]-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

The pharmacokinetics of trametinib were characterised in 64 patients enrolled in clinical trials with trametinib who had mild hepatic impairment (defined by National Cancer Institute classification) using a population pharmacokinetic analysis. Trametinib oral clearance and thus exposure to trametinib was not significantly different in these patients relative to patients with normal hepatic function. No data are available in patients with moderate or severe hepatic impairment *(*see DOSAGE AND ADMINISTRATION*)*.

Renal Impairment

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

Elderly

Based on the population pharmacokinetics analysis, age had no relevant clinical effect on trametinib pharmacokinetics.

Children

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

Drug Interactions

Effects of Trametinib on Drug Metabolising Enzymes and Transporters: There are limited in vivo data about the effect of trametinib on the pharmacokinetics of other drugs. Considerations of both the low efficacious dose and in vitro data suggest that trametinib is unlikely to affect the pharmacokinetics of other drugs. 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 efficacious dose and clinical trametinib systemic exposure (0.04 μM) relative to the *in vitro* inhibition or induction values (IC_{50} or EC_{50} ≥0.34 μM), trametinib is not considered to be *in vivo* inhibitor of these enzymes/transporters. Repeat dose administration of once-daily 2 mg trametinib had no effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate, while a small increase in exposure was noted with repeat dose dabrafenib as discussed below.

Effects of Other Drugs on Trametinib: In vitro data suggest that trametinib is unlikely to be affected by other drugs. Trametinib is not a substrate of the efflux transporters P-gp or BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk. Trametinib is a substrate of CYP3A4, but this plays a minor role in the metabolism of trametinib. Following concomitant administration of trametinib and dabrafenib, a CYP3A4 inducer, repeat-dose C_{max} and AUC of trametinib were generally consistent with the exposure observed in monotherapy, although a small decrease in bioavailability was estimated as discussed below.

Combination with Dabrafenib: Co-administration of repeat dosing of dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in an increase of 16% and 23% for dabrafenib C_{max} and AUC, respectively. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 16%, was estimated when trametinib is administered in combination with dabrafenib using a population pharmacokinetic analysis.

CLINICAL TRIALS

Monotherapy

The efficacy and safety of MEKINIST in patients with BRAF mutant melanoma (V600E and V600K) were evaluated in a randomised open label study (MEK114267). Measurement of patients $BRAF^{V600}$ mutation status was required. Screening included central testing of BRAF mutation (V600E and V600K) using a BRAF mutation assay conducted on the most recent tumour sample available.

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 MEKINIST 2 mg once daily 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 MEKINIST 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 MEKINIST arm after independent confirmation of progression. A total of 51 (47%) of patients with confirmed disease progression in the chemotherapy arm, crossed over to receive MEKINIST.

Baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population. In the ITT population, the majority of patients were male (54%) and all were Caucasian (100%). The median age was 54 years (22% were ≥65 years), most patients (64%) had ECOG performance status of 0, and 11 patients (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.

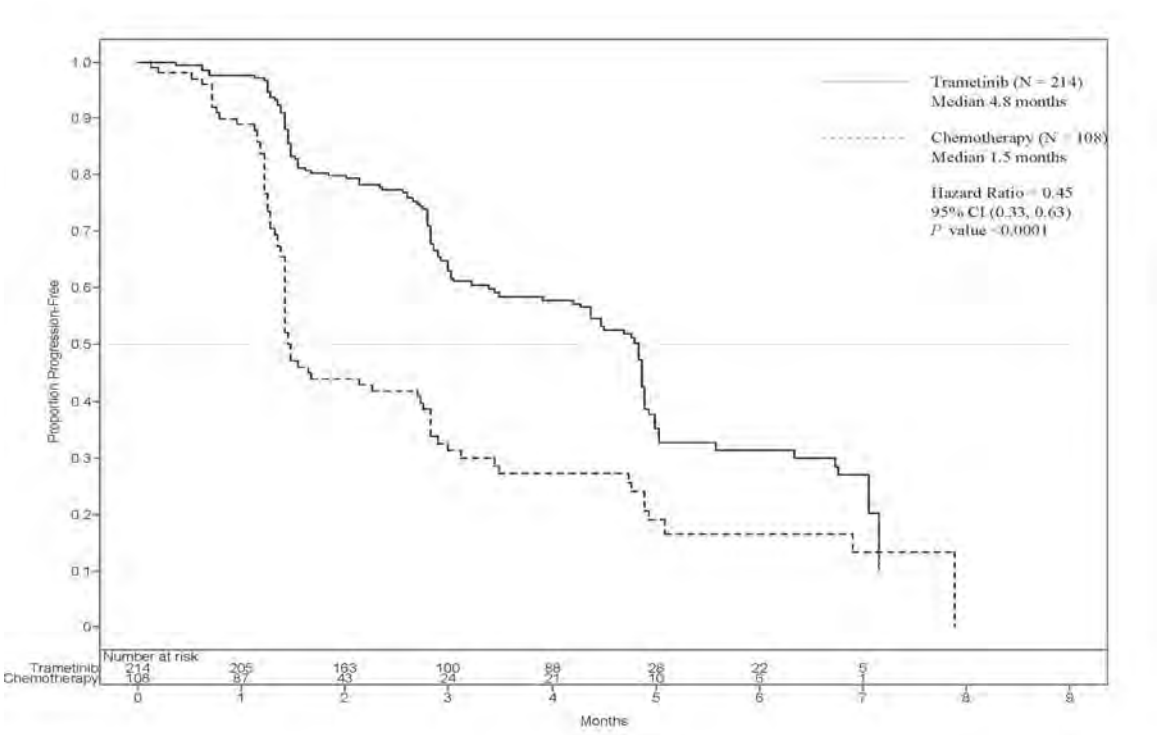
The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 1.

Table 1. Investigator-Assessed Efficacy Results (ITT Population)

Endpoint	**MEKINIST**	**Chemotherapy[a]**
Progression-Free Survival	**(N = 214)**	**(N = 108)**
Median , months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95% CI)	0.45 (0.33, 0.63)	
P value	<0.0001	
Overall Survival		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio (95% CI)	0.54 (0.32, 0.92)	
P value	0.0136	
Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
Overall Response Rate (%)	22	8

At the time of the data cut off, 51 patients (47%) on the chemotherapy arm had crossed over to the MEKINIST arm after disease progression. These patients are included in the OS analysis.
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.

Figure 1. Investigator-Assessed Progression-Free Survival (ITT population)



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).

BRAF pre-treated treatment

In a single arm Phase II study, designed to evaluate the objective response rate, safety and pharmacokinetics following dosing of MEKINST at 2.0 mg QD in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma, 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, MEKINIST did not demonstrate clinical activity in patients who progressed on a prior BRAF inhibitor therapy in one of the cohorts *(*see INDICATIONS*)*.

Combination with dabrafenib

In an open-label study (BRF113220), the safety, pharmacokinetics, pharmacodynamics and clinical activity of MEKINIST and dabrafenib in combination were evaluated in patients with BRAF V600 mutation-positive melanoma. This study had four parts, A-D:

- Part A: drug / drug interaction study (n=8),
- Part B: dose escalation and expansion study (n=135),
- Part C: see description below
- Part D: pharmacokinetic and safety evaluation of Hydroxy Propyl Methyl Cellulose (HPMC) dabrafenib capsules (n=110).

The determination of BRAF mutation positive status was required and was established by institutional laboratory for all patients enrolled in Parts A-D.

Part C was an open-label randomised three-arm phase II study to assess safety and efficacy of dabrafenib at 150 mg given twice daily in combination with two different doses of MEKINIST (1 mg once daily and 2 mg once daily) relative to dabrafenib alone (150 mg twice daily) in 162 patients. The primary efficacy endpoints were PFS, ORR, and duration of response. Patients on the dabrafenib monotherapy arm were permitted to cross-over to the full-dose combination arm (150 mg dabrafenib plus 2 mg MEKINIST) upon progression. A total of 43 patients (81%) in the dabrafenib monotherapy arm with disease progression crossed over to receive dabrafenib 150 mg and MEKINIST 2 mg combination.

Baseline characteristics were balanced between treatment groups. The majority of patients were male (57%) and Caucasian (>99%). The median age was 53 years, most patients (66%) had ECOG performance status of 0, and 13 patients (8%) had history of brain metastases in all treatment arms. Most patients (85%) in all treatment arms had BRAF V600E mutation and 15% of patients had BRAF V600K.

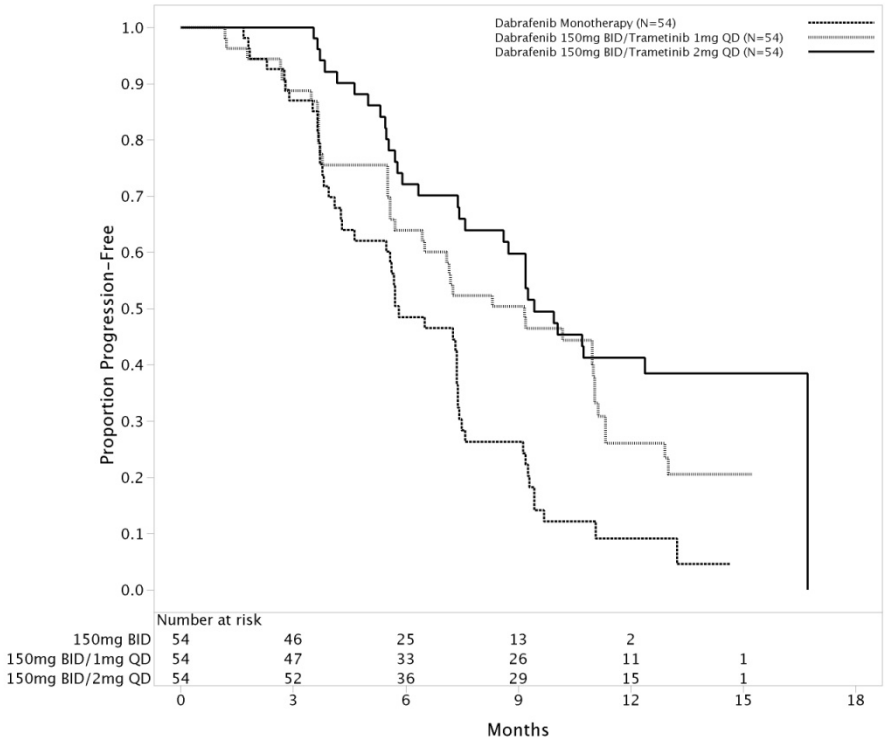
The results of efficacy endpoints for part C based on investigator assessment are presented in Table 2; with Kaplan-Meier curves of investigator-assessed progression-free survival presented in Figure 2.

Table 2 Investigator-Assessed Efficacy Endpoints (ITT population)

Endpoint	**Dabrafenib 150 mg BID Monotherapy (N = 54)**	**Dabrafenib 150 mg BID plus MEKINIST 1mg QD Combination (N = 54)**	**Dabrafenib 150 mg BID plus MEKINIST 2mg QD Combination (N = 54)**
Progression-Free Survival			
Median PFS (months)	5.8	9.2	9.4
(95% CI)	(4.6, 7.4)	(6.4, 11.0)	(8.6, 16.7)
Hazard Ratio		0.56	0.39
(95% CI)		(0.37, 0.87)	(0.25, 0.62)
P value		0.0057	<0.0001
Overall Response Rate (%)	54	50	76
(95% CI)	(39.6, 67.4)	(36.1, 63.9)	(62.4, 86.5)
P value		0.7730	0.0264
CR	4	6	9
PR	50	44	67
Median Duration of Response (months)	5.6	9.5	10.5

BID = twice daily; QD = once daily; PFS = Progression-free survival; CI = confidence interval; CR = Complete response; PR = Partial response

Figure 2 Investigator-Assessed Progression-Free Survival (ITT population)



The investigator-assessed ORR, Duration of Response, and PFS were consistent in the subgroup of patients with BRAF V600E and BRAF V600K mutation positive melanoma receiving 150 mg dabrafenib plus 2 mg MEKINIST combination.

A retrospective blinded independent committee review (BICR) was conducted and had the following results: 61% ORR (95 CI: 46.9%, 74.1%; *P* = 0.1486) for the 150 mg dabrafenib plus 2 mg MEKINISTcombination, 39% (95% CI: 25.9, 53.1; *P* = 0.5008) for the 150 mg dabrafenib plus 1 mg MEKINIST combination, and 46% (95 % CI: 32.6%, 60.4%) for the dabrafenib monotherapy group. The median PFS was 9.2 months (95% CI: 7.6, NR; *P* = 0.0121) and 8.3 months (95% CI: 5.6, 11.3; *P* = 0.1721) for patients treated with 150 mg dabrafenib plus 2 mg MEKINIST combination and 150 mg dabrafenib plus 1 mg MEKINIST combination arms respectively, and 7.3 months (95% CI: 5.5, 9.4) for patients treated with dabrafenib monotherapy.

Prior BRAF inhibitor therapy

Part B of this open-label study included a cohort of 26 patients that had progressed on a BRAF inhibitor. The combination of 150 mg dabrafenib with 2 mg MEKINIST demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor. The Investigator-assessed ORR was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 43 patients who crossed over from dabrafenib monotherapy to the combination of 150 mg dabrafenib plus 2 mg

MEKINIST in Part C of this study. In these patients a 9 % (95% CI: 2.6, 22.1) ORR was observed with a median PFS of 3.6 months (95% CI: 1.8, 3.9).

INDICATIONS

MEKINIST in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

MEKINIST as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.

MEKINIST as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see CLINICAL TRIALS).

CONTRAINDICATIONS

MEKINIST is contraindicated in patients with known hypersensitivity to the active substance trametinib dimethyl sulfoxide or any of the excipients (See DESCRIPTION).

PRECAUTIONS

BRAF V600 testing

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for MEKINIST monotherapy and in combination with dabrafenib. Patients enrolled in the melanoma clinical studies were required to have BRAF V600 mutation status measured. The safety and efficacy of MEKINIST have not been evaluated in patients whose melanoma tested negative for the BRAF V^{600} mutation.

Non-Cutaneous Malignancies

New primary malignancies can occur when MEKINIST is used in combination with dabrafenib and with dabrafenib as a single agent [refer to Full Prescribing Information for dabrafenib].

Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms (refer to the Product Information for dabrafenib). In patients receiving MEKINIST in combination with dabrafenib, four cases of non-cutaneous malignancies were identified: KRAS mutation-positive pancreatic adenocarcinoma (n = 1), recurrent NRAS mutation-positive colorectal carcinoma (n = 1), head and neck carcinoma (n = 1), and glioblastoma (n = 1). Monitor patients receiving the combination closely for signs or symptoms of non-cutaneous malignancies. If used in combination with dabrafenib, no dose modification is required for MEKINIST in patients who develop non-cutaneous malignancies. Permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies (see DOSAGE AND ADMINISTRATION).

Haemorrhage

Haemorrhages, including major haemorrhages defined as symptomatic bleeding in a critical area or organ, can occur when MEKINIST is used in combination with dabrafenib.

In Study BRF113220, treatment with MEKINIST in combination with dabrafenib resulted in an increased incidence and severity of any haemorrhagic event: 16% (9/55) of patients

treated with MEKINIST in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. The major haemorrhagic events of intracranial or gastric haemorrhage occurred in 5% (3/55) of patients treated with MEKINIST in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial haemorrhage was fatal in two (4%) patients receiving the combination of MEKINIST and dabrafenib.

Permanently discontinue MEKINIST, and also permanently discontinue dabrafenib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve. Withhold MEKINIST for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level. Withhold dabrafenib for Grade 3 haemorrhagic events; if improved resume at a lower dose level (see DOSAGE AND ADMINISTRATION).

Cardiomyopathy

Across clinical trials of MEKINIST at the recommended dose (N = 329), 11% of patients developed evidence of cardiomyopathy (decrease in left ventricular ejection fraction, or LVEF, below institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline) and 5% demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.

LVEF should be evaluated by echocardiogram or multigated acquisition (MUGA) scan in all patients prior to initiation of treatment with MEKINIST, one month after initiation of therapy, and then at approximately 3 monthly intervals while on treatment.

MEKINIST 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). If MEKINIST is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with MEKINIST may be restarted, but the dose should be reduced by one dose level with careful monitoring.

With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover MEKINIST should be permanently discontinued. If MEKINIST is being used in combination with dabrafenib then therapy with dabrafenib should be withheld and resumed at the same dose upon recovery of cardiac function (see DOSAGE AND ADMINISTRATION).

Ocular Adverse Events

The data from clinical trials demonstrates that when all reported ocular events are pooled, there was a higher reported rate in the subjects treated with combination therapy than monotherapy (20% vs 13%, respectively). The median exposure time for combination therapy was substantially longer than MEKINIST monotherapy (6.41 vs. 3.84 months, respectively).

Disorders associated with visual disturbance, including retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO), have been observed with MEKINIST as monotherapy and in combination with dabrafenib. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with MEKINIST (see ADVERSE EFFECTS). If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on MEKINIST therapy, a prompt ophthalmological assessment is recommended.

Retinal Pigment Epithelial Detachment (RPED)

Retinal pigment epithelial detachments (RPED) can occur during treatment with MEKINIST. Across all clinical trials of MEKINIST, the incidence of RPED was 0.8% (14/1749). Retinal

detachments were often bilateral and multifocal, occurring in the macular region of the retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range: 3 to 71 days) following the interruption of dosing with MEKINIST, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

If RPED is diagnosed, follow the dose modification schedule in Table 9 (see DOSAGE AND ADMINISTRATION).

Retinal Vein Occlusion (RVO)

Across all clinical trials of MEKINIST, the incidence of RVO was 0.2% (4/1749). An RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented retinal vein occlusion.

Interstitial lung disease (ILD)/Pneumonitis:

Any diagnosis of ILD or pneumonitis warrants immediate discontinuation of MEKINIST.

In a Phase 3 trial, 2% (5/211) of patients treated with MEKINIST monotherapy developed ILD or pneumonitis; all five patients required hospitalisation. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days).

Withhold MEKINIST 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 MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis. If MEKINIST is used in combination with dabrafenib, do not modify the dose of dabrafenib.

Pyrexia

See full prescribing information for dabrafenib PRECAUTIONS.

Pyrexia was reported in the clinical trials with MEKINIST monotherapy and in combination with dabrafenib. The incidence and severity of pyrexia are increased when MEKINIST is used in combination with dabrafenib (see ADVERSE EFFECTS). In patients who received the combination dose of dabrafenib 150 mg twice daily and MEKINIST 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About half of the patients who experienced pyrexia had a single event. Pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency. Renal failure was reported in 7% of patients who received the combination dose of dabrafenib 150 mg twice daily and MEKINIST 2 mg once daily, a higher frequency than observed in dabrafenib monotherapy patients (<1%), and was often seen in the context of pyrexia and dehydration.

For management of pyrexia see DOSAGE AND ADMINISTRATION.

Serious Skin Toxicity

Serious skin toxicity can occur when MEKINIST is administered as a single agent or when used in combination with dabrafenib. Serious skin toxicity can also occur with dabrafenib as a single agent (refer to Product Information for dabrafenib)

In MEK114267, the overall incidence of any skin toxicity, the most common of which were rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema, was 87% in patients treated with MEKINIST and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients treated with MEKINIST. Skin toxicity requiring hospitalization occurred in 6% of patients treated with MEKINIST, most commonly for secondary infections of the skin requiring intravenous antibiotics or severe skin toxicity without secondary infection. In comparison, no patients treated with chemotherapy required hospitalization for severe skin toxicity or infections of the skin. The median time to onset of skin toxicity in patients treated with MEKINIST was 15 days (range: 1 to 221 days) and median time to resolution of skin toxicity was 48 days (range: 1 to 282 days). Reductions in the dose of MEKINIST were required in 12% and permanent discontinuation of MEKINIST was required in 1% of patients with skin toxicity.

In BRF113220, the incidence of any skin toxicity was similar for patients receiving MEKINIST in combination with dabrafenib (65% [36/55]) compared with patients receiving dabrafenib as a single agent (68% [36/53]). The median time to onset of skin toxicity in patients treated with MEKINIST in combination with dabrafenib was 37 days (range: 1 to 225 days) and median time to resolution of skin toxicity was 33 days (range: 3 to 421 days). No patient required dose reduction or permanent discontinuation of MEKINIST or dabrafenib for skin toxicity.

Across clinical trials of MEKINIST administered in combination with dabrafenib (n = 202), severe skin toxicity and secondary infection of the skin requiring hospitalization occurred in 2.5% (5/202) of patients treated with MEKINIST in combination with dabrafenib.

Withhold MEKINIST, and dabrafenib if used in combination, for intolerable or severe skin toxicity until further assessment (see Dosage and Administration). MEKINIST and dabrafenib may be resumed at a lower dose level in patients with improvement or recovery from skin toxicity within three weeks.

Hepatic Events

Hepatic adverse events have been reported in clinical trials with MEKINIST as monotherapy and in combination with dabrafenib. It is recommended that patients receiving treatment with MEKINIST monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6 months after treatment initiation with MEKINIST (see ADVERSE EFFECTS).

Effects on Fertility

There is no information on the effect of MEKINIST on human fertility. In animals, no fertility studies have been performed, but an increase in ovarian cystic follicles and decrease in corpora lutea were seen in female rats at 0.016 mg/kg/day (0.3 times the clinical exposure based on AUC. MEKINIST may impair female fertility in humans. However, in rat and dog toxicity studies up to 3 weeks in duration, there were no treatment-related effects observed on male reproductive tissues.

Men taking MEKINIST in combination with dabrafenib: Male fertility studies in animals with the trametinib/dabrafenib combination have not been conducted. Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. See prescribing information for dabrafenib for more detail.

Use in Pregnancy (Category D)

There are no adequate and well-controlled studies of MEKINIST in pregnant women. Animal studies with trametinib have shown reproductive toxicity. MEKINIST should not be administered to pregnant women or nursing mothers. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following

discontinuation of MEKINIST. When MEKINIST is used in combination with dabrafenib, patients should use a non-hormonal method of contraception since dabrafenib can render hormonal contraceptives ineffective. If MEKINIST is used during pregnancy, or if the patient becomes pregnant while taking MEKINIST, the patient should be informed of the potential hazard to the foetus.

In embryofetal development studies in rats, maternal and developmental toxicity (decreased foetal weights) were seen at ≥0.031 mg/kg/day (approximately 0.3 times human clinical exposure based on AUC). In pregnant rabbits, maternal and developmental toxicity (decreased foetal body weight and increased incidence of ossification defects) was seen at ≥0.039 mg/kg/day (approximately 0.1 times human clinical exposure based on AUC).

Use in Lactation:

It is not known whether MEKINIST is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the suckling child cannot be excluded. A decision should be made whether to discontinue nursing or discontinue MEKINIST taking into account the importance of the MEKINIST to the mother.

Paediatric Use:

The safety and efficacy of MEKINIST has not been yet established in children and adolescents (< 18 years).

Use in the Elderly:

No initial dose adjustments are required in patients over 65 years of age (see PHARMACOKINETICS).

More frequent dose adjustments (see Table 7 and Table 8) may be required in patients over 65 years of age (see ADVERSE EFFECTS). Across clinical trials of MEKINIST administered in combination with dabrafenib (n = 202), adverse events resulting in dose interruption were reported for 71% of those aged ≥65 years as compared to 60% of those <65 years, while adverse events resulting in dose reduction occurred in 64% of those aged ≥65 years as compared to 44% of those <65 years.

Clinical trials of MEKINIST administered as a single agent or in combination with dabrafenib did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In MEK114267, 49 patients (23%) were 65 years of age and older, and 9 patients (4%) were 75 years of age and older. Across clinical trials of MEKINIST administered in combination with dabrafenib (n = 202), 42 patients (21%) were 65 years of age and older, and 12 patients (6%) were 75 years of age and older.

Genotoxicity:

Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Carcinogenicity:

Carcinogenicity studies with MEKINIST have not been conducted.

Effects on ability to drive and use machines

There have been no studies to investigate the effect of MEKINIST on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of MEKINIST. The clinical status of the patient and the adverse event profile of MEKINIST should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

INTERACTIONS WITH OTHER MEDICINES

Monotherapy

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. A small, non-clinically relevant, decrease in trametinib bioavailability (16%) was noted with co-administration with a CYP3A4 inducer (see PHARMACOKINETICS).

Based on in vitro data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters (see PHARMACOKINETICS).

Combination with dabrafenib

Co-administration of repeat dosing of dabrafenib 150 mg twice daily and MEKINIST 2 mg once daily resulted in no clinically meaningful changes in dabrafenib or trametinib C_{max} and AUC (see PHARMACOLOGY).

See Product Information for dabrafenib for guidelines on drug interactions associated with dabrafenib monotherapy.

ADVERSE EFFECTS

Clinical trial data

Monotherapy:

The safety of MEKINIST monotherapy has been evaluated in an integrated population of 329 patients with metastatic melanoma treated with MEKINIST 2 mg orally once daily. Of these patients, 211 patients were treated with MEKINIST for BRAF mutant melanoma in a randomized open label study (see CLINICAL TRIALS). The most common adverse reactions (≥ 20%) for MEKINIST include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical trials with MEKINIST, adverse reactions of diarrhoea and rash were managed with appropriate supportive care *(*see DOSAGE AND ADMINISTRATION).

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 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data.

Table 3. Adverse Reactions With MEKINIST Monotherapy

Infections and Infestations	
Common	Folliculitis Paronychia Cellulitis Rash pustular
Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity *May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances*
Metabolism and Nutrition Disorders	
Common	Dehydration
Eye disorders	
Common	Vision blurred Periorbital oedema Visual impairment
Uncommon	Chorioretinopathy Retinal vein occlusion Papilloedema Retinal detachment
Cardiac disorders	
Common	Left ventricular dysfunction Ejection fraction decreased
Uncommon	Cardiac failure
Vascular Disorders	
Very common	Hypertension Haemorrhage[a]
Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough Dyspnoea
Common	Epistaxis Pneumonitis
Uncommon	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhoea Nausea Vomiting Constipation Abdominal pain Dry Mouth
Common	Stomatitis
Hepatobiliary disorders	
Common	Aspartate aminotransferase increased Alanine aminotransferase increased Blood alkaline phosphatase increased

Skin and Subcutaneous Tissue Disorders	
Very common	Rash Dermatitis acneiform Dry skin Pruritus Alopecia
Common	Skin chapped Erythema Palmar-plantar erythrodysaesthesia syndrome Skin fissures
Musculoskeletal and connective tissue disorder	
Common	Blood creatine phosphokinase increased
Uncommon	Rhabdomyolysis
General disorders	
Very common	Fatigue Oedema peripheral Pyrexia
Common	Face oedema Mucosal inflammation Asthenia

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

Table 4 lists the very common adverse events (≥10%) reported in patients receiving MEKINIST.

Table 4. Adverse Events (%) Occurring in ≥10% of Patients Treated With MEKINIST

	MEKINIST (N = 211)			**Chemotherapy (N = 99)**		
Events	**All Grades[a]**	**Grade 3**	**Grade 4**	**All Grades[a]**	**Grade 3**	**Grade 4**
Skin and subcutaneous tissue disorders						
Rash	57	7	<1	10	0	0
Dermatitis acneiform	19	<1	0	1	0	0
Alopecia	17	<1	0	19	0	0
Dry skin	11	0	0	0	0	0
Pruritus	10	2	0	1	0	0
Gastrointestinal disorders						
Diarrhea	43	0	0	16	1	1
Nausea	18	<1	0	37	1	0
Constipation	14	0	0	23	1	0
Vomiting	13	<1	0	19	2	0
General disorders and administrative site conditions						
Fatigue	26	4	0	27	3	0
Edema peripheral	26	<1	0	3	0	0
Vascular disorders						
Hypertension	15	12	0	7	3	0
Haemorrhage[b]	13	<1	0	0	0	0
Infections and infestations						
Paronychia	10	0	0	1	0	0

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

[b]Events include: epistaxis, haematochezia, gingival bleeding, haematuria, melaena, and rectal, haemorrhoidal, , and conjuntival haemorrhage

Combination with dabrafenib:
In addition to adverse reactions observed with monotherapy treatments (see Table 3 above and the dabrafenib prescribing information), Table 5 lists adverse reactions which are specific to/much more common when MEKINIST is used in combination with dabrafenib.
Frequencies in Table 5 are based on subjects receiving dabrafenib (150 mg twice daily) + MEKINIST (2 mg once daily) combination therapy (n = 55) in Part C of study BRF113220 (data cut-off 31 May 2012).

The following convention has been utilised for the classification of frequency:
Very common: ≥ 1/10
Common: ≥ 1/100 and < 1/10

Note: As patient numbers are small the frequencies of uncommon or rare events could not be determined.

Table 5. Adverse Reactions Specific for MEKINIST In Combination With Dabrafenib

Infections and infestations	
Very common	Urinary tract infection
Blood and lymphatic system disorders	
Very common	Neutropenia
Common	Thrombocytopenia
Metabolism and nutrition disorders	
Common	Hyponatraemia
Nervous system disorders	
Very common	Dizziness
Vascular disorders	
Very Common	Haemorrhage[a]
Common	Hypotension
Hepatobiliary disorders	
Common	Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	
Very common	Night sweats
Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very Common	Muscle spasms
Common	Rhabdomyolysis

[a]Events include: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage

The common adverse events based on ≥15% of patients in the Dabrafenib 150mg twice daily in combination with MEKINIST 2 mg once daily are provided in Table 6.

Table 6. Adverse Events (%) Occurring in ≥10% of Patients in the Dabrafenib 150 mg BID/ MEKINIST 2mg QD Combination Arm

Reactions	Dabrafenib 150 mg BID								
	Monotherapy (N = 53)			MEKINIST 1mg QD Combination (N = 54)			MEKINIST 2mg QD Combination (N = 55)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Skin and subcutaneous tissue disorders									
Rash	36	0	0	20	0	0	27	0	0
Night Sweats	6	0	0	15	0	0	24	0	0
Dry Skin	6	0	0	9	0	0	18	0	0
Dermatitis acneiform	4	0	0	11	0	0	16	0	0
Actinic keratosis	9	0	0	7	0	0	15	0	0
Erythema	2	0	0	6	0	0	15	0	0
Pruritus	13	0	0	11	0	0	11	0	0
Rash generalized	8	0	0	4	2	0	11	0	0
Metabolism and nutritional disorders									
Decreased appetite	19	0	0	30	0	0	22	0	0
Dehydration	2	0	0	6	2	0	11	0	0
Nervous system disorders									
Headache	28	0	0	37	2	0	29	0	0
Dizziness	9	0	0	13	0	0	16	0	0
Vascular Disorders									
Haemorrhage[b]	2	0	0	11	0	0	16	0	2
Respiratory, thoracic, and mediastinal disorders									
Cough	21	0	0	11	0	0	29	0	0
Oropharyngeal pain	0	0	0	7	0	0	13	0	0
Gastrointestinal disorders									
Diarrhea	28	0	0	26	0	0	36	2	0
Nausea	21	0	0	46	4	2	44	2	0
Vomiting	15	0	0	43	4	0	40	2	0
Constipation	11	0	0	17	2	0	22	0	0
Abdominal pain upper	8	0	0	7	0	0	16	0	0
Abdominal pain	13	2	0	15	2	0	15	2	0
Dry mouth	6	0	0	11	0	0	11	0	0
General disorders and administrative site conditions									
Pyrexia	26	0	0	69	9	0	71	5	0
Chills	17	0	0	50	2	0	58	2	0
Fatigue	40	6	0	57	2	0	53	4	0
Edema peripheral	17	0	0	24	0	0	29	0	0
Musculoskeletal, connective tissue, and bone disorders									
Arthralgia	34	0	0	44	0	0	27	0	0
Myalgia	23	2	0	24	0	0	22	2	0
Back pain	11	2	0	11	0	0	18	5	0
Muscle spasm	4	0	0	2	0	0	16	0	0
Pain in	19	0	0	11	2	0	16	0	0

extremity									
Renal and urinary disorders									
Urinary tract infection	9	2	0	6	0	0	13	2	0
Blood and Lymphatic System Disorders									
Neutropenia	2	2	0	9	2	0	15	5	5
Anemia	6	0	0	20	6	0	13	4	0
Psychiatric Disorders									
Insomnia	8	2	0	11	0	0	18	2	0

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.
[b]Events include: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage
BID = twice daily; QD = once daily

Table 7. Treatment Emergent Abnormalities in Liver Function Tests Occurring in Patients Treated With MEKINIST in Combination with Dabrafenib

Test	Dabrafenib 150 mg BID Monotherapy (N = 53)			MEKINIST 1mg QD Combination (N = 54)			MEKINIST 2mg QD Combination (N = 55)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Increased Alkaline phosphatase	26	2	0	67	6	0	60	2	0
Increased AST	15	0	0	54	0	0	60	5	0
Increased ALT	11	0	0	35	4	0	42	4	0
Hyperbilirubinemia	0	0	0	7	4	0	15	0	0

[a] No Grade 4 events were reported in dabrafenib arm.

QT Prolongation
In BRF113220, QTcF prolongation to >500 msec occurred in 4% (2/55) of patients treated with MEKINIST in combination with dabrafenib and in 2% (1/53) of patients treated with dabrafenib as a single agent. The QTcF was increased more than 60 msec from baseline in 13% (7/55) of patients treated with MEKINIST in combination with dabrafenib and 2% (1/53) of patients treated with dabrafenib as a single agent.

Special Populations

Elderly population:
In the phase III study with MEKINIST 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 study drug, dose reduction and dose interruption than those < 65 years.

In the phase I/II study of MEKINIST in combination with dabrafenib in patients with unresectable or metastatic melanoma (n = 202), 42 patients (21%) were ≥ 65 years of age, and 12 patients (6%) were ≥ 75 years of age. The proportion of subjects experiencing AEs was similar in the subjects aged < 65 years and those aged ≥ 65 years.
Patients ≥ 65 years were more likely to experience SAEs, fatal SAEs and AEs leading to permanent discontinuation of study drug, dose reduction and dose interruption than those < 65 years.

DOSAGE AND ADMINISTRATION

Confirmation of $BRAF^{V600}$ mutation using an approved/validated test is required, for selection of patients appropriate for MEKINIST monotherapy and in combination with dabrafenib (see CLINICAL TRIALS).

When MEKINIST is used in combination with dabrafenib, refer to the full dabrafenib prescribing information, DOSAGE AND ADMINISTRATION, for dabrafenib dosing instructions

Adult

The recommended dose of MEKINIST used as monotherapy or in combination with dabrafenib is 2 mg given orally once daily with a full glass of water.

MEKINIST should be taken without food, at least 1 hour before or 2 hours after a meal (see PHARMACOKINETICS).

When MEKINIST and dabrafenib are taken in combination, the dose of MEKINIST should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

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

Dose modifications

Monotherapy and in combination with dabrafenib

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 7 and Table 8).

Table 8. Recommended Dose Level Reductions For MEKINIST

Dose Level	MEKINIST Dose
Starting dose	2 mg QD
1st dose reduction	1.5 mg QD
2nd dose reduction	1 mg QD

QD = Once daily

Refer to the full dabrafenib prescribing information, DOSAGE AND ADMINISTRATION, for dabrafenib dosing instructions

Dose adjustment for MEKINIST, whether used as monotherapy or in combination with dabrafenib, below 1 mg QD is not recommended.

Table 9. MEKINIST Dose Modification Schedule

Grade (CTC-AE)*	Dose Modifications
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)

If treatment related toxicities occur when MEKINIST is used in combination with dabrafenib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below.

Exception where dose modification is necessary for only dabrafenib:

- **New Primary Non-Cutaneous Malignancies**
- **Pyrexia**

Exceptions where dose modifications are necessary for only MEKINIST:

- **Left ventricular ejection fraction (LVEF) reduction**
- **Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)**
- **Interstitial lung disease (ILD)/Pneumonitis**

Detailed dosing modifications for selected adverse reactions

New Primary Malignancies: For New Primary Cutaneous Malignancies no dose modifications are required. For New Primary Non-Cutaneous Malignancies no dose modifications are required for MEKINIST. If used in combination with dabrafenib, permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies.

Haemorrhagic events: Permanently discontinue MEKINIST, and also permanently discontinue dabrafenib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve. Withhold MEKINIST for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level. Withhold dabrafenib for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

Pyrexia Management:

If the patient's temperature is > 40ºC or if fever is complicated by rigors, hypotension, dehydration, or renal failure

When MEKINIST is used as monotherapy, withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.

When MEKINIST is used in combination with dabrafenib, withhold MEKINIST and dabrafenib.

Initiate treatment with anti-pyretics such as ibuprofen (preferred) or acetaminophen/paracetamol. Patients should be evaluated for signs and symptoms of infection (see PRECAUTIONS).

Upon resolution of pyrexia, therapy can be restarted with appropriate anti-pyretic prophylaxis either:

- MEKINIST at the same or lower dose level, dabrafenib at a lower dose level,
- Or, permanently discontinue dabrafenib

If the patient's temperature is ≥ 38.5ºC and ≤ 40ºC

When MEKINIST is used as monotherapy, do not modify the MEKINIST dose.

When MEKINIST is used in combination with dabrafenib, withhold dabrafenib. MEKINIST should be continued at the same dose.

Initiate treatment with anti-pyretics such as ibuprofen (preferred) or acetaminophen/paracetamol. Patients should be evaluated for signs and symptoms of infection (see PRECAUTIONS).

Upon resolution of pyrexia, dabrafenib can be restarted with appropriate anti-pyretic prophylaxis either:

- At the same dose level.
- Or, reduce one dose level, if pyrexia is recurrent

The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

LVEF Reduction/Left Ventricular Dysfunction: MEKINIST 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 PRECAUTIONS). If MEKINIST is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with MEKINIST may be restarted, but reduce dose by one dose level with careful monitoring.

Permanently discontinue MEKINIST with Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover. If MEKINIST is being used in combination with dabrafenib then therapy with dabrafenib should be withheld and resumed at the same dose upon recovery of cardiac function.

Retinal Vein Occlusion and Retinal Pigment Epithelial Detachment: If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on MEKINIST therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with retinal vein occlusion (RVO), treatment with MEKINIST, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. Dabrafenib treatment can continue at the same dose. If retinal pigment epithelial detachment (RPED) is diagnosed follow the dose modification schedule in Table 9 below for MEKINIST and continue dabrafenib at the same dose (see PRECAUTIONS).

Table 10. Recommended dose modifications for MEKINIST for retinal pigment epithelial detachments (RPED)

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

Interstitial lung disease (ILD)/Pneumonitis

Withhold MEKINIST 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 MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis. If MEKINIST is used in combination with dabrafenib, do not modify the dose of dabrafenib.

Serious Skin Toxicity:

For dosing instructions for intolerable or severe skin toxicity for MEKINIST and MEKINIST in combination with dabrafenib see Table 11. Dose reduction, interruption or discontinuation should be applied to both treatments.

Table 11. Guidelines for Cutaneous toxicity

Severity of Adverse Reaction	MEKINIST	Dabrafenib (When Used in Combination)
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold MEKINIST for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold dabrafenib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.

The following rash management guidance should be considered whether MEKINIST is given as monotherapy or in combination with dabrafenib, and if dose reduction, interruption or discontinuation is necessary it should be applied to both treatments.

Treatment of rash has not been formally studied and should be based on rash severity. The following guidelines were used in clinical studies with MEKINIST as monotherapy or in combination with dabrafenib and can be used to manage rash (see Table 12).

Table 12. Supportive Care Guidelines for Rash

Step	Rash grading	Rash severity	Management of Rash
1	Mild	Localised Minimally symptomatic No impact on ADL No sign of superinfection	Initiate prophylactic regimen[a] if not already started. Reassess after two weeks; if rash worsens or does not improve, proceed to step 2
2	Moderate	Generalised Mild symptoms (e.g. pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen[a] if not already started, using moderate strength topical steroids. Reassess after two weeks; if rash worsens or does not improve, proceed to step 3
3	Severe	Generalised Severe symptoms (e.g. pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen[a] if not already started, using moderate strength topical steroids PLUS systemic corticosteroids. Manage rash per dermatologist's recommendation.

a. broad-spectrum sunscreen (skin protection factor ≥ 15), alcohol-free emollient cream, mild-strength topical steroid, and oral antibiotics for first 2-3 weeks

ADL= Activity of Daily Living

Populations

Children

The safety and efficacy of MEKINIST has not been yet established in children and adolescents (< 18 years).

Elderly

No dose adjustments are required in patients over 65 years (see PHARMACOKINETICS).

Renal impairment

No dosage adjustment required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of MEKINIST (see PHARMACOKINETICS). There are no clinical data with MEKINIST in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. MEKINIST should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment. In a population pharmacokinetic analysis, MEKINIST oral clearance and thus exposure was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function (see PHARMACOKINETICS).

There are no clinical data in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined. MEKINIST should be used with caution in patients with moderate or severe hepatic impairment.

OVERDOSAGE

Symptoms and Signs

There were no cases of MEKINIST dose above 4mg once daily reported from the clinical trials. Doses of up to 4 mg orally once daily, and loading doses of 10 mg orally once daily administered on two consecutive days have been evaluated in clinical trials.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of MEKINIST. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Haemodialysis is not expected to enhance the elimination as MEKINIST is highly bound to plasma proteins.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The MEKINIST 0.5 mg tablets are, yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face. The MEKINIST 0.5 mg tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 7 or 30 tablets. This product is packaged with a desiccant.

The MEKINIST 1 mg tablets are, white, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘LHE’ on the opposing face. The MEKINIST 1 mg tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 7 or 30 tablets. This product is packaged with a desiccant.

The MEKINIST 2 mg tablets are, pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face. The MEKINIST 2 mg tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 7 or 30 tablets. This product is packaged with a desiccant.

Not all pack sizes, may be distributed in Australia.

Storage Conditions

Store 2°C to 8°C (Refrigerate. Do not freeze)

Store in the original package to protect from light and moisture. Keep the bottle tightly closed. Do not remove the desiccant.

In-use stability has been demonstrated for 30 days when stored up to 30°C.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
14 February 2014

Version 1.0