AUSTRALIAN PRODUCT INFORMATION - MEKINIST® (trametinib) tablets

1. NAME OF THE MEDICINE

Trametinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

MEKINIST 0.5 mg film coated tablet

Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to trametinib 500 micrograms.

MEKINIST 2 mg film coated tablet

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

Excipients

For the list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

MEKINIST 0.5 mg film coated tablet

Yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

MEKINIST 2 mg film coated tablet

Pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

MEKINIST in combination with dabrafenib is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

MEKINIST as a monotherapy is indicated for the treatment of patients with BRAF V600 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 section 5.1 Clinical trials).

Adjuvant treatment of melanoma

MEKINIST in combination with dabrafenib is indicated for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of the lymph node(s), following complete resection.

4.2 Dose and method of administration

Treatment with MEKINIST should be initiated by a physician experienced in the use of anticancer therapies.

Confirmation of the BRAF V600 mutation, using an approved/validated test, is required for the selection of patients appropriate for MEKINIST monotherapy and MEKINIST in combination with dabrafenib (see section 5.1 - Clinical trials).

For dabrafenib dosing instructions, when MEKINIST is used in combination with dabrafenib, refer to the full dabrafenib (Tafinlar®) product information.

Adult dose

Recommended Dosage for Unresectable or Metastatic Melanoma

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.

Recommended Dosage for the Adjuvant Treatment of Melanoma

The recommended dosage of TAFINLAR is 150 mg orally taken twice daily in combination with trametinib until disease recurrence or unacceptable toxicity for up to 1 year.

Dose modifications

MEKINIST as monotherapy and in combination with dabrafenib

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

Table 1 Recommended dose level reductions for MEKINIST

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

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

Table 2 MEKINIST dose modification schedule

Grade (CTC-AE)*	Recommended dose modifications
Grade 1 or Grade 2 (tolerable)	Continue MEKINIST treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt MEKINIST therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue MEKINIST 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 MEKINIST dose should not exceed 2 mg once daily.

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

following exceptions shown below.

Exception where dose modification is necessary for only dabrafenib:

- New Primary Non-Cutaneous Malignancies
- Pyrexia.

For dose modification guidelines, refer to the dabrafenib product information.

Exceptions where dose modifications are necessary for only MEKINIST:

- LVEF reduction
- RVO and RPED
- 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

Pyrexia may occur with MEKINIST monotherapy and with dabrafenib combination therapy. Initiate treatment with anti-pyretics such as ibuprofen (preferred) or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Follow the management given in Table 10. Patients should be evaluated for signs and symptoms of infection (see section 4.4 Special Warnings and Precautions for Use). Follow the management given in Table 3.

Table 3 Recommended MEKINIST dose modifications in pyrexia management

Patient's temperature	MEKINIST monotherapy	MEKINIST combination therapy with dabrafenib
38.5ºC - 40ºC	Do not modify the MEKINIST dose	Do not modify the MEKINIST dose. Withhold dabrafenib. Upon resolution of pyrexia, resume dabrafenib with appropriate anti-pyretic prophylaxis either at the same dose level, or reduce dabrafenib one

Patient's temperature	MEKINIST monotherapy	MEKINIST combination therapy with dabrafenib
		dose level, if pyrexia is recurrent.
> 40ºC or if fever is complicated by rigors, hypotension, dehydration, or renal failure	Withhold MEKINIST until fever resolves. Upon resolution of pyrexia, resume MEKINIST at same or lower dose level.	Withhold MEKINIST and dabrafenib. Initiate treatment with anti-pyretics such as ibuprofen (preferred) or paracetamol. Upon resolution of pyrexia, resume therapy with appropriate anti-pyretic prophylaxis with: · MEKINIST at the same or at a lower dose level and · dabrafenib at either a lower dose level or permanently discontinue dabrafenib

Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

Left Ventricular Ejection Fraction (LVEF) reduction/left ventricular dysfunction management

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 section 4.4 Special Warnings and Precautions for Use). 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-reduction 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.

RVO and RPED management

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 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 RPED is diagnosed, follow the dose modification schedule (intolerable) in Table 4 for MEKINIST and, if MEKINIST is being used in combination with dabrafenib, continue dabrafenib at the same dose (see section 4.4 Special Warnings and Precautions for Use).

Table 4 Recommended dose modifications for MEKINIST for retinal pigment epithelial detachments (RPED)

RPED Grade	Recommended dose modifications
1	Continue treatment with retinal evaluation monthly until

RPED Grade	Recommended dose modifications
	resolution. If RPED worsens follow instructions below and withhold MEKINIST for up to 3 weeks
2-3	Withhold MEKINIST for up to 3 weeks
2-3 that improves to 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
2-3 that does not improve to at least 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, dyspnoea, 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 5. Dose reduction, interruption or discontinuation should be applied to both treatments.

Table 5 Guidelines for Cutaneous toxicity

Severity of Adverse Reaction	MEKINIST	Dabrafenib (when used in combination)
Intolerable Grade 2 skin toxicity.	Withhold MEKINIST for up to 3 weeks.	Withhold dabrafenib for up to 3 weeks.
Grade 3 or 4 skin toxicity.	If improved, resume at a lower dose level.	If improved, resume at a lower dose level.
	If not improved, permanently discontinue.	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 6).

Table 6 Supportive Care Guidelines for Rash

Step	Rash grading	Rash severity	Management of Rash
1	Mild	Localised Minimally symptomatic No impact on ADL	Initiate prophylactic regimen[a] if not already started. Reassess after two weeks; if rash worsens or does not improve, proceed to

Step	Rash grading	Rash severity	Management of Rash
		No sign of superinfection	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

Paediatric use

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

Use in the elderly

No dose adjustments are required in patients over 65 years (see section 5.2 Pharmacokinetic properties).

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 section 5.2 Pharmacokinetic properties). 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 section 5.2 Pharmacokinetic properties).

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.

Administration

MEKINIST should be administered for twelve (12) months only in the adjuvant treatment of melanoma.

MEKINIST should be taken without food, at least 1 hour before or 2 hours after a meal (see section 5.2 Pharmacokinetic properties).

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 or 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.

4.3 Contraindications

MEKINIST is contraindicated in patients with known hypersensitivity to the active substance trametinib dimethyl sulfoxide or any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

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 V600 mutation.

New primary melanoma

New primary malignancies can occur when MEKINIST is used in combination with dabrafenib and with dabrafenib as a single agent [refer to Product Information for dabrafenib (Tafinlar®)]. 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).

Non-cutaneous secondary/ recurrent malignancies

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 section 4.2 Dose and method of administration).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events have occurred in patiens taking MEKINIST as monotherapy and in combination with dabrafenib (see section 4.8 Adverse Effects (Undesirable Effects)). If patients develop symptoms of hemorrhage they should immediately seek medical care.

Six (6) out of 559 unresectable or metastatic melanoma patients (1.1 %) receiving MEKINIST in combination with dabrafenib in phase III trials had fatal intracranial haemorrhagic events. Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). No fatal hemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma (0/438). If patients develop symptoms of hemorrhage they should immediately seek medical care.

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 three 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 section 4.2 Dose and method of administration).

Cardiac Effects

QT prolongation

Initially, the QT prolongation potential of trametinib was assessed as part of the first time in human study MEK111054 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 patients 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 Cmax 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).

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 millisecond (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.

To confirm the lack of effect on QTc, the QT prolongation potential of MEKINIST was further assessed in a dedicated, stand-alone Phase I study MEK114655 in 35 patients with solid tumours. Patients received 3 mg matched placebo on study day 1 followed by a 2 mg once daily dose of trametinib and 2 tablets of 0.5 mg matched placebo on study days 2 to 14. On study day 15, all patients received a single dose of 3 mg MEKINIST (supratherapeutic dose). The study showed no potential for MEKINIST to alter the QTcF interval after repeat dose administration of 2 mg trametinib, including at the supratherapeutic dose of 3 mg on day 15. At a dose 1.5 times the maximum recommended dose, MEKINIST does not prolong the QT interval to any clinically relevant extent.

Bradycardia

A dedicated cardiac study in solid tumour patients (n=30) confirmed early exploratory analyses in showing statistically significant changes in both PR interval (mean 21.68 msec increase, normal = 120 to 200) and heart rate (mean 8.12 bpm decrease) with trametinib versus placebo. The clinical significance of this small increase in PR interval is unclear, however in a large ongoing trial (n = 704), heart rate decrease to < 60 bpm has been recorded in 23 % of 348 patients on trametinib and dabrafenib combined therapy compared to 12 % of patients in the vemurafenib monotherapy control arm.

LVEF reduction/Left ventricular dysfunction

MEKINIST has been reported to decrease LVEF (see section 4.8 Dose and method of administration). MEKINIST should be used with caution in patients with conditions that could

impair left ventricular function. In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure, and LVEF decrease in patients treated with MEKINIST (as monotherapy or in combination with dabrafenib) was between two to five months. LVEF should be evaluated in all patients prior to initiation of treatment with MEKINIST with a recommendation of periodic follow-up within eight weeks of initiating therapy, as clinically appropriate. LVEF should continue to be evaluated during treatment with MEKINIST as clinically appropriate (see section 4.2 Dose and method of administration).

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 $\geq$ 10 % below baseline) and 5 % demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of $\geq$ 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 three monthly intervals while on treatment.

MEKINIST should be interrupted in patients who have an asymptomatic, absolute decrease of $\geq$ 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, therapy with dabrafenib should be withheld and resumed at the same dose upon recovery of cardiac function (see section 4.2 Dose and method of administration).

Visual impairment

A thorough ophthalmological evaluation should be performed at baseline and during treatment with MEKINIST, if clinically warranted. If a retinal abnormality is noted, treatment with MEKINIST should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, follow the dose modification schedule (intolerable) in Table 2 (see section 4.2 Dose and method of administration). The data from clinical trials demonstrates that when all reported ocular events are pooled, there was a higher reported rate in the patients 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 section 4.8 Adverse effects (Undesirable 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 (intolerable) in Table 9 (see section 4.2 Dose and method of administration).

Retinal Vein Occlusion (RVO)

MEKINIST is not recommended in patients with a history of RVO. Across all clinical trials of MEKINIST, the incidence of RVO was 0.2 % (4/1749). In patients who experience RVO, treatment with trametinib should be permanently discontinued.

RVO may lead to macular oedema, 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 RVO.

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.

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

DVT and PE can occur on MEKINIST monotherapy and when MEKINIST is used in combination with dabrafenib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis they should immediately seek medical care.

Pyrexia and serious non-infectious febrile events

Pyrexia was reported in the clinical trials with MEKINIST. The incidence and severity of pyrexia are increased when MEKINIST is used in combination with dabrafenib (see section 4.8 Adverse effects (Undesirable effects)). In patients with unresectable or metastatic melanoma 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 one-third of the patients receiving combination therapy who experienced pyrexia had 3 or more events. Pyrexia may be accompanied by severe rigors, dehydration, and hypotension, which in some cases can lead to acute renal insufficiency. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia. 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.

Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

For management of pyrexia also see section 4.2 Dose and method of administration - Pyrexia

Management and the Product Information for dabrafenib (TAFINLAR®).

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 section 4.2 Dose and method of 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 section 4.8 Adverse effects (undesirable effects)).

Colitis and gastrointestinal perforation

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

If patients develop symptoms of colitis and gastrointestinal perforation, they should immediately seek medical care.

Brain metastases

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

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8 Adverse effects (undesirable effects)). Also refer to the TAFINLAR Product Information for additional information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking TAFINLAR in combination with MEKINIST (see section 4.8 Adverse effects (undesirable effects)). Also refer to the TAFINLAR Product Information for additional information.

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 section 5.2 Pharmacokinetic properties).

More frequent dose adjustments (see Table 8 and Table 9) may be required in patients over 65 years of age (see section 4.8 Adverse effects (undesirable 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 patients aged 65 and over to determine whether they respond differently from younger patients. 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.

Effects on laboratory tests

Treatment-emergent laboratory abnormalities may include any of the following serum elevations: gamma-glutamyltransferase (GGT), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, and kidney function results. Also refer to Section 4.8 Adverse Effects (undesirable effects).

4.5 Interactions with other medicines and other forms of interactions

Trametinib monotherapy

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (including carboxylesterases), 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 cytochrome P450 (CYP) 3A4 inducer (see section 5.2 Pharmacokinetic properties).

Based on *in vitro* data, MEKINIST is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes (see section 5.2 Pharmacokinetic properties) or transporters.

Trametinib in combination with dabrafenib

Repeat dose administration of once-daily MEKINIST 2 mg had no effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate. Co-administration of repeat dosing of dabrafenib 150 mg twice daily and MEKINIST 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 12 %, was estimated when MEKINIST is administered in combination with dabrafenib using a population PK analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant.

See Product Information for dabrafenib (TAFINLAR®) for guidelines on drug interactions associated with dabrafenib monotherapy.

Effects of other drugs on Trametinib

In vitro and *in vivo* data suggest that the PK of MEKINIST are unlikely to be affected by other drugs. Trametinib is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is not a substrate of the following transporters: organic anion transporting polypeptides (OATP) 1B1, 1B3, 2B1, organic cation transporter (OCT) 1, breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. Trametinib is an *in vitro* substrate of the efflux transporter P-glycoprotein (Pgp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability. 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 in the "Combination of MEKINIST with dabrafenib" in the previous paragraph.

Effects of MEKINIST on drug metabolising enzymes and transporters

In vitro and *in vivo* data suggest that trametinib is unlikely to affect the PK 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 OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, Pgp and BCRP. However, based on the low dose and low clinical trametinib systemic exposure relative to the *in vitro* potency of inhibition or induction, trametinib is not considered to be an *in vivo* inhibitor or inducer of these enzymes or transporters.

4.6 Fertility, pregnancy, and lactation

Effects on fertility

Infertility

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 13 weeks in duration, there were no treatment-related effects observed on male reproductive tissues.

Males 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 Product information for dabrafenib for more detail.

Use in Pregnancy (Category D)

MEKINIST can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus.

There are no adequate and well-controlled studies of MEKINIST in pregnant women. 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.

Reproductive studies in animals (rats and rabbits) with trametinib have demonstrated maternal and developmental toxicity. In embryofetal development studies in rats, maternal and developmental toxicity (decreased foetal weights) were seen following maternal exposure to trametinib at ³ 0.031 mg/kg/day (approximately 0.3 times the exposure in humans at the highest recommended dose of 2 mg once daily based on AUC). Post implantation loss was increased at 0.125 mg trametinib/kg/day. In pregnant rabbits, maternal and developmental toxicity (decreased foetal body weight and increased incidence of variations in ossification) were seen at ³ 0.039 mg/kg/day (approximately 0.1 times the exposure in humans at the highest recommended dose of 2 mg once daily based on AUC). Post implantation loss and incidence of skeletal defects were increased at 0.154 mg trametinib/kg/day.

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing MEKINIST to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when using MEKINIST during treatment and for four months after stopping treatment with MEKINIST.

Females of reproductive potential receiving MEKINIST in combination with Tafinlar should be advised that Tafinlar may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as barrier methods, should be used.

Use in Lactation

There are no data on the effect of MEKINIST on the breast-fed child, or the effect of MEKINIST on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from MEKINIST, a nursing woman should be advised of the potential risk to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for MEKINIST and any potential adverse effects on the breast-fed child from MEKINIST or from the underlying maternal condition.

4.7 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.

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

Unresectable or metastatic melanoma

MEKINIST monotherapy

The safety of MEKINIST monotherapy has been evaluated in an integrated population of 329 patients with BRAF V600 mutant unresectable or 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 section 5.1 - Clinical trials). The most common adverse reactions (³ 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 section 4.2 Dose and method of administration).

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

The following convention has been utilised for the classification of frequency in all of the following AE tables:

Very common ³ 1 in 10

Common ³ 1 in 100 and < 1 in 10

Uncommon ³ 1 in 1,000 and < 1 in 100

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

Table 7 and Table 8 respectively lists the very common adverse events (³ 10%) reported in patients receiving MEKINIST monotherapy.

Table 7 Unresectable or metastatic melanoma - adverse events with MEKINIST monotherapy

Infections and Infestations	
Common	Folliculitis, Paronychia, Cellulitis, Rash pustular
Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity[b]
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,
Common	Stomatitis
Uncommon	Gastrointestinal perforation, colitis
Investigations	
Common	Aspartate aminotransferase increased, Alanine aminotransferase
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. The majority of bleeding events were mild; major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported

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

Table 8 Adverse events (%) occurring in ³ 10 % of patients treated with MEKINIST

Events	MEKINIST (N = 211)			Chemotherapy (N = 99)		
	All	Grade 3	Grade 4	All	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						

Events	MEKINIST (N = 211)			Chemotherapy (N = 99)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
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 conjunctival haemorrhage

MEKINIST in combination with dabrafenib

The safety of trametinib and dabrafenib combination therapy has been evaluated in two randomized Phase III studies and one small phase II study of patients with BRAF mutant unresectable or metastatic melanoma treated with trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily (see section 5.1- Clinical trials). The most common adverse reactions (≥ 20 %) for trametinib and dabrafenib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema and cough.

Table 9 lists adverse reactions when MEKINIST was used in combination with dabrafenib from the randomized double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomized open-label Phase III study MEK116513 (N=350).

Table 9 Unresectable or metastatic melanoma - adverse events for MEKINIST in combination with dabrafenib from randomised double-blind phase III combination study MEK115306, and the integrated safety data from two randomized phase III combination studies, MEK115306 and MEK116513 (integrated safety data)

		Frequency category	
		COMBI-d n=209	COMBI-d and COMBI-v n=559
Infections and Infestations			
	Urinary tract infection	Very common	Common
	Nasopharyngitis	Very common	Very common
	Cellulitis	Common	Common
	Folliculitis	Common	Common
	Paronychia	Common	Common
	Rash pustular	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
	Cutaneous squamous cell carcinoma(SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma	Common	Common
	Papilloma including skin papilloma	Common	Common
	Seborrhoeic keratosis	Common	Common
	Acrochordon (skin tags)	Common	Uncommon
	New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders			
	Neutropenia	Very Common	Common
	Anaemia	Common	Common
	Thrombocytopenia	Common	Common
	Leukopenia	Common	Common
Immune system disorders			
	Hypersensitivity	Uncommon	Uncommon
Metabolic and nutrition disorders			
	Decreased appetite	Very common	Very common
	Dehydration	Common	Common
	Hyperglycemia	Common	Common
	Hyponatraemia	Common	Common
	Hypophosphataemia	Common	Common
Nervous system disorders			
	Headache	Very common	Very common
	Dizziness	Very common	Very common
Eye disorders	Vision blurred	Common	Common
	Visual impairment	Common	Common
	Chorioretinopathy	Uncommon	Uncommon
	Uveitis	Uncommon	Uncommon
	Retinal detachment	Uncommon	Uncommon
	Periorbital oedema	Uncommon	Uncommon
Cardiac disorders			
	Ejection fraction decreased	Common	Common
	Bradycardia	Common	Common
	Left ventricular dysfunction	NR	Uncommon
	Cardiac failure	NR	Uncommon
Vascular disorders	Hypertension	Very common	Very common
	Haemorrhage*	Very common	Very common
	Hypotension	Common	Common
Respiratory, thoracic and mediastinal disorders			

	Frequency category	
	COMBI-d n=209	**COMBI-d and COMBI-v n=559**
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	NR	Uncommon

	Frequency category	
	COMBI-d n=209	**COMBI-d and COMBI-v data n=559**
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
Gastrointestinal perforation	NR	Uncommon
Colitis	Uncommon	Uncommon
Investigations		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common
Skin and subcutaneous tissue disorders		
Dry skin	Very common	Very common
Pruritus	Very common	Very common
Rash	Very common	Very common
Dermatitis acneiform	Very common	Common
Erythema	Common	Common
Actinic keratosis	Common	Common
Night sweats	Common	Common
Hyperkeratosis	Common	Common
Alopecia	Common	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	NR	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	NR	Uncommon
General disorders and administration site disorders		

	Frequency category	
	COMBI-d n=209	**COMBI-d and COMBI-v n=559**
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common

NR = Not reported.
*The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported

Table 10 Study MEK115306 (Combi-d) - treatment emergent abnormalities (worst case on therapy) in Liver Function Tests occurring in unresectable or metastatic melanoma patients treated with placebo and MEKINIST plus dabrafenib

Test	Dabrafenib 150 mg BID plus placebo (N = 211)			MEKINIST 2 mg QD plus darafenib 150 mg BID (N = 209)		
	All Grades[a]	**Grade 3**	**Grade 4**	**All Grades[a]**	**Grade 3**	**Grade 4**
Increased ALP	20	<1	0	45	<1	0
Increased AST	17	<1	0	53	3	<1
Increased ALT	25	<1	0	38	3	<1
Hyperbilirubinaemia	2	0	0	4	<1	<1

ALP = Alkaline phosphatase; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase

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

Adjuvant treatment of melanoma

MEKINIST in combination with dabrafenib

The safety of MEKINIST in combination with Tafinlar was evaluated in a Phase III, randomized, double-blind study of MEKINIST in combination with Tafinlar versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection (see section 5.1 – Clinical trials).

In the MEKINIST 2 mg once daily and Tafinlar 150 mg twice daily arm, the most common adverse reactions (≥ 20 %) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhoea, vomiting, and arthralgia.

Table 11 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥ 10 % for all grade adverse reactions or at an incidence ≥ 2 % for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the MEKINIST in combination with TAFINLAR arm.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug

reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

Very common	³ 1 in 10
Common	³ 1 in 100 and < 1 in 10
Uncommon	³ 1 in 1,000 and < 1 in 100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000

Table 11 Adjuvant treatment of melanoma - Adverse drug reactions for MEKINIST in combination with Tafinlar versus placebo

Adverse drug reactions	MEKINIST in combination with Tafinlar N=435 %		Placebo N=432 %		Frequency category (MEKINIST in combination with Tafinlar arm)
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades
Infections and infestations					
Nasopharyngitis[1]	12	<1	12	NR	Very common
Blood and lymphatic system disorders					
Neutropenia[2]	10	5	<1	NR	Very common
Metabolism and nutrition disorders					
Decreased appetite	11	<1	6	NR	Very common
Nervous system disorders					
Headache[3]	39	1	24	NR	Very common
Dizziness[4]	11	<1	10	NR	Very common
Eye disorders					
Uveitis	1	<1	<1	NR	Common
Chorioretinopathy[5]	1	<1	<1	NR	Common
Retinal detachment[6]	1	<1	<1	NR	Common
Vascular disorders					
Haemorrhage[7]	15	<1	4	<1	Very common
Hypertension[8]	11	6	8	2	Very common
Respiratory, thoracic, and mediastinal disorders					
Cough[9]	17	NR	8	NR	Very common
Gastrointestinal disorders					
Nausea	40	<1	20	NR	Very common
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	NR	Very common
Abdominal pain[10]	16	<1	11	<1	Very common
Constipation	12	NR	6	NR	Very common
Skin and subcutaneous tissue disorders					
Rash[11]	37	<1	16	<1	Very common
Dry skin[12]	14	NR	9	NR	Very common
Dermatitis acneiform	12	<1	2	NR	Very common
Erythema[13]	12	NR	3	NR	Very common
Pruritus[14]	11	<1	10	NR	Very common
Palmar-plantar erythrodysaesthesia	6	<1	1	<1	Common
Musculoskeletal and connective tissue disorders					
Arthralgia	28	<1	14	NR	Very common

Adverse drug reactions	MEKINIST in combination with Tafinlar N=435 %		Placebo N=432 %		Frequency category (MEKINIST in combination with Tafinlar arm)
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades
Myalgia[15]	20	<1	14	NR	Very common
Pain in extremity	14	<1	9	NR	Very common
Muscle spasms[16]	11	NR	4	NR	Very common
Rhabdomyolysis	<1	<1	NR	NR	Uncommon
Renal and urinary disorders					
Renal failure	<1	NR	NR	NR	Uncommon
General disorders and administration site conditions					
Pyrexia[17]	63	5	11	<1	Very common
Fatigue[18]	59	5	37	<1	Very common
Chills	37	1	4	NR	Very common
Oedema peripheral[19]	16	<1	6	NR	Very common
Influenza-like illness	15	<1	7	NR	Very common
Investigations					
Alanine aminotransferase increased[20]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	NR	2	<1	Common

[1] *Nasopharyngitis also includes pharyngitis*

[2] *Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia*

[3] *Headache also includes tension headache*

[4] *Dizziness also includes vertigo*

[5] *Chorioretinopathy also includes chorioretinal disorder*

[6] *Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium*

[7] *Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events*

[8] *Hypertension also includes hypertensive crisis*

[9] *Cough also includes productive cough*

[10] *Abdominal pain also includes abdominal pain upper and abdominal pain lower*

[11] *Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular*

[12] *Dry skin also includes xerosis and xeroderma*

[13] *Erythema also includes generalized erythema*

[14] *Pruritus also includes puritus generalized and pruritus genital*

[15] *Myalgia also includes musculoskeletal pain and musculoskeletal chest pain*

[16] *Muscle spasms also includes musculoskeletal stiffness*

[17] *Pyrexia also includes hyperpyrexia*

[18] *Fatigue also includes asthenia and malaise*

[19] *Oedema peripheral also includes peripheral swelling*

[20] *Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia*

[21] *Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia*

NR: not reported

Table 12 Treatment-emergent laboratory abnormalities (all grades) occurring in Study BRF115532 (COMBI-AD) with between arm difference ³ 10 %

Test result	TAFINLAR in combination with MEKINIST (N=435)	Placebo (N=432)
Serum albumin abnormalities	25 %	<1 %
Hyponatraemia	16 %	3 %
Hyperglycaemia	63 %	47 %
Serum phosphate abnormalities	42 %	10 %

Special Populations

Use in the elderly

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. 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms and Signs

There were no cases of MEKINIST dose above 4 mg 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

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 Poisons Information Centre on telephone number 13 11 26.

5. PHARMALOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor.
Anatomical Therapeutic Chemical (ATC) code: L01XE25.

5.1 Pharmacodynamic properties

Mechanism of Action

Trametinib monotherapy (Melanoma)

Trametinib (MEKINIST) is a reversible allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and 2 (MEK2) activation and kinase activity. MEK proteins are critical components of the extracellular signal-regulated 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.

Trametinib in combination with dabrafenib (Melanoma)
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 patients 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-hour dosing interval, thereby providing sustained inhibition of the MEK pathway.

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 patients with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

Clinical trials

Unresectable or metastatic melanoma

MEKINIST monotherapy

Open label studies

MEK114267

The efficacy and safety of MEKINIST in patients with BRAF mutant unresectable or metastatic 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

(unresectable or 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 (DoR) 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. Fifty-one (47 %) 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 ³ 65 years), most patients (64 %) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 11 patients (3 %) had a history of brain metastases. Most patients (87 %) in the ITT population had BRAF V600E mutation and 12 % of patients had a BRAF V600K mutation. 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 13 and Figure 1.

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).

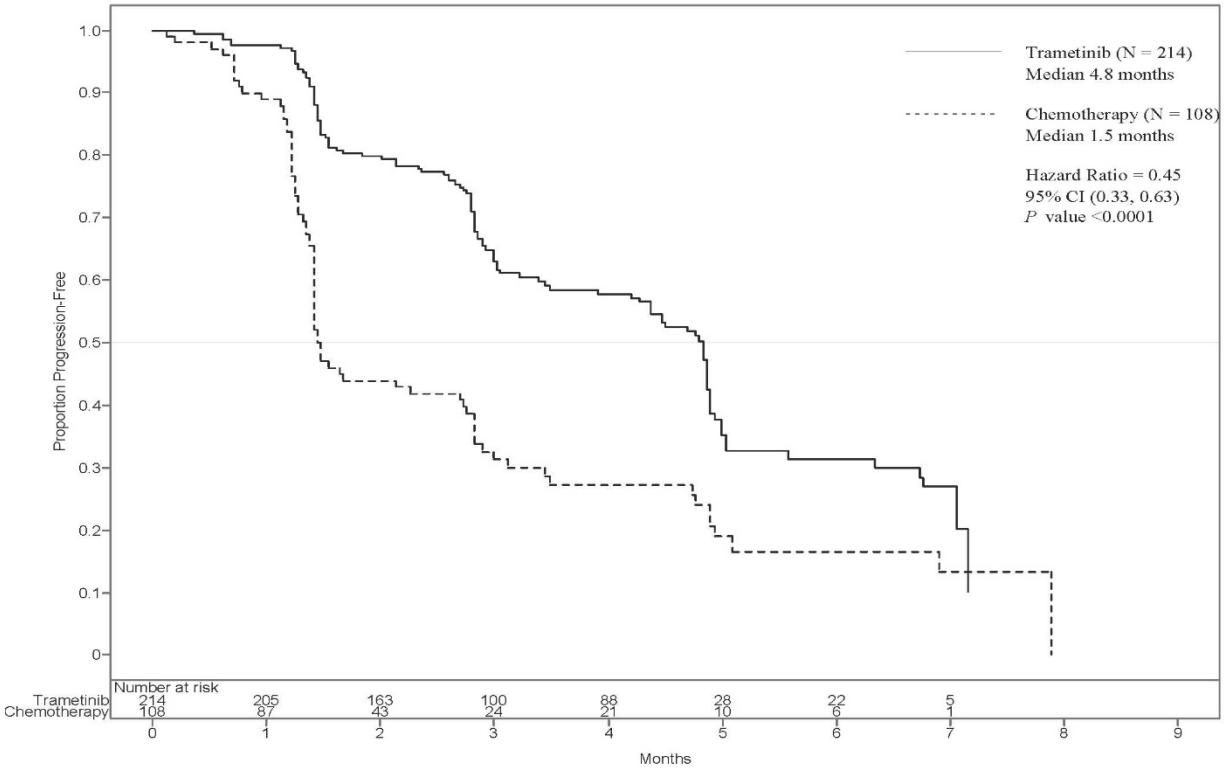
Table 13 Investigator-Assessed Efficacy Results (ITT Population)

Endpoint	MEKINIST (N = 214)	Chemotherapy[a] (N = 108)
Progression-Free Survival		
Median PFS (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)	
Overall Survival		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio (95 % CI)	0.54 (0.32, 0.92)	
Survival at 6 months (%) (95 %	81 (73, 86)	67 (55, 77)
Overall Response Rate (%)	22	8

[a] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks.

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.

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



MEK113583 – Phase II BRAF inhibitor pre-treatment study

In a single arm, multi-centre, Phase II study, MEK113583 evaluated the ORR, safety and PK following once daily oral dosing of MEKINIST 2 mg in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma, previously treated with or without a BRAF inhibitor (BRAFi). Patients were enrolled into two separate cohorts, defined by therapy received prior to MEKINIST. Cohort A patients (n=40) had received prior treatment with a BRAFi. Cohort B patients (n=57) were BRAFi-naïve and had received at least one prior chemotherapy or immunotherapy. MEKINIST did not demonstrate clinical activity in Cohort A (patients who progressed on a prior BRAFi therapy) (see section 4.2 Dose and method of administration).

MEKINIST in combination with dabrafenib

The efficacy and safety of the recommended dose of MEKINIST (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in Phase I/II study BRF113220 and two pivotal phase III studies, MEK116513 and MEK115306.

Randomised open label studies

BRF113220 (Phase I/II Studies)

In this open label study, the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of MEKINIST and dabrafenib combination therapy were evaluated in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma. This study had four parts, A-D:

- Part A was a drug/drug interaction (DDI) study to determine the effect of repeat doses of MEKINIST on the PK of a single dose of dabrafenib and its metabolites (n=8);
- Part B was a dose escalation and expansion study to determine optimal doses and safety of MEKINIST when administered in combination with dabrafenib (n=135);

- Part C was an open-label, randomised phase II study to determine the efficacy, safety, and tolerability of MEKINIST and dabrafenib in patients with BRAF mutant metastatic melanoma (n=162); and
- Part D was a PK and safety evaluation of the combination of MEKINIST and dabrafenib capsules (n=110).

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

Prior BRAFi therapy

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

Part B of open-label study BRF113220 included a cohort of 26 patients that had progressed on a BRAFi. The combination of 150 mg Tafinlar with 2 mg trametinib demonstrated limited clinical activity in patients who had progressed on a BRAFi. 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 Tafinlar monotherapy to the combination of 150 mg Tafinlar plus 2 mg trametinib 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).

Part C

Part C of this open-label, randomised, three-arm, phase II study assessed the 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 DoR. 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 the MEKINIST 2 mg and dabrafenib 150 mg combination.

Baseline characteristics were balanced between treatment groups. Most patients (85 %) in all treatment arms had BRAF V600E mutation and 15 % of patients had BRAF V600K. Investigator assessed median PFS for dabrafenib 150 mg twice daily plus MEKINIST 2 mg once daily was 9.4 months (95 % CI: 8.6, 16.7) compared to 5.8 months (95 % CI: 4.6, 7.4 months) for dabrafenib 150 mg twice daily monotherapy. The hazard ratio was 0.39 (95 % CI 0.25, 0.62, $p < 0.0001$). Overall response rate for dabrafenib 150 mg twice daily plus MEKINIST 2 mg once daily was 76 % (95 % CI: 62.4, 86.5, p=0.0264) compared to 54 % (95 % CI: 39.6, 67.4) for dabrafenib 150 mg twice daily monotherapy.

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

A retrospective blinded independent committee review (BICR) was conducted and obtained the following results:

- 61 % ORR (95 % CI: 46.9 %, 74.1 %; $p = 0.1486$) for the 150 mg dabrafenib plus 2 mg MEKINIST combination,
- 39 % ORR (95 % CI: 25.9, 53.1; $p = 0.5008$) for the 150 mg dabrafenib plus 1 mg MEKINIST combination, and
- 46 % ORR (95 % CI: 32.6%, 60.4%) for the dabrafenib monotherapy group.

- Median PFS was 9.2 months (95 % CI: 7.6, NR; *P* = 0.0121) for patients treated with 150 mg dabrafenib plus 2 mg MEKINIST combination therapy,
- Median PFS was 8.3 months (95 % CI: 5.6, 11.3; *p* = 0.1721) for patients treated with 150 mg dabrafenib plus 1 mg MEKINIST combination therapy, and
- Median PFS was 7.3 months (95 % CI: 5.5, 9.4) for patients treated with dabrafenib monotherapy.

Randomised open label study in BRAFi-treatment-naïve patients

MEK116513 (COMBI-v, Phase III Study)

Study MEK116513 was a 2-arm, randomized, open-label, Phase III study comparing trametinib and dabrafenib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS (see Figure 2), and the key secondary endpoint was PFS. Other secondary objectives included ORR, DoR, and safety. Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

Seven hundred and four (704) patients were randomized 1:1 to either the combination therapy arm (trametinib 2 mg once daily and dabrafenib 150 mg twice daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were white (> 96 %) and male (55 %), with a median age of 55 years (24 % were ≥ 65 years). The majority of patients had Stage IV M1c disease (61 %). Most patients had LDH ≤ ULN (67 %), ECOG performance status of 0 (70 %), and visceral disease (78 %) at baseline. Overall, 54 % of patients had < 3 disease sites at baseline. The majority of patients had a BRAF V600E mutation (89 %).

The OS analysis for Study MEK116513 was conducted when 222 total deaths (77 % of the required events for the final analysis) occurred. The Independent Data Monitoring Committee (IDMC) recommended stopping the study since the OS results crossed the pre-specified efficacy boundary. As a consequence the interim OS summary was considered as the final comparative OS analysis.

The OS analysis was based on 222/704 (32 %) deaths in the study [MEKINIST and dabrafenib combination therapy: 100 deaths (28 %) and vemurafenib monotherapy: 122 deaths (35 %)]. The median follow up time on study treatment was 11 months for the combination arm and 9 months in the vemurafenib arm. Study MEK116513 showed a statistically significant 31 % reduction in the risk of death for trametinib and dabrafenib combination therapy compared with vemurafenib monotherapy (HR = 0.69, 95 % CI: 0.53, 0.89; p = 0.005). The median OS was not yet reached for the combination arm, and was 17.2 months for vemurafenib monotherapy. The results of the secondary efficacy endpoints for PFS, ORR and DoR are summarized in Table 14.

Figure 2: Kaplan-Meier Overall Survival Curves (ITT Population)

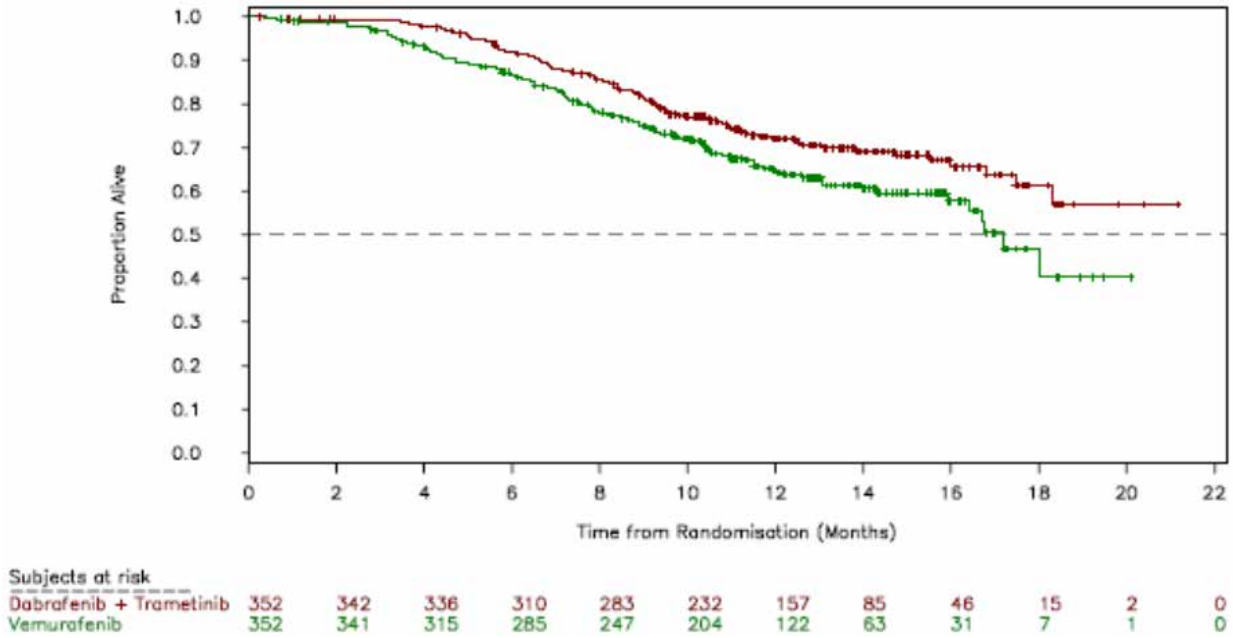


Table 14 Investigator-Assessed Efficacy Results for MEK116513 (COMBI-v) study

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

PFS= Progression Free Survival; ORR = Overall Response Rate; RR = response rate; CR = complete response; PR = partial response; DoR= Duration of Response; NR= Not reached

Randomised double blind study in BRAFi-treatment-naïve patients

MEK115306 (COMBI-d, Phase III Study)

This Phase III, randomized, double-blind study comparing the combination of dabrafenib and MEKINIST to dabrafenib and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was investigator assessed PFS with a key secondary endpoint of OS (Figure 3). Patients were stratified by lactate dehydrogenase (LDH) level (> ULN versus ≤ ULN) and BRAF mutation (V600E versus V600K).

Four hundred and twenty three (423) patients were randomized 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and MEKINIST 2 mg once daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was

56 years; Majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the BRAF V600E mutation (85 %); the remaining 15 % of patients had the BRAF V600K mutation. Patient with brain metastases were not included in the trial.

At the time of final OS analysis, a total of 222 deaths (52.5 %) [MEKINIST and dabrafenib combination therapy: 99 deaths (47 %), dabrafenib monotherapy: 123 deaths (58 %)] out of the randomized (or ITT) population were reported. The median follow up time on study treatment was 20 months in the combination therapy arm and 16 months in the dabrafenib monotherapy arm. Study MEK115306 showed a statistically significant 29 % reduction in the risk of death for the combination therapy arm compared with the dabrafenib monotherapy arm (HR = 0.71, 95 % CI: 0.55, 0.92; p = 0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the dabrafenib monotherapy arm. The 12-month (74 %) and 24-month (51.4 %) OS estimates for the combination were also greater than those for dabrafenib monotherapy (67.6 % and 42.1 %, respectively). Efficacy Results of PFS, ORR and Duration of Response are summarized in Table 15.

Figure 3 Kaplan-Meier Overall Survival Curves for MEK115306 (COMBI-d) study (Primary Data Cut and Final Data Cut) (ITT Population)

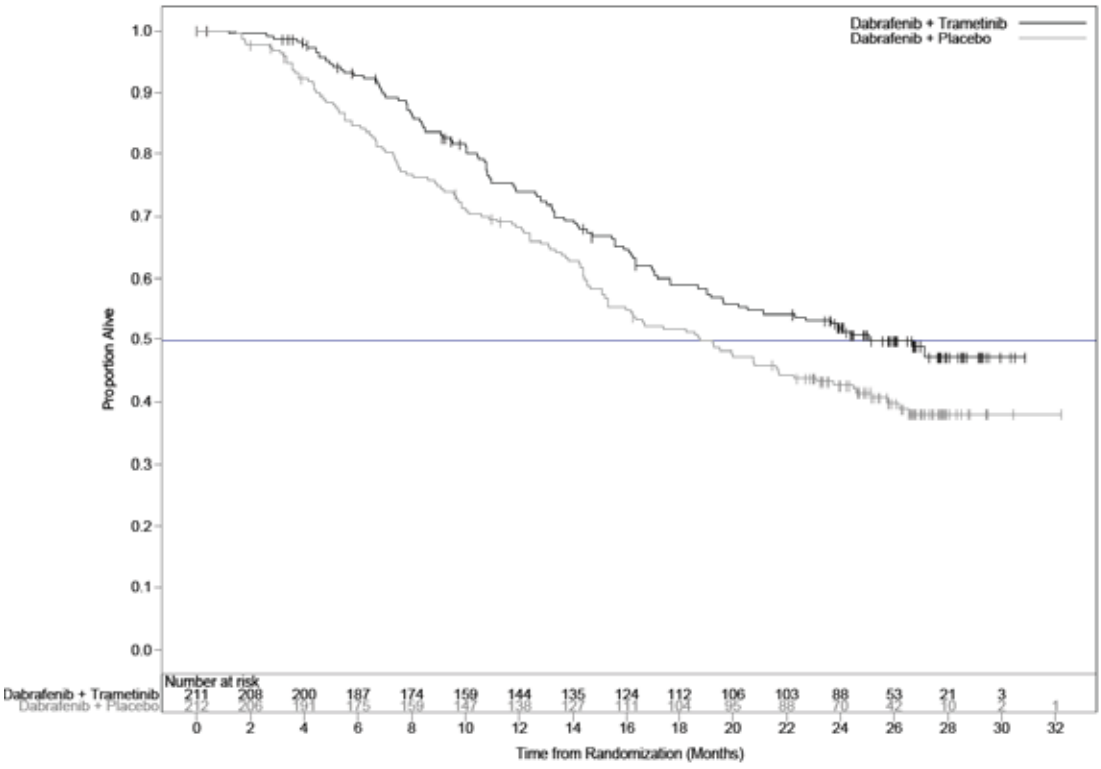


Table 15 Investigator-Assessed Efficacy Results for MEK115306 (COMBI-d) study (Primary Data Cut and Final Data Cut)

	Primary analysis*		Final analysis*	
Endpoints	dabrafenib plus MEKINIST® (N=211)	dabrafenib (N=212)	dabrafenib plus MEKINIST® (N=211)	dabrafenib (N=212)
Investigator Assessed PFS				
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9,9.3)
Hazard Ratio (95% CI)	0.75 (0.57,0.99)		0.67 (0.53, 0.84)	
p value (log-rank test)	0.035		< 0.001	
	(N=210)	**(N=210)**	**(N=210)**	**(N=210)**
Overall Response Rate[b] % (95% CI)	67 (59.5,73.0)	51 (44.5,58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)
% Difference in response rate[#] (CR+PR)	15		15	
95% CI for difference	(5.9, 24.5)		(6.0, 24.5)	
p value	0.0014		0.0014	
Median DoR (months)	9.2^	10.2^	12.9	10.6
(95 % CI)	(7.4, NR)	(7.5, NR)	(9.4, 19.5)	(9.1,13.8)

*Primary data cut: 26 August 2013, Final data cut: 12 January 2015
[#]ORR difference calculated based on the ORR result not rounded
^At the time of the reporting the majority (≥ 59 %) of investigator-assessed responses were still ongoing
CI: Confidence interval
Overall Response Rate (ORR) = Complete Response (CR) + Partial Response (PR)
DoR = Duration of Response
NR = Not reached

Adjuvant treatment of melanoma

MEKINIST in combination with dabrafenib

Randomised double blind study

Study BRF115532 / DRB436F2301 (COMBI-AD)

The efficacy and safety of MEKINIST in combination with Tafinlar was studied in a Phase III, multicentre, randomized, double blind, placebo-controlled study in patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (MEKINIST 2 mg once daily and Tafinlar 150 mg twice daily) or two placebos for a period of 12 months. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. Any prior systemic anticancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS

mutations were not eligible. Patients were stratified by BRAF mutation status (V600E or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomized to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%). The median duration of follow-up (time from randomization to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Figure 4 and in Table 16. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53 % risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95 % CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and has not yet been reached for the combination arm.

Table 16 COMBI-AD – Relapse-free survival results

RFS parameter	Dabrafenib + Trametinib N=438		Placebo N=432
Number of events, n (%)	166 (38%)		248 (57%)
Recurrence	163 (37%)		247 (57%)
Relapsed with distant metastasis	103 (24%)		133 (31%)
Death	3 (<1%)		1 (<1%)
Median (months)	NE		16.6
(95% CI)	(44.5, NE)		(12.7, 22.1)
Hazard ratio[1]		0.47	
(95% CI)		(0.39, 0.58)	
p-value[2]		1.53×10^{-14}	
1-year rate (95% CI)	0.88 (0.85, 0.91)		0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)		0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)		0.39 (0.35, 0.44)

[1] Hazard ratio is obtained from the stratified Pike model.

[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)

NE = not estimable

Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26 % information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95 % CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-

specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomization were 97 % and 91 % in the combination arm and 94 % and 83 % in the placebo arm, respectively. The Kaplan-Meier curve for this OS interim analysis is shown in Figure 5.

Figure 4 COMBI-AD - Relapse-free survival Kaplan-Meier curves (ITT Population)

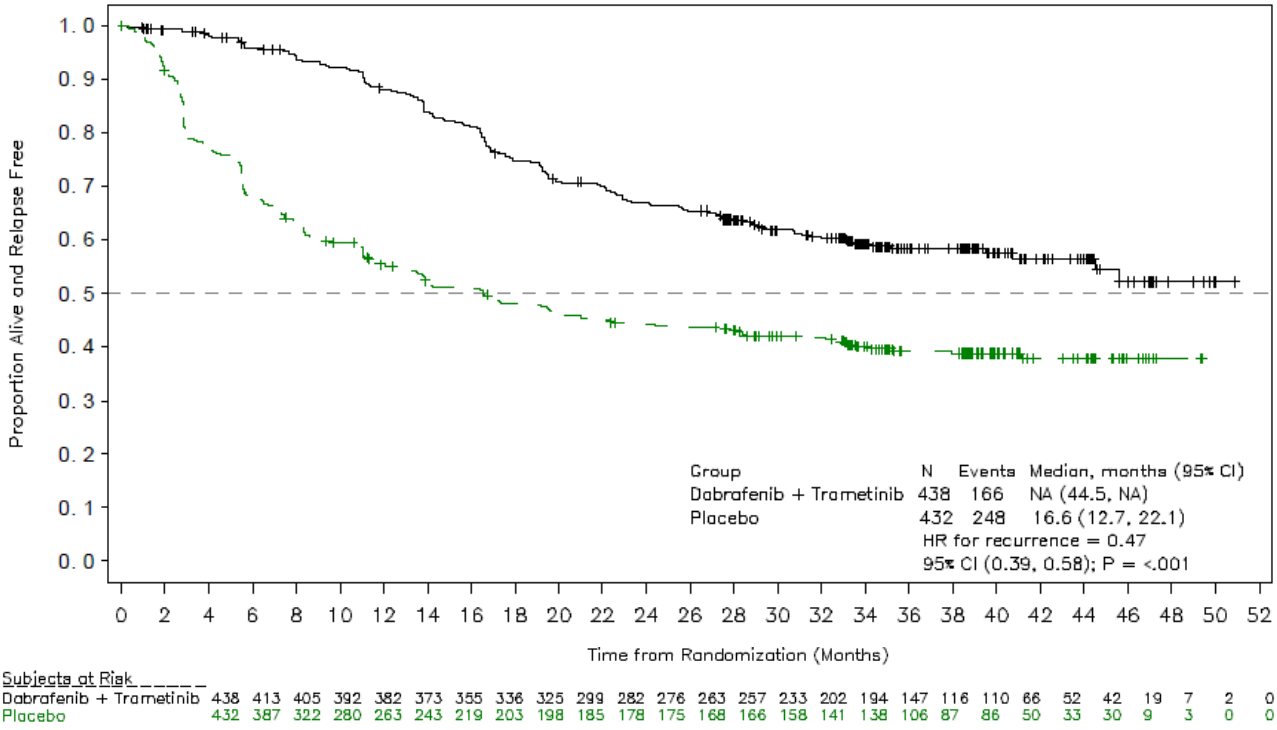
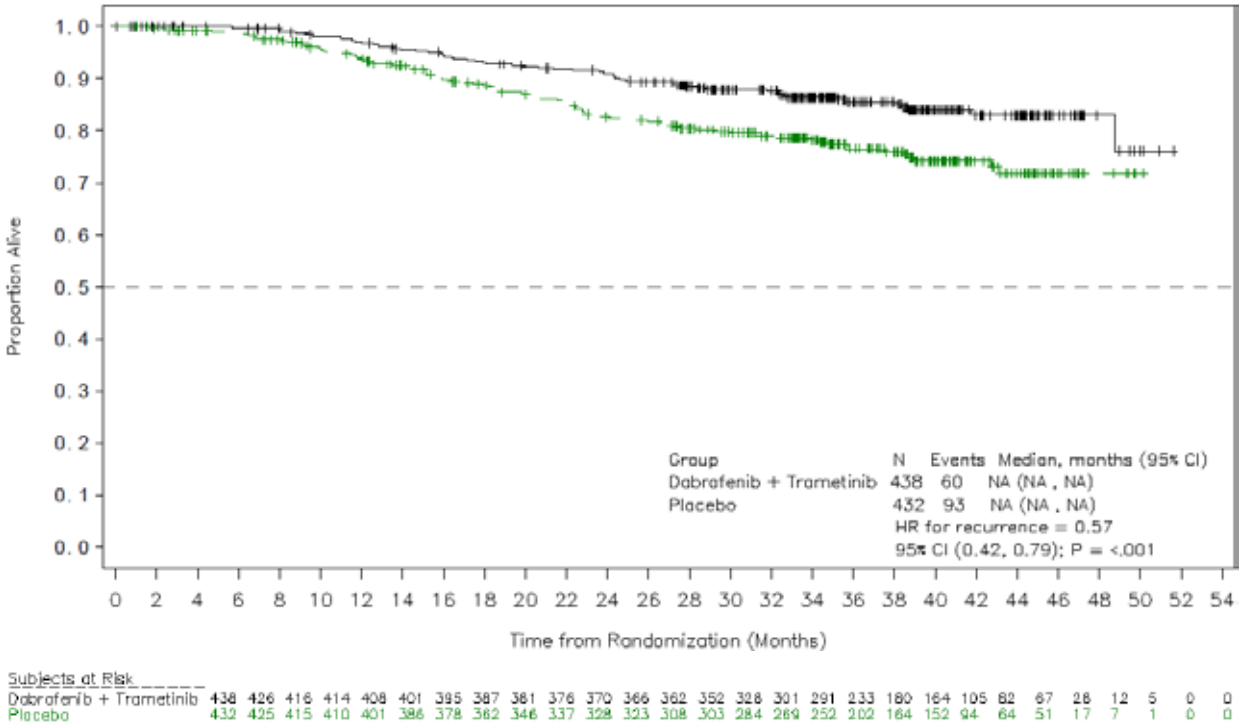


Figure 5 COMBI-AD – Overall survival Kaplan-Meier curves (ITT Population)



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, 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-patient variability was low (< 28%).

Effect of food on trametinib

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 section 4.2 Dose and method of administration).

Trametinib in 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 12 %, was estimated when trametinib is administered in combination with dabrafenib using a population pharmacokinetic analysis.

Distribution

Binding of trametinib to human plasma proteins is 97.4 %. Trametinib has a volume of distribution of 1,060 L determined following administration of a 5 microgram IV microdose.

Metabolism

In vitro and *in vivo* 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 the carboxyl-esterases 1b, 1c and 2, and may also be mediated by other hydrolytic enzymes.

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, ³ 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 section 4.2 Dose and method of 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 section 4.2 Dose and method of administration).

Use in the elderly

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

Paediatric use

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

Race/Ethnicity

There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics.

5.3 Preclinical Safety Data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List Of Excipients

The core tablets contain mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulphate, anhydrous colloidal silica. The film coating contains hypromellose, titanium dioxide, macrogol, iron oxide yellow (0.5 mg tablet only), polysorbate 80, and iron oxide red (2 mg tablet only).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf-life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store 2°C to 8°C (Refrigerate.)

Store MEKINIST tablets 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 1 month when stored up to 30°C.

6.5 Nature and contents of the container

MEKINIST tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures and desiccant, containing 7* or 30 tablets.

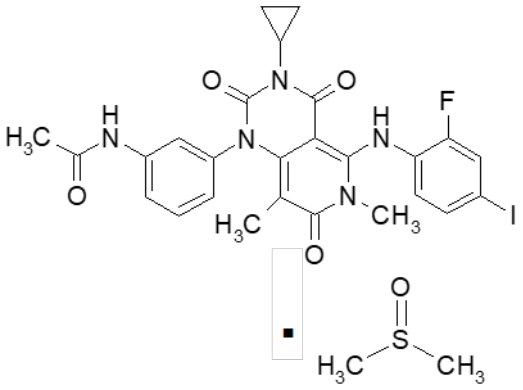
* Not all pack sizes, may be distributed in Australia.

6.6 Special precautions for disposal

Any unused product should not be disposed of in household waste or wastewater. Return it to a pharmacist for safe disposal.

6.7 Physicochemical properties

Chemical structure



Chemical Abstracts Service (CAS) registry number 1187431-43-1

Chemical name	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
Molecular formula	$C_{26}H_{23}FIN_5O_4.C_2H_6OS$
Molecular weight	693.5

Trametinib dimethyl sulfoxide is a polycyclic, nitrogen-containing heterocycle also possessing aromatic halide and amide functionality, and is a dimethyl sulfoxide solvate. Trametinib dimethyl sulfoxide is a white to almost white powder. It is almost insoluble in water. The calculated partition coefficient of trametinib dimethyl sulfoxide is 4.99.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113
Telephone 1 800 671 203
Web site: www.novartis.com.au

® = Registered Trademark

9. DATE OF FIRST APPROVAL

14 February 2014

10. DATE OF REVISION

6 June 2018

Summary table of changes

Section changed	Summary of new information
All	Product Information has been reformatted according to TGA guidance and includes the adjuvant melanoma indication

Internal document code
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