PRODUCT MONOGRAPH

PrTAFINLAR®

Dabrafenib (as dabrafenib mesylate)

Capsules, 50 mg and 75 mg

Protein Kinase Inhibitor

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Pr TAFINLAR®

Dabrafenib (as dabrafenib mesylate) Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules / 50 mg and 75 mg	*There are no clinically relevant nonmedicinal ingredients. For a complete listing of ingredients see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TAFINLAR (dabrafenib mesylate) is indicated as a monotherapy, or in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

A validated test is required to identify BRAF V600 mutation status.

TAFINLAR should not be used in patients with BRAF wild-type melanoma (see WARNINGS AND PRECAUTIONS, General).

Effectiveness of TAFINLAR monotherapy is based on overall response rate (ORR) and progression-free survival (PFS) results. Prolongation of overall survival (OS) and improvement in quality-of-life has not been demonstrated (see Part II, Clinical Trials).

Clinical data supporting the effectiveness of TAFINLAR monotherapy in patients with BRAF V600K mutations are limited, and clinical studies report fewer responses in BRAF V600K patients compared to BRAF V600E patients (see PART II, Clinical Trials).

There are no clinical data for TAFINLAR in the treatment of patients with other less common BRAF V600 mutations.

TAFINLAR monotherapy has not been studied in patients previously treated with BRAF inhibitors.

TAFINLAR in combination with trametinib is not recommended in patients who have previously progressed on a BRAF inhibitor due to its limited efficacy in patients who progressed on TAFINLAR monotherapy (see WARNINGS AND PRECAUTIONS).

When TAFINLAR is used in combination with trametinib, see also the MEKINIST® Product Monograph.

Geriatrics (≥ 65 years of age)

In clinical studies, elderly patients (≥ 65 years) experienced more serious adverse events when taking TAFINLAR (see WARNINGS AND PRECAUTIONS, Special Populations).

Paediatrics (< 18 years of age)

The safety and efficacy of TAFINLAR have not been established in children and adolescents less than 18 years of age (see WARNINGS AND PRECAUTIONS, Special Populations). Studies in juvenile animals have shown adverse effects which had not been observed in adult animals including shorter bone lengths and in very young animals renal toxicity. TAFINLAR is not recommended for use in children and adolescents (see WARNINGS AND PRECAUTIONS, Special Populations and TOXICOLOGY, Juvenile Toxicity).

CONTRAINDICATIONS

TAFINLAR is contraindicated in patients who are hypersensitive to dabrafenib or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

WARNINGS AND PRECAUTIONS

When TAFINLAR is used in combination with trametinib, **also consult the MEKINIST® Product Monograph** for important warnings and precautions for trametinib in regard to left ventricular dysfunction, retinal pigment epithelial detachment and retinal vein occlusion, interstitial lung disease, skin toxicity including serious cases, PR interval prolongation, hypertension, rhabdomyolysis and use in females, paediatrics and geriatrics.

Serious Warnings and Precautions

TAFINLAR (dabrafenib mesylate) should be prescribed by a physician experienced in the administration of anti-cancer agents.

TAFINLAR is teratogenic and embryotoxic in animals (see Special Populations, Paediatrics below).

TAFINLAR may decrease the efficacy of oral contraceptives (see Special Populations, Pregnant Women below).

TAFINLAR has not been studied in patients with moderate or severe hepatic impairment (see Special Populations, Hepatic Impairment below).

The following are significant adverse drug reactions identified in clinical trials conducted with TAFINLAR:

- Secondary malignancies (see Malignancies below)
- Non-infectious febrile events (see General below)

In addition to the above events, the following are significant adverse drug reactions identified in clinical trials conducted with TAFINLAR in combination with Trametinib:

- Venous Thromboembolism (see Cardiovascular below)
- Major haemorrhagic events (see Haematologic below)

General

Wild-type BRAF Melanoma and BRAF V600 Testing: Confirmation of BRAF V600 mutation in a tumour biopsy using a validated test is required for selection of patients appropriate for treatment with TAFINLAR.

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild-type cells exposed to BRAF inhibitors. This may promote growth of wild-type BRAF melanomas. New primary melanomas have been reported in patients taking TAFINLAR (see Malignancies below). TAFINLAR should not be used in patients with wild-type BRAF melanoma or in patients where the BRAF mutational status is not known.

Prior BRAF Inhibitory Therapy: TAFINLAR monotherapy has not been studied in patients previously treated with BRAF inhibitors.

The combination of TAFINLAR and trametinib demonstrated limited clinical activity in patients who had progressed on TAFINLAR monotherapy and is not recommended for patients who have progressed on a prior BRAF inhibitor. Of 43 patients in a phase I/II study who crossed over from TAFINLAR monotherapy to the combination of TAFINLAR plus trametinib following progression, only 9 % (95% CI: 2.6, 22.1) had an ORR and the median PFS was 3.6 months (95% CI: 1.8, 3.9).

Cytochrome P450 (CYP) Interactions: Dabrafenib is a moderate to strong *in vivo* inducer of CYP3A4, a weak *in vivo* inducer of CYP2C9 and may induce CYP2B6, CYP2C8, and CYP2C19. Medicinal products that are substrates for these CYPs, particularly those sensitive to induction, should be avoided, if possible. Dabrafenib is

likely to increase their metabolism and in most cases decrease their clinical effectiveness. In cases where metabolites are the active agent, an increase in toxicities associated with these medicinal products may be observed.

Dabrafenib is primarily metabolized by CYP3A4 and CYP2C8. There is potential for a greater risk of drug-related reactions following co-administration of moderate to strong CYP3A4 and CYP2C8 inhibitors as they may increase the systemic exposure of dabrafenib and its active metabolites (see DRUG INTERACTIONS, Drug-Drug Interactions).

Pyrexia and Serious Non-Infectious Febrile Events: Pyrexia was reported in clinical trials with TAFINLAR, and typically first occurred within two months of initiating therapy. The incidence and severity of pyrexia are increased when TAFINLAR is used in combination with trametinib (see below and ADVERSE REACTIONS, Clinical Trial Adverse Reactions). Serious febrile drug reactions, which are defined as serious cases of fever including fever of any severity accompanied by severe rigors or chills, dehydration, hypotension or renal failure in the absence of another cause (e.g. infection), have occurred following treatment with TAFINLAR.

In the phase III study, comparing TAFINLAR monotherapy to dacarbazine, serious febrile drug reactions occurred in 4.8% (9/187) of patients who received TAFINLAR monotherapy compared to no patients in the dacarbazine control arm. In this study, 12% (22/187) and 9% (17/187) of patients had their dose interrupted or reduced, respectively, due to febrile-related events. The median time to initial onset of febrile events was 3 weeks (range 0 to 54 weeks).

In the phase III study comparing TAFINLAR in combination with trametinib to TAFINLAR monotherapy, pyrexia occurred in 57% (119/209; 7% Grade 3) of patients who received combination therapy compared to 33% (69/211; 2% Grade 3) of patients treated with monotherapy. Serious febrile drug reactions occurred in 17% (35/209) of patients who received combination therapy compared to 7% (15/211) of patients treated with the monotherapy. The median time to initial onset of any (non-serious and serious) febrile event was 38 days (range 1 to 716 days) and 20 days (range 1 to 698 days) in patients receiving combination therapy and monotherapy, respectively. Thirty-one percent (64/209) of patients treated with the combination had 3 or more occurrences of pyrexia (any grade) compared to 7% (14/211) of patients treated with monotherapy. Permanent discontinuation of therapy due to pyrexia events was reported in 2% (4/209) of patients receiving combination therapy and in < 1% (2/211) of patients treated with monotherapy. Pyrexia events resulted in hospitalization in 14% of patients treated with the combination and in 5% of patients treated with monotherapy. In this study, the majority of patients in the combination therapy group with pyrexia required TAFINLAR dose modification to manage pyrexia events (dose interruption, dose reduction or permanent discontinuation). As compared to trametinib, approximately twice as many patients required TAFINLAR dose interruption, and approximately 5 times as many patients required TAFINLAR dose reduction, to manage events of pyrexia in the combination therapy group. A higher percentage of patients treated with the combination

(41%, 86/209) received medication for treatment of pyrexia than patients treated with the monotherapy (24%, 51/211). More patients receiving combination therapy (22%, 46/209) were also administered medications for secondary prophylactic treatment of pyrexia than patients receiving the monotherapy (9%, 19/211). Corticosteroids were used to manage pyrexia in 29% (61/209) of patients treated with the combination and 22% (47/211) of patients treated with single agent TAFINLAR. The median duration of corticosteroid use was approximately twice as long in patients treated with the combination (29 vs. 12 days).
Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia. TAFINLAR therapy should be interrupted if the patient's temperature is ≥ 38.5ºC or for any serious febrile drug reaction. Initiate treatment with anti-pyretics and evaluate patients for signs and symptoms of infection. Depending on the severity and duration of fever, TAFINLAR can be restarted once the fever resolves; prophylaxis using anti-pyretics may be required when resuming TAFINLAR. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Following resolution of grade 1 and 2 fevers (38.5-40.0 ºC) TAFINLAR can be restarted at the recommended daily dose (150 mg twice daily). Following resolution of fevers > 40.0°C or fevers associated with other severe signs or symptoms, if a decision is made to restart TAFINLAR, the dose should be reduced according to dose modification protocols (see DOSAGE AND ADMINISTRATION, Dose Modifications, Table 5 and Table 6).

For patients treated with the combination therapy, trametinib should be continued at the same dose for Grade 1 and 2 fevers (38.5-40.0 ºC). For fevers > 40°C or for any serious febrile drug reactions trametinib should also be interrupted until resolution of the adverse reaction and then resumed at the same or a reduced dose (see DOSAGE AND ADMINISTRATION, Dose Modifications, Table 5).

Brain Metastases: The safety and efficacy of the combination of TAFINLAR and trametinib has not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasized to the brain. Three patients who developed brain metastases while on treatment with TAFINLAR in combination with trametinib in phase III trials experienced fatal cerebral haemorrhage (see WARNINGS AND PRECAUTIONS, Haematologic).

Malignancies

Cutaneous Squamous Cell Carcinoma (CuSCC): Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with TAFINLAR (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

CuSCC occurred in 11% (86/797) of patients in the overall[1] TAFINLAR monotherapy population. In a pivotal phase III monotherapy study cuSCC occurred in 9% of patients treated with TAFINLAR, and in no patients treated with dacarbazine (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions). In the phase III combination study, cuSCC occurred in 3% (6/209) of patients receiving combination treatment with trametinib, compared to 10% (22/211) of patients receiving TAFINLAR monotherapy. In the study, the median time to onset of the first occurrence of cuSCC was 223 days for patients receiving combination therapy, and 60 days for patients in the monotherapy arm. All patients treated with monotherapy or combination therapy with trametinib who developed cuSCC continued on treatment without dose modification. Amongst the patients with cuSCC 67% (4/6) of patients receiving combination treatment with trametinib, and 32% (7/22) of patients receiving TAFINLAR monotherapy, developed subsequent lesions.

Skin examination should be performed prior to initiation of TAFINLAR and every 2 months during treatment with TAFINLAR. Monitoring should continue every 2 to 3 months for 6 months following discontinuation of TAFINLAR.

Cases of cuSCC should be managed by dermatological excision and TAFINLAR treatment can be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New Primary Melanoma: New primary melanomas were reported in 1% (11/797) of the overall TAFINLAR monotherapy population. In the phase III study comparing TAFINLAR to dacarbazine, new primary melanomas were reported in 2% (4/187) of patients treated with TAFINLAR monotherapy and in no patients treated with dacarbazine (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions). In the phase III combination study, new primary melanomas were reported in < 1% (1/209) of patients treated with combination treatment with trametinib and in 2% (4/211) of patients receiving TAFINLAR monotherapy.

Perform dermatologic monitoring as recommended for cuSCC above.

Non-Cutaneous Malignancy: The paradoxical activation of MAP-kinase signalling in BRAF wild type cells exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations, in patients treated with TAFINLAR. In clinical trials, cases of RAS-associated malignancies have been reported including colorectal adenocarcinoma, bile duct adenocarcinoma and pancreatic adenocarcinoma, which have resulted in discontinuation of TAFINLAR.

Non-cutaneous malignancies were reported in 2% (4/187) of patients receiving TAFINLAR monotherapy in the phase III study comparing TAFINLAR to dacarbazine.

[1] The overall monotherapy population includes integrated safety population of 586 patients with advanced metastatic melanoma and the monotherapy arm patients (N=211) of the phase III combination treatment study

In the phase III combination study, non-cutaneous malignancies were reported in 1% (3/209) and 3% (6/211) of patients receiving the combination treatment with trametinib and TAFINLAR monotherapy, respectively.

Evaluate patients for symptoms or clinical signs of non-cutaneous malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Consider the benefits and risks before continuing treatment with TAFINLAR in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with TAFINLAR.

Following discontinuation of TAFINLAR, monitoring for non-cutaneous malignancies should continue for up to 6 months. Abnormal findings should be managed according to clinical practices.

Cardiovascular

Valve Abnormalities: Patients were excluded from clinical studies of TAFINLAR if they had abnormal valve morphology of ≥ grade 2. Right sided heart valve defects were reported in one of 10 dogs treated with 50 mg/kg/day dabrafenib at > 5 times human clinical exposure (see TOXICOLOGY, General Animal Toxicity).

Worsening of baseline valve disease resulting in permanent discontinuation was reported in < 1% of patients (1/797) in the overall TAFINLAR monotherapy population.

QTc Prolongation: Patients were excluded from clinical studies of TAFINLAR if they had a baseline QTc of ≥ 480 mec. TAFINLAR is associated with QTc interval prolongation (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Particular care should be exercised when administering TAFINLAR to patients who are suspected to be at an increased risk of experiencing torsade de pointes.

Venous Thromboembolism: Fatal venous thromboembolism events have occurred when TAFINLAR was used in combination with trametinib.

In a phase I/II study, deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 6% (12/204) of patients treated with TAFINLAR in combination with trametinib, including 2 fatalities (1%). In the phase III combination study, DVT or PE occurred in 3% (6/209) of patients receiving combination therapy and in < 1% (2/211) of patients receiving TAFINLAR monotherapy.

If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care.

Endocrine and Metabolism

Hyperglycaemia: Grade 3 elevations of hyperglycaemia based on laboratory values were reported in 5% (39/797) of patients treated with TAFINLAR monotherapy; in addition, 1 subject reported a Grade 4 elevation. In the phase III combination study, a higher percentage of patients receiving TAFINLAR and trametinib combination therapy (7%, 15/209) had hyperglycaemia adverse events than patients receiving monotherapy (3%, 7/211). In this study, 2% (5/209) of patients in the combination arm reported Grade 3 events compared to < 1% (1/211) in the monotherapy arm. In addition, there was 1 subject with Grade 4 hyperglycaemia in the combination arm, compared to no Grade 4 cases in the monotherapy arm. In the phase III combination study all subjects with hyperglycaemia events in both treatment arms continued dosing. Four of 15 patients with a history of diabetes receiving TAFINLAR in combination with trametinib, and 2 of 16 patients with a history of diabetes receiving monotherapy, required more intensive hypoglycaemic therapy in this study.

Monitor glucose regularly in patients with diabetes or hyperglycaemia and adjust anti-diabetic treatments accordingly. Advise patients to report symptoms of severe hyperglycaemia such as excessive thirst or any increase in the volume or frequency of urination.

Gastrointestinal

Pancreatitis: Cases of pancreatitis have been reported in the overall TAFINLAR monotherapy population (< 1%, 3/797 patients) and in the post-marketing setting, generally occurring soon after initiation of TAFINLAR. One of the events occurred on the first day of dosing and recurred following re-treatment at a reduced dose. In phase I/II and phase III studies, pancreatitis has been reported in 2% (4/204) and < 1% (1/209), respectively, of patients treated with the combination of TAFINLAR and trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should interrupt dosing and should be closely monitored if re-starting TAFINLAR after an episode of pancreatitis.

Hematologic

Haemorrhage: An increase in bleeding events including major haemorrhagic events (defined as symptomatic bleeding in a critical site, and fatal intracranial haemorrhages), have been reported when TAFINLAR is used in combination with trametinib.

In a phase I/II study, bleeding events (any grade) were reported in 31% (17/55) of patients treated with combination therapy, compared to 6% (3/53) treated with single agent TAFINLAR. Intracranial haemorrhage occurred in 5% (3/55) of patients in the combination arm, and was fatal in two patients (4%). Gastrointestinal haemorrhage occurred in 7% (4/55) of patients in the combination arm; none of the events were fatal. No intracranial or gastrointestinal haemorrhage was reported in the monotherapy arm. In a phase III study, bleeding events (any grade) were reported in 19% (40/209) of patients treated with combination therapy compared to 15% (32/211) of patients receiving TAFINLAR monotherapy. Intracranial haemorrhage was fatal in 1% (3/209) of patients

in the study treated with combination therapy. Gastrointestinal haemorrhage occurred in 6% (12/209) of patients in the combination arm; none of the events were fatal. Gastrointestinal haemorrhage occurred in 3% (6/211) of patients in the Tafinlar monotherapy arm; none of the events were fatal. No intracranial haemorrhage was reported in the monotherapy arm.
In the phase III trials, 6 patients (1%) taking TAFINLAR in combination with trametinib experienced fatal cerebral haemorrhage, including 2 who were taking anticoagulants and 3 who had developed brain metastases. The risk for serious haemorrhagic events in patients with unstable and/or symptomatic brain metastases or low platelets (< 75,000) is not established, as patients with these conditions were excluded from clinical trials. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy or in patients who develop brain metastases while on treatment. If haemorrhage occurs, patients should be treated as clinically indicated.

Patients should be advised to seek immediate medical care if they develop symptoms of haemorrhage.

Cerebral haemorrhage (including fatal cases) associated with TAFINLAR in combination with trametinib were reported in clinical trials and during post-marketing use.

Neutropenia: Neutropenia as an adverse event, including Grade 3 or 4 occurrences (14%, 30/209), has been reported in association with the combination of TAFINLAR and trametinib. Patients receiving the combination therapy should have their complete blood counts determined at baseline and periodically on treatment (see Monitoring and Laboratory Results).

Hepatic

Hepatotoxicity: Hepatic adverse events have been reported when TAFINLAR is used in combination with trametinib. In the phase III combination study a higher percentage of patients had hepatic events in the combination therapy arm (39 patients, 19%), including Grade 3 adverse events (7%), than in the TAFINLAR monotherapy arm [25 patients, 12%; Grade 3 (1%); Grade 4 (< 1%)]. In the combination arm, adverse events that led to dose reduction occurred in 3 patients (1%) due to TAFINLAR and 4 patients (2%) due to trametinib; no cases were reported in the monotherapy arm; adverse events that led to dose interruption occurred in 8 patients (4%) due to TAFINLAR and in 9 patients (4%) due to trametinib in the combination arm compared to 4 patients (2%) in the monotherapy arm; adverse events that led to the drug being withdrawn occurred in 2 patients (< 1%) due to TAFINLAR and in 1 patient (< 1%) due to trametinib; no cases were reported in the monotherapy arm. Two patients receiving the combination therapy permanently discontinued either TAFINLAR or both TAFINLAR and trametinib due to elevations in liver enzymes (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Ophthalmologic

Uveitis: Ophthalmologic reactions, most notable uveitis (including iritis), have been reported in patients treated with TAFINLAR. The severity of uveitis is increased when TAFINLAR is used in combination with trametinib (see below and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). Uveitis was observed in 1% (11/797) of patients in the overall TAFINLAR monotherapy population. All cases reported were Grade 1 or 2.

Uveitis was reported in 2% (9/559) of patients treated with the combination of TAFINLAR and trametinib in a large phase III clinical trial population. The 9 patients experienced 10 events; four events were Grade 3. Four of the 10 events were managed without dose interruption of TAFINLAR (or trametinib). Five of the 10 events resulted in interruption (4 cases) or discontinuation (1 case) of both TAFINLAR and trametinib. In the remaining case only trametinib was interrupted, while the doses of both TAFINLAR and trametinib were reduced. All but one of the Grade 3 cases resulted in dose interruption of TAFINLAR and trametinib (2 cases) or discontinuation of both drugs (1 case), the remaining case did not modify dosing due to uveitis.

Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy and withhold TAFINLAR (and trametinib when used in combination therapy) in patients with uveitis whose symptoms do not improve despite local ocular therapy (see DOSAGE AND ADMINISTRATION, Dose Modifications).

Reproduction

Infertility: There are no fertility data in humans. Adverse effects of dabrafenib on male reproductive organs have been seen in animals (see Part II, TOXICOLOGY, Reproductive and Developmental Toxicity). Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

Renal

Renal Failure: Renal failure was reported in 1.5% of patients in the overall TAFINLAR monotherapy population (12/797). Renal failure was associated with pyrexia and/or dehydration in 4 of 12 cases. In a phase I/II trial, renal failure was reported in 7% (4/55) of patients treated with TAFINLAR in combination with trametinib compared to 4% (2/53) of patients treated with TAFINLAR monotherapy; all events were Grade 3/Grade 4 (combination therapy) or Grade 2 (monotherapy). In a phase III trial, renal failure was reported in 4% (8/209) of patients treated with the combination of TAFINLAR and trametinib and in 2% (5/211) of patients treated with TAFINLAR monotherapy. In the combination therapy, renal failure was associated with pyrexia and/or dehydration in 5 of the 8 cases. In this study, 2 patients in the combination therapy arm and no patients in the TAFINLAR monotherapy arm reported Grade 3 events of increased blood creatinine and nephritis. Granulomatous/tubulointerstitial nephritis has also been reported in the phase

III clinical study of the combination of TAFINLAR and trametinib as well as in the post-marketing setting with TAFINLAR monotherapy (see ADVERSE REACTIONS).

Monitor serum creatinine and other evidence of renal function routinely during treatment and in events of severe pyrexia.

Special Populations

Pregnant Women: TAFINLAR should not be administered to pregnant women. Dabrafenib may cause foetal harm by interfering with BRAF function, which is essential for the developing embryo. There are no adequate and well-controlled studies of TAFINLAR in pregnant women. Dabrafenib caused reproductive toxicity and teratogenicity in rats (see Part II, TOXICOLOGY, Reproductive and Developmental Toxicity).

Women of childbearing potential should use effective methods of contraception during therapy (methods that result in less than 1% pregnancy rates) and for 4 weeks following discontinuation of TAFINLAR and at least 4 months following the last dose of trametinib when taken in combination with TAFINLAR. Dabrafenib is likely to decrease the efficacy of hormonal contraceptives and alternate methods of contraception should be used (see DRUG INTERACTIONS, Effect of Dabrafenib on Other Drugs).

If TAFINLAR is used during pregnancy, or if the patient becomes pregnant while taking TAFINLAR, the patient should be advised of the potential risk to the foetus.

Nursing Women: No studies have been conducted with TAFINLAR in nursing mothers. TAFINLAR should not be used by nursing women. It is not known whether dabrafenib is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from dabrafenib in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Paediatrics (< 18 years of age): The safety and efficacy of TAFINLAR have not been established in children and adolescents less than 18 years of age. Studies in juvenile animals have shown adverse effects, including effects on growth and renal toxicity, which had not been observed in adult animals. Renal toxicity was observed in juvenile rats, primarily in animals < 22 days old, which suggests a higher risk for tubular injury for human infants < 1 year of age. The mean lengths of the femur and tibia were shorter compared to controls, and physeal hypertrophy of these bones was observed in 2 of 40 juvenile rats (see TOXICOLOGY, Juvenile Toxicity). TAFINLAR is not recommended for use in children and adolescents.

Geriatrics (≥ 65 years of age): Of the total number of patients in clinical studies of TAFINLAR monotherapy (N = 797), 23% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger patients (< 65 years), more patients ≥ 65 years old had adverse events that led to dabrafenib dose reductions (23% versus 14%) or interruptions (46% versus 30%). In addition, older patients experienced more serious adverse events compared to younger patients (46% versus 27%).

Of the number of patients in a phase III clinical study receiving TAFINLAR in combination with trametinib (N = 209), 56 patients (27%) were 65 years of age and older, and 11 patients (5%) were 75 years of age and older. Compared with younger patients (< 65 years), more patients ≥ 65 years old had adverse events that led to dose reductions (43% versus 23%) or interruptions (66% versus 53%) of therapy with TAFINLAR or trametinib. In addition, older patients experienced more serious adverse events compared to younger patients (59% versus 36%). The incidences of peripheral oedema in the combination (34% vs. 16%) and monotherapy arms (18% vs. 5%) and of decreased appetite in the combination (21% vs. 9%) and monotherapy arms (15% vs. 13%) were more frequent in patients ≥ 65 years than in patients < 65 years, respectively.

Hepatic Impairment: There are no clinical data in patients with moderate to severe hepatic impairment. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites. Therefore, patients with moderate to severe hepatic impairment may have increased exposure and increased toxicities. No dosing recommendations have been established for TAFINLAR in these patients (see DOSING AND ADMINISTRATION, Hepatic Impairment; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal Impairment: There are no clinical data in patients with severe renal impairment. TAFINLAR should be used with caution in patients with severe renal impairment (see DOSING AND ADMINISTRATION, Renal Impairment; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations).

Monitoring and Laboratory Tests

Before taking TAFINLAR, confirmation of the existence of a BRAF V600 mutation in a tumour specimen is required, using a validated test.

Before taking TAFINLAR, at every 2 months during therapy and every 2 to 3 months for 6 months after discontinuation, patients should be monitored for cuSCC and new primary melanomas. Monitor for non-cutaneous malignancies as clinically appropriate. Patients should also be monitored for uveitis including visual disturbances during therapy.

Electrolytes (including phosphate) and glucose determinations should be performed at baseline and periodically while on TAFINLAR therapy. Glucose should be monitored more often in patients with pre-existing diabetes or hyperglycaemia.

Blood pressure should be measured at baseline and periodically during treatment (see ACTION and CLINICAL PHARMACOLOGY).

Monitor serum creatinine and other evidence of renal function routinely during treatment and in events of severe pyrexia.

Monitor patients receiving TAFINLAR in combination with trametinib carefully for

bleeding events and neurologic symptoms.

Patients receiving the combination therapy should have their complete blood counts determined at baseline and periodically on treatment.

Monitor liver function in patients receiving treatment with TAFINLAR in combination with trametinib approximately every 4 weeks for 6 months after treatment initiation of this combination therapy. Liver monitoring may be continued thereafter as clinically indicated during therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of TAFINLAR monotherapy has been evaluated in an integrated safety population of 586 patients with BRAF V600-mutant advanced or metastatic melanoma, with a median duration of treatment of 5.5 months (range 0 to 23 months). Approximately 46% of patients received treatment with TAFINLAR for more than 6 months.

The most common adverse drug reactions (≥ 15%) of any grade for TAFINLAR in either the overall monotherapy safety population or phase III pivotal study comparing TAFINLAR to dacarbazine include hyperkeratosis, headache, pyrexia, palmar-plantar erythrodysaesthesia (PPE), arthralgia, fatigue, nausea, skin papilloma, alopecia, and rash.

The safety of TAFINLAR in combination with trametinib has been evaluated in a multicentre, randomized phase III study (MEK115306) in a safety population of 209 patients with advanced or metastatic melanoma. In this study, approximately 71% of patients received treatment with TAFINLAR and trametinib for more than 6 months. The median durations of treatment in the combination and monotherapy arms were 11 and 8 months, respectively.

A higher percentage of patients had AEs leading to permanent discontinuation of study treatment in the combination therapy arm of the MEK115306 study (11%) than in the monotherapy arm (7%). The percentage of patients with AEs leading to dose interruptions and dose reductions was also higher in the combination therapy arm than with TAFINLAR monotherapy. Fifty six percent (56%) and 28% of patients receiving the combination therapy had dose interruptions and reductions, respectively, compared to 37% and 14% of patients treated with the monotherapy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug

reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

TAFINLAR Monotherapy

Table 1 reports adverse drug reactions from the pivotal phase III study comparing TAFINLAR monotherapy to dacarbazine (DTIC) in previously untreated patients with advanced or metastatic melanoma (BRF113683) and one phase II single-arm study in patients with melanoma metastatic to the brain (BRF113929) (see Part II, CLINICAL TRIALS). The laboratory abnormalities presented in Table 2 were identified from the pivotal phase III study. In study BRF113683, patients were allocated to TAFINLAR 150 mg orally twice daily or to DTIC intravenously 1000 mg/m^2 every 3 weeks. In study BRF113929, TAFINLAR was administered as 150 mg orally twice daily in an open label fashion. Adverse reactions are presented in Table 1.

In the phase III study, 28% of patients treated with TAFINLAR and 24% of patients treated with dacarbazine experienced serious adverse events (SAEs). The most common treatment-related SAEs in patients treated with TAFINLAR were cuSCC and pyrexia. Serious cases of pyrexia occurred in 10 of 187 patients (5%). Serious cases of cuSCC occurred in 12 of 187 patients (6%).

The incidence of adverse events resulting in permanent discontinuation of study medication in study BRF113683 was 3% for patients treated with TAFINLAR and 2% for patients treated with DTIC. In study BRF113929, the incidence of adverse events resulting in permanent discontinuation of study medication for TAFINLAR was 2%. The median duration of study treatment was 7.5 months for TAFINLAR and 2.8 months for DTIC in study BRF113683, and 3.9 months for TAFINLAR in study BRF113929. The incidence of adverse events leading to dose reductions was 20% for TAFINLAR and 17% for DTIC in study BRF113683 and was 14% for TAFINLAR in study BRF113929. The incidence of adverse events leading to dose interruptions was 32% for TAFINLAR and 27% for DTIC in study BRF113683 and was 32% for TAFINLAR in study BRF113929.

Table 1 Adverse Reactions Occurring in ≥ 10% (All grades) or ≥ 2% (Grades 3 or 4) of Patients in 2 Clinical Trials of TAFINLAR Monotherapy

	BRF113683: Treatment Naïve Patients				**BRF113929: Patients With Brain Metastases**	
	TAFINLAR N = 187		**DTIC N = 59**		**TAFINLAR N = 172**	
Event	**All Grades (%)**	**Grade 3 and Grade 4 (%)**	**All Grades (%)**	**Grade 3 and Grade 4 (%)**	**All Grades (%)**	**Grade 3 and Grade 4 (%)**
Neoplasms benign and malignant (including cysts and polyps)						
Skin papilloma	25	0	2	0	15	0
cuSCC[a, b]	9	7	0	0	6	4
Metabolism and nutritional disorders						

	BRF113683: Treatment Naïve Patients				BRF113929: Patients With Brain Metastases	
	TAFINLAR N = 187		DTIC N = 59		TAFINLAR N = 172	
Event	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Decreased appetite	12	0	8	3	12	2
Hyperglycaemia	7	3	7	0	5	1
Hypophosphatemia	5	2	0	0	5	2
Nervous system disorders						
Headache	34	0	8	0	28	2
Respiratory, thoracic and mediastinal disorders						
Cough	14	0	7	0	10	0
Gastrointestinal disorders						
Constipation	13	2	15	0	8	0
Diarrhoea	14	< 1	12	0	13	< 1
Nausea	27	< 1	53	0	26	2
Vomiting	18	1	25	0	20	1
Skin and subcutaneous disorders						
Alopecia	29	< 1	3	0	15	0
Hyperkeratosis	39	2	2	0	26	< 1
PPE[c]	20	2	2	0	15	2
Rash	18	0	0	0	17	0
Dry Skin	10	0	0	0	8	0
Musculoskeletal, connective tissue and bone disorders						
Arthralgia	32	2	2	0	17	0
Myalgia	13	0	0	0	15	0
Pain in extremity	13	< 1	10	0	12	0
General disorders and administration site conditions						
Asthenia	19	< 1	15	2	5	0
Fatigue	22	1	24	0	25	1
Pyrexia	31	3	14	0	26	< 1
Chills	12	0	2	0	11	< 1
Infections and infestations						
Nasopharyngitis	16	0	7	0	6	0

[a] Includes squamous cell carcinoma of the skin, squamous cell carcinoma *in situ* (Bowen's disease) and keratoacanthoma

[b] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol

[c] PPE = Palmar-plantar erthyrodysesthesia syndrome (hand-foot syndrome)

Less Common Clinical Trial Adverse Drug Reactions with TAFINLAR Monotherapy

Other clinically relevant adverse reactions reported in < 10% of patients or < 2% of

patients with Grade 3 or 4 events treated with TAFINLAR monotherapy in the integrated safety population are presented below.

Cardiac Disorders: Atrial fibrillation (2%), Hypotension (< 1%)

Eye Disorders: Uveitis (1%)

Gastrointestinal: Pancreatitis (< 1%)

Immune: Influenza-like illness (4%), Hypersensitivity (1%)

Metabolic and Nutritional: Hyponatremia (3%)

Renal: Acute renal failure (1%), Renal failure (1%)

Skin and Subcutaneous Disorders: Actinic keratosis (9%), Seborrhoeic keratosis (8%), Erythema (6%), Acrochordon (5%), Skin lesion (5%), Pruritus (7%), Photosensitivity (3%), Panniculitis, including erythema nodosum (1%), New primary melanoma (1%)

Table 2 Laboratory Abnormalities Increased from Baseline in the Phase III Study BRF113683*

	TAFINLAR N = 187		**DTIC N = 59**	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycaemia	56	8	45	0
Hypophosphatemia	41	6	18	2
Hyponatremia	8	2	3	0
Increased Alkaline Phosphatase	23	0	16	2

*No grade 4 laboratory abnormalities in dabrafenib-treated or DTIC-treated patients were reported

TAFINLAR in Combination with Trametinib

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities, respectively, from the phase III study of TAFINLAR 150 mg given twice daily in combination with trametinib 2 mg given once daily compared to TAFINLAR monotherapy (see Part II, CLINICAL TRIALS). The common adverse reactions in Table 3 were reported in ≥ 10% of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in ≥ 2% of patients treated with the combination treatment.

Table 3 Adverse Reactions (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 or 4) of Patients Treated with TAFINLAR in Combination with Trametinib in Study MEK115306

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Neoplasms benign and malignant (including cysts and polyps)				
cuSCC[a,b]	3	3	10	10
Metabolism and nutritional disorders				
Decreased appetite	12	< 1	13	< 1
Hyperglycaemia[c]	7	3	3	< 1
Nervous system disorders				
Headache	33	< 1	30	1
Dizziness	14	0	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough	21	0	21	0
Gastrointestinal disorders				
Nausea	34	< 1	27	1
Diarrhoea	30	1	16	< 1
Vomiting	25	< 1	14	< 1
Constipation	13	< 1	10	0
Abdominal pain	13	< 1	9	2
Skin and subcutaneous tissue disorders				
Rash	27	0	22	< 1
Dry skin	12	0	16	0
Pruritus	12	0	14	0
Dermatitis acneiform	10	0	4	0
Musculoskeletal, connective tissue and bone disorders				
Arthralgia	26	< 1	31	0
Pain in extremity	15	1	17	< 1
Myalgia	13	< 1	13	0
General disorders and administrative site conditions				
Pyrexia	57	7	33	2
Fatigue	39	2	37	1
Chills	31	0	17	< 1
Asthenia	12	1	14	< 1
Oedema peripheral	21	< 1	9	< 1
Infections and infestations				
Nasopharyngitis	12	0	10	0
Urinary tract infection	11	2	3	< 1
Vascular disorders				
Hypertension	25	6	16	6

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Hypotension	6	2	3	< 1
Haemorrhage	19	2	15	2
Cardiac disorders				
Ejection fraction decreased	6	1	3	2
Blood and lymphatic system disorders				
Neutropenia	10	3	2	< 1
Anaemia	6	3	9	4
Hepatobiliary disorders				
ALT increased	13	2	6	< 1
AST increased	13	3	4	< 1

[a] Includes squamous cell carcinoma of skin, squamous cell carcinoma *in situ* (Bowen's disease) and keratoacanthoma

[b] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol

[c] Includes hyperglycemia, type 2 diabetes, diabetes mellitus, and blood glucose increase

Less Common Clinical Trial Adverse Drug Reactions with TAFINLAR in combination with trametinib

In addition to adverse reactions observed in the monotherapy studies, other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR 150 mg twice daily in combination with trametinib 2 mg once daily in the safety population from the phase III clinical trial include:

Blood and Lymphatic System Disorders: Thrombocytopenia (4%), Leukopenia (4%)

Cardiac Disorders: Bradycardia (< 1%)

Eye Disorders: Vision blurred (3%), Visual impairment (2%), Periorbital oedema (< 1%), Chorioretinopathy (< 1%), Uveitis (< 1%), Retinal detachment (< 1%)

Gastrointestinal Disorders: Dry mouth (8%), Stomatitis (1%), Pancreatitis (< 1%)

General Disorders: Mucosal inflammation (2%), Influenza-like illness (8%), Face oedema (2%)

Hepatobiliary Disorders: Gamma-glutamyltransferase increased (2%), Blood alkaline phosphatase increased (8%)

Immune: Hypersensitivity (< 1%)

Infections and Infestations: Cellulitis (3%), Folliculitis (6%), Paronychia (2%), Rash pustular (3%)

Metabolism and Nutrition Disorders: Hyponatremia (2%), Dehydration (1%), Hypophosphatemia (4%)

Musculoskeletal and Connective Tissue Disorders: Muscle spasm (9%), Blood creatine phosphokinase increased (3%)

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Seborrheic keratosis (4%), Skin papilloma (2%), Acrochordon (skin tags) (1%), New primary melanoma (< 1%)

Renal: Renal failure (< 1%), Granulomatous/tubulointerstitial nephritis (< 1%)

Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea (6%), Pneumonitis (< 1%)

Skin and Subcutaneous Tissue Disorders: Erythema (9%), Alopecia (9%), Night sweats (6%), Hyperhidrosis (7%), Hyperkeratosis (7%), Skin lesion (3%), Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (5%), Actinic keratosis (5%), Urticaria (3%), Panniculitis, including erythema nodosum (3%), Skin fissures (2%)

Vascular Disorders: Deep vein thrombosis and pulmonary embolism (3%), Lymphedema (<1%)

Table 4 Laboratory Abnormalities Changed from Baseline in the Phase III Study MEK115306

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		**TAFINLAR 150 mg BID + Placebo (N = 211)**	
Preferred Term	**All Grades (%)**	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Hyperglycaemia	65	6	57	4
Hypophosphatemia	38	4	35	7
Hyponatremia	24	6	14	3
Hypoalbuminemia	53	1	27	0
Creatinine	10	< 1	7	< 1
Increased Alkaline Phosphatase	50	< 1	25	< 1

Post-Market Adverse Drug Reactions

The following adverse reaction has been identified during post-approval use of TAFINLAR. These include spontaneous case reports as well as serious adverse events from registries, investigator-sponsored studies, clinical pharmacology studies and exploratory studies in unapproved indications.

Renal and urinary disorders: nephritis/tubulointerstitial nephritis

DRUG INTERACTIONS

Serious Drug Interactions

Dabrafenib is teratogenic and embryofoetal toxic in animals and is likely to reduce the effectiveness of oral contraceptives. Alternative means of contraception should be considered in women of childbearing potential taking TAFINLAR.

Overview

Dabrafenib is a moderate to strong *in vivo* inducer of CYP3A4, a weak *in vivo* inducer of CYP2C9 and may induce other enyzmes or transporters including additional CYPs (CYP2B6, CYP2C8, CYP2C19), UDP glucuronosyltransferases (UGTs) and P-glycoprotein (P-gp). Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Because dabrafenib induces CYPs involved in its own metabolism steady-state exposure to dabrafenib is lower than exposure following a single daily dose (see ACTION AND CLINICAL PHARMACOLOGY).

Drug interactions have the potential to affect circulating concentrations of dabrafenib and its 3 predominant metabolites (hydroxy-, desmethyl- and carboxy-dabrafenib). The hydroxy and desmethyl metabolites have similar exposure and BRAF inhibitory activity compared to dabrafenib. The carboxy metabolite is less active but has > 10-fold higher exposure compared to the parent drug and the other two metabolites (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The concomitant use of TAFINLAR with medicinal products known to prolong QTc interval or medicinal products able to induce torsades de pointes should be avoided if possible. Medicinal products that are generally accepted to carry the risk of QT prolongation and torsades de pointes include: Class IA (e.g. quinidine, disopyramide, procainamide), Class III (e.g. amiodarone, sotalol, ibutilide), or Class IC (e.g. flecainide), antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine, haloperidol, pimozide), opioids (e.g. methadone), macrolide antibiotics (e.g. erythromycin), clarithromycin, quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. chloroquine), GI stimulants or others (e.g. domperidone, droperidol).

Drug-Drug Interactions

Effect of Dabrafenib on Other Drugs: In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. In a clinical study of 12 patients, repeat-dose of dabrafenib lowered the C_{max} and AUC of a single-dose of midazolam, a CYP3A4 substrate, by 61 % and 74 %, respectively. In a separate trial in 14 subjects, repeat-dose dabrafenib decreased the single-dose AUC of S-warfarin (a substrate of CYP2C9) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37 % and 33 %, respectively, with small increases in C_{max} (18 and 19 % respectively). Thus, dabrafenib is considered a moderate to strong inducer of CYP3A4 and a weak inducer of CYP2C9 at the recommended therapeutic dose and may induce other enzymes or transporters including CYP2B6, CYP2C8, CYP2C19, and UGTs and P-gp.

Co-administration of TAFINLAR with medications such as hormonal contraceptives (see WARNINGS AND PRECAUTIONS, Special Populations), warfarin, or dexamethasone may result in decreased concentrations and loss of their efficacy. Consider substitution of these medicinal products. If co-administration of these medications is necessary, monitor patients for loss of efficacy.

Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and the clinical relevance of this inhibition can not be excluded. Therefore, caution is recommended at co-administration of dabrafenib and OATB1B1 or OATP1B3 substrates such as statins.

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro*, the risk of a drug-drug interaction is minimal based on clinical exposure. Dabrafenib and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP); however, based on clinical exposure, the risk of a drug-drug interaction is minimal.

Effect of Other Drugs on Dabrafenib: Results of *in vitro* studies indicate that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib while hydroxy-dabrafenib and desmethyl-dabrafenib are metabolized primarily by CYP3A4. Therefore, inhibitors or inducers of these enzymes have the potential to affect the PK of dabrafenib or its metabolites. Patients experienced an increase in steady-state dabrafenib C_{max} (33 %) and AUC (71%) with co-administration of the CYP3A4 inhibitor ketoconazole, and increases in the active metabolites hydroxy- and desmethyl-dabrafenib (AUC increases of 82 and 68 %, respectively). A decrease in exposure was noted for the less active carboxy-metabolite (AUC decrease of 16%). Co-administration of dabrafenib and gemfibrozil (a CYP2C8 inhibitor) resulted in an increase in steady-state dabrafenib AUC (47%) and no relevant change in the concentrations of the metabolites.

Strong (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir, gemfibrozil) CYP3A4 or CYP2C8 inhibitors should be avoided if possible and alternative agents should be considered during administration with TAFINLAR.

Co-administration with strong inducers of CYP3A4 and CYP2C8 (e.g., rifampin, phenytoin, carbamazepine, Phenobarbital, St John's wort) should be avoided due to the possibility of sub-therapeutic exposure to dabrafenib. Monitor patients for loss of efficacy or consider substitutions of these medicinal products.

Drugs that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When TAFINLAR is co-administered with a proton pump inhibitor, H2-receptor antagonist, or antacid, systemic exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is unknown.

Dabrafenib is a substrate of human P-gp and BCRP1 *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a drug-drug interaction is minimal.

Drug-Food Interactions

High fat foods reduce the exposure to dabrafenib (see DOSAGE and ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Drug-Life Interactions

There have been no studies to investigate the effect of TAFINLAR on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of TAFINLAR should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

Patients should be made aware of the potential for fatigue and eye problems to affect these activities.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Recommended Dose

When using TAFINLAR in combination with trametinib, please refer to the MEKINIST Product Monograph for full dosing instructions.

The recommended dose regimens of TAFINLAR are:

Monotherapy: 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg).

Combination with trametinib: 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg) with 2 mg of trametinib given orally once daily.

TAFINLAR alone or in combination with trametinib should be taken without food and with a full glass of water at least one hour before, or at least two hours after a meal, leaving an interval of approximately 12 hours between doses (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). TAFINLAR should be taken at similar times every day.

When TAFINLAR and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of TAFINLAR.

Treatment should continue until disease progression or the development of unacceptable toxicity (Table 5).

Dose Modifications

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation of TAFINLAR (see Table 5 and Table 6).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see WARNINGS AND PRECAUTIONS).

Specific dose modifications and reductions for febrile related drug reactions and non-febrile related events as graded by the Common Terminology Criteria for Adverse Events

(CTC-AE) are provided in Table 5. Dose level reductions are listed in Table 6. Dosing adjustments resulting in a TAFINLAR dose lower than 50 mg twice daily are not recommended and TAFINLAR should be permanently discontinued in these instances.

Table 5 Dose Modification Schedule for TAFINLAR-Related Adverse Events

Adverse Reaction[a]	TAFINLAR	Trametinib (when used in combination)
Cardiac		
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pre-treatment value	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Withhold trametinib for up to 4 weeks
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below LLN that improves to normal LVEF value within 4 weeks following interruption of trametinib	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily
• Absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption of trametinib	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Permanently discontinue trametinib
• Symptomatic congestive heart failure	• Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level	• Permanently discontinue trametinib
• Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	• Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level	• Permanently discontinue trametinib
Febrile Drug Reaction		
• Fever of 38.5 – 40 °C without complications	• Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level	• Trametinib may be continued at the same dose
• Fever > 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure	• Discontinue treatment with TAFINLAR permanently, or withhold therapy until adverse reaction resolves. If resuming TAFINLAR	• Withhold trametinib until adverse reaction resolves and resume trametinib at the same or a reduced dose

Adverse Reaction[a]	TAFINLAR	Trametinib (when used in combination)
	therapy, administer at a reduced dose level.	
Ocular		
• Grade 2-3 retinal pigment epithelial detachments (RPED)	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Withhold trametinib for up to 3 weeks
• Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• If improved to grade 0-1 within 3 weeks, resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily
• Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks OR recurrence of RPED (any Grade) after dose interruption or reduction	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Permanently discontinue trametinib
• Retinal vein occlusion	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Permanently discontinue trametinib
• Uveitis that responds to local ocular therapy	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Trametinib may be continued at the same dose
• Uveitis that does not improve despite ocular therapy	• Withhold TAFINLAR until adverse reaction resolves and reduce by one dose level when resuming therapy	• Withhold trametinib until adverse reaction resolves and resume at the same or a reduced dose
Pulmonary		
• Interstitial lung disease / pneumonitis	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Permanently discontinue trametinib
Other		
• Grade 1 or Grade 2 (Tolerable)	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.	• Trametinib may be continued at the same dose. Monitor as clinically indicated.

Adverse Reaction[a]	TAFINLAR	Trametinib (when used in combination)
• Grade 2 (intolerable) OR Grade 3 adverse reaction	• Withhold TAFINLAR until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy	• Withhold trametinib. If adverse reaction resolves or improves to Grade 1, reduce by one dose level when resuming therapy
• Grade 4 adverse reaction OR Grade 3 adverse reaction that does not improve to Grade 0-1	• Permanently discontinue TAFINLAR OR withhold therapy until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy	• Permanently discontinue trametinib

[a] The intensity of clinical adverse events (with the exception of febrile drug reactions) graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

Table 6 Recommended Dose Level Reductions for TAFINLAR

Dose Level Reductions for TAFINLAR	
First reduction	100 mg twice daily (2 x 50 mg twice daily)
Second reduction	75 mg twice daily (1 x 75 mg twice daily)
Third reduction	50 mg twice daily (1 x 50 mg twice daily)
If unable to tolerate 50 mg twice daily	Discontinue TAFINLAR
Dose Level Reductions for Trametinib When Used in Combination with TAFINLAR	
First reduction	1.5 mg once daily
Second reduction	1 mg once daily
If unable to tolerate 1 mg once daily	Discontinue trametinib

Dosing Considerations

Concomitant Use with CYP3A4 Inhibitors or Inducers: Avoid administering strong CYP3A4 inhibitors or inducers as they will alter (increase or decrease) the levels of dabrafenib and may lead to increased toxicities or reduced efficacy (see WARNINGS and PRECAUTIONS, General and DRUG INTERACTIONS, Drug-Drug Interactions).

Concomitant Use with CYP3A4 Substrates: Dabrafenib is a moderate to potent inducer of CYP3A4 and concomitant use of sensitive CYP3A4 substrates can result in loss of efficacy. Substitute for these medications or monitor patients for loss of efficacy if use of these medications in unavoidable (see WARNINGS and PRECAUTIONS, General and DRUG INTERACTIONS, Drug-Drug Interactions).

Paediatrics: TAFINLAR is not recommended for use in children and adolescents (see WARNINGS AND PRECAUTIONS, Special Populations).

Geriatrics: No dose adjustment is required in patients over 65 years (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations).

Renal Impairment: No dose adjustment is required for patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on dabrafenib oral clearance or on the concentrations of its metabolites (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment has not been determined. TAFINLAR should be used with caution in patients with severe renal impairment.

Hepatic Impairment: No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on dabrafenib oral clearance or on the concentrations of its metabolites (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations). There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment has not been determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure and increased toxicities. .

Missed Dose

If a dose of TAFINLAR is missed, it should not be taken if it is less than 6 hours until the next dose.

OVERDOSAGE

Symptoms and Signs

There is currently no experience with overdosage of TAFINLAR or trametinib.

Treatment

There is no specific antidote for overdosage of TAFINLAR or trametinib. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, TAFINLAR or trametinib should be withheld and supportive care instituted.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TAFINLAR monotherapy: Dabrafenib is a small molecule inhibitor of RAF kinases, including BRAF. Oncogenic mutations in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway (including RAS/RAF/MEK/ERK) and may promote tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanomas. The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for approximately 95% of BRAF mutations found in patients with melanoma. A number of less common substitutions include V600D, V600G and V600R.

TAFINLAR in combination with trametinib: Trametinib is a small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the MAPK pathway (including RAS/RAF/MEK/ERK). Dabrafenib and trametinib provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively. The combination of dabrafenib with trametinib was synergistic in BRAF V600 mutation-positive melanoma cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts.

Pharmacodynamics

Cardiac Electrophysiology: In a phase I, open-label, multiple-dose, dose escalation, first time-in-human study of dabrafenib in patients with solid tumours, serial ECG data were collected pre-dose and at 1, 2, 4, 6, and 8 h post-dosing on days 1, 8, and 15 of cycle 1 in temporal association with pharmacokinetic sampling. A statistically significant positive relationship was demonstrated between concentrations of the three major metabolites of dabrafenib and the QTc interval. At the 4 h time point, the mean increase in the QTc interval from baseline was 4.8 ms on day 1, 10.5 ms on day 8, and 6.6 ms on day 15 for all patients (N = 110). The mean increase in the QTc interval from baseline was 5.2 ms on day 1, 7.3 ms on day 8 and, 12.2 ms on day 15, in patients receiving a 150 mg twice daily dose (N = 20).

Blood Pressure: TAFINLAR 150 mg BID was associated with decreases in systolic and diastolic blood pressure in the pivotal phase III study of patients with BRAF mutation positive melanoma. During the first 18 weeks of treatment, the magnitude of the systolic blood pressure decrease averaged -4.0 to -7.5 mmHg, while for diastolic blood pressure the decrease averaged -2.0 to -3.6 mm Hg.

Pharmacokinetics

The pharmacokinetics (PK) of dabrafenib were determined in patients with BRAF mutation-positive metastatic melanoma after single dose and after repeat dosing at 150 mg twice daily with dosing approximately 12 hours apart.

Absorption: Dabrafenib is absorbed orally with a mean absolute bioavailability of 95% (with a lower 90% CI of 81%) and with a median time to achieve peak plasma concentration of 2 hours post-dose in the fasted state. Across a range of doses there was less than a dose-proportional increase after repeat twice daily dosing. There is a decrease in exposure observed with repeat dosing, due to induction of its own metabolism. The steady-state $AUC_{(0-\tau)}$ and C_{max} to single dose values were 0.73 and 1.0, respectively. Interpatient variability (CV%) in steady-state C_{max} and AUC for 14 patients in the phase III study was determined to be 37.1% and 37.7%, respectively. Single dose and steady-state PK parameters are shown in Table 7.

Administration of dabrafenib capsules with food reduced the bioavailability (C_{max} and AUC decreased by 51 % and 31 %, respectively) and delayed absorption of dabrafenib when compared to the fasted state (see DOSING AND ADMINISTRATION).

Distribution: Dabrafenib and its metabolites hydroxy-, carboxy-, and desmethyl-dabrafenib, are highly bound to plasma proteins with percent bound of 99.7, 96.3, 99.5, and 99.9%, respectively. The apparent volume of distribution of dabrafenib (Vc/F) is 70.3 L.

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Elimination: Dabrafenib terminal half-life is 8 hours after oral administration. Apparent clearance was estimated to be 34.6 L/h using the recommended 150 mg BID dosing regimen. Faecal excretion is the major route of elimination after oral dosing, accounting for 71 % of a radioactive dose while urinary excretion accounted for 23 % of radioactivity.

Combination with Trametinib: Co-administration of TAFINLAR 150 mg twice daily and trametinib 2 mg once daily resulted in a 16% increase in dabrafenib C_{max} and 25 % increase in AUC at steady-state. A small decrease in trametinib bioavailability was also observed with the combination therapy, corresponding to a decrease in the trametinib AUC of 12 % (estimated by Population PK analysis).

Table 7 Dabrafenib's Pharmacokinetic Parameters Following a Single Dose and at Steady-State

	T_{max} (h) Median (Min, Max)	C_{max} (ng/mL) Geometric Mean (95% CI)	AUC[a] (ng*hr/mL) Geometric Mean (95% CI)	$t_{1/2}$ (hr) Geometric Mean (95% CI)
Single dose [b] (150mg) N = 13 or 14	2.0 [d] (1.0, 4.0)	2160[d] (1601, 2914)	12120 [e] (9138, 16075)	8.4[e] (4.8, 14.5)
Repeat dose [c] (150mg BID) Week 6, N = 17	1.9 (0.9, 6.0)	1478 (1229, 1777)	4341 (3599, 5235)	NA

CI = confidence interval; NA = not applicable

a. AUC refers to AUC(0-∞) for single dose and AUC(0-τ) for repeat dose; b. Data from phase I food effect study (fasting conditions); c. Data from steady-state phase III study (PK subset); d. N = 14; e. N = 13

Special Populations and Conditions

Paediatrics: No studies have been conducted to investigate the pharmacokinetics of dabrafenib in paediatric patients (less than 18 years of age).

Geriatrics: Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40 % greater exposure in patients ≥ 75 years of age, relative to patients < 75 years' old.

Gender/Weight: Based on the population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance (< 20%); weight also impacted oral volume of distribution and distributional clearance.

Race/Ethnicity: There are insufficient data to evaluate the potential effect of race on dabrafenib pharmacokinetics.

Hepatic Impairment: The pharmacokinetics of dabrafenib has been characterized in 65 patients with mild hepatic impairment (based on National Cancer Institute [NCI] classification) enrolled in clinical trials using a population analysis. Dabrafenib oral clearance was not significantly different between these patients and patients with normal hepatic function (4 % difference). In addition, mild hepatic impairment did not have a significant effect on dabrafenib metabolite plasma concentrations. Administration of TAFINLAR in patients with moderate to severe hepatic impairment has not been studied and may lead to increased exposure to dabrafenib and its metabolites and the possibility of increased toxicities (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment: The pharmacokinetics of dabrafenib were characterized in 233 patients with mild renal impairment (GFR 60 to 89 ml/min/1.73 m^2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m^2) enrolled in clinical trials using a population analysis. The effect of mild or moderate renal impairment on dabrafenib oral clearance was small (< 6 % for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant

effect on hydroxy-, carboxy-, and desmethyl-dabrafenib plasma concentrations. No data are available in patients with severe renal impairment (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Store between 15-30 °C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TAFINLAR 50 mg hard capsules are opaque, dark red capsules, monogrammed with 'GS TEW' and '50 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

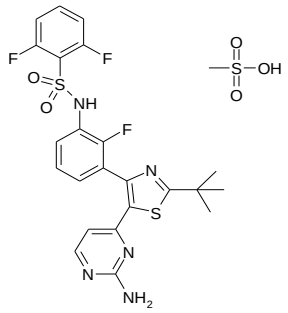
TAFINLAR 75 mg hard capsules are opaque, dark pink capsules, monogrammed with 'GS LHF' and '75 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

TAFINLAR hard capsules contain dabrafenib as dabrafenib mesylate, and the following non-medicinal ingredients: magnesium stearate, colloidal silicon dioxide, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171). Monogramming ink contains black iron oxide, shellac, and propylene glycol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Dabrafenib mesylate
Chemical name:	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt
Molecular formula:	$C_{23}H_{20}F_3N_5O_2S_2$. CH_4O_3S
Molecular mass:	519.57 g/mol (dabrafenib free base) 615.6 g/mol (dabrafenib mesylate)
Structural formula:	
Physicochemical properties:	Dabrafenib mesylate is a white to slightly coloured solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

CLINICAL TRIALS

The efficacy and safety of TAFINLAR (dabrafenib mesylate) monotherapy in the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in three multi-centre, international clinical studies:

- BRF113683: a phase III randomized open-label study of 250 treatment-naive patients with BRAF V600E mutation.
- BRF113929; a phase II open-label study of 172 patients with BRAF V600E or BRAF V600K mutation, and melanoma metastatic to the brain. This trial included two cohorts; no prior local therapy, and prior local therapy for brain metastases.
- BRF113710; a phase II open-label single arm study of 92 patients with BRAF V600E or BRAF V600K mutation who were previously-untreated or who had failed at least one prior systemic therapy.

The efficacy and safety of TAFINLAR in combination with trametinib in the treatment of patients with BRAF V600E/K mutation positive unresectable or metastatic melanoma has been evaluated in a phase III multi-centre, international clinical study MEK115306.

Screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available from either a primary tumour or a tumour from a metastatic site. The assay used in clinical studies differentiates between V600E and V600K mutations.

TAFINLAR Monotherapy

Phase III Pivotal Study BRF113683: Treatment Naive Patients

Trial design

The efficacy and safety of TAFINLAR in previously untreated patients with BRAF V600E mutation positive advanced (Stage III unresectable) or metastatic (Stage IV) cutaneous melanoma were evaluated in study BRF113683 comparing TAFINLAR to dacarbazine (DTIC).

Patients were permitted to have prior IL-2 treatment, surgery and radiotherapy. The primary objective was to evaluate the efficacy of TAFINLAR compared to DTIC with respect to progression-free survival (PFS) per investigator assessment. Secondary efficacy endpoints included comparison of overall survival (OS), overall response rate (ORR), duration of response and health-related quality of life (HRQoL) status.

Patients were randomized (3:1) to receive either TAFINLAR 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. Randomization was stratified according to disease stage. Patients on the DTIC arm were permitted to cross over to TAFINLAR after initial progression.

Study Demographics and Baseline Characteristics

Study demographics and baseline characteristics were balanced between treatment groups (see Table 8).

Table 8 Demographic and Baseline Characteristics, Study BRF113683

	TAFINLAR (N = 187)	DTIC (N = 63)
Age (years)		
Median (Min-Max)	53.0 (22-93)	50.0 (21-82)
Age Group, n (%)		
< 65	146 (78)	51 (81)
≥ 65	41 (22)	12 (19)
Sex, n (%)		
Female	75 (40)	26 (41)
Male	112 (60)	37 (59)
ECOG PS at Baseline, n (%)		
ECOG PS = 0	124 (66)	44 (70)
ECOG PS ≥ 1	62 (33)	16 (25)
Unknown	1 (< 1)	3 (5)
Baseline LDH, n (%)		
≤ ULN	119 (64)	43 (68)
> ULN	67 (36)	19 (30)
Unknown	1 (< 1)	1 (2)
TNM staging at Screening: distant metastasis, n (%)		
M0	6 (3)	1 (2)
M1a	23 (12)	10 (16)
M1b	34 (18)	12 (19)
M1c	124 (66)	40 (63)

Study results

Treatment with TAFINLAR monotherapy was associated with a statistically significant improvement on the primary endpoint, investigator-assessed PFS, compared to treatment with DTIC (HR 0.30, 95% CI: 0.18, 0.51; $p < 0.0001$). This represents a relative reduction of 70% in the risk of disease progression or death compared with DTIC. Across subgroups, a consistent PFS benefit of the same magnitude as the overall study population was seen. Independent reviewer-assessed PFS results were consistent with investigator-assessed results.

The secondary endpoint of investigator assessed best confirmed ORR favoured dabrafenib over DTIC (Table 9). Overall survival data were not mature at the time of the study's primary analysis.

There was no statistically significant difference in health-related quality of life (HRQOL), as measured by the EORTC QLQ C-30 questionnaire, between patients treated with TAFINLAR vs. DTIC.

Efficacy results are presented in Table 9 and Figure 1.

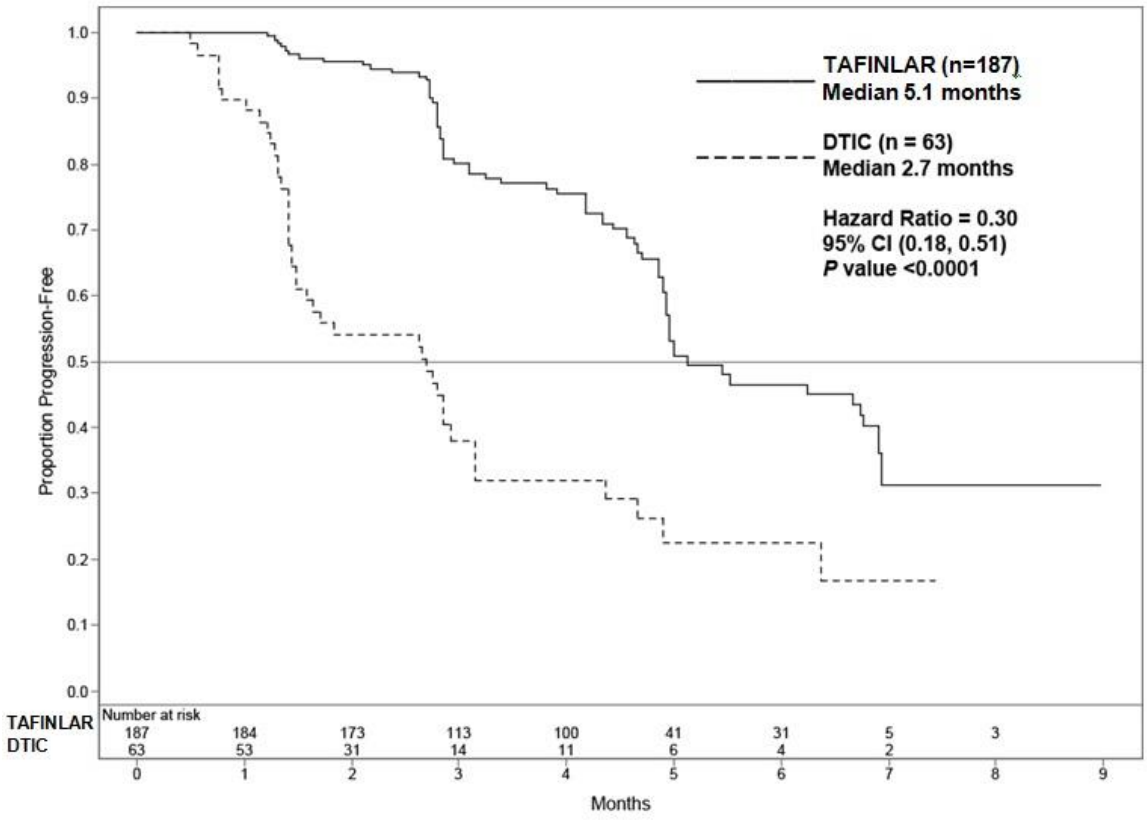
Table 9 Efficacy Results, Study BRF113683

Endpoint	**TAFINLAR (N = 187)**	**DTIC (N = 63)**
PFS Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR (95% CI)	0.30 (0.18, 0.51) p < 0.0001	
OS[a]		
% at 6 months (95% CI)	87 (79.2, 91.9)	79 (59.7, 89.5)
HR (95% CI)	0.61 (0.25, 1.48)	
ORR		
CR, n (%)	6 (3)	0
PR, n (%)	93 (50)	12 (19)
ORR (CR+PR), n (%)	99 (53)	12 (19)
(95% CI)	(45.5, 60.3)	(10.2, 30.9)
Duration of Response	N = 99	N = 12
Median, months (95% CI)	5.6 (4.8, NR)	NR (5.0, NR)

DTIC = dacarbazine, PFS = Progression-free Survival; CI: confidence interval; HR = Hazard Ratio; ORR = Overall Response Rate; CR = Complete Response; PR = Partial Response, NR = not reached

[a] Includes patients from DTIC arm (44%) who crossed over to TAFINLAR post-progression

Figure 1 Kaplan-Meier Curves for PFS, Study BRF113683



Study BRF113929: Patients with Brain Metastases with or without Prior Local Treatment

Trial Design

The efficacy and safety of TAFINLAR 150 mg twice daily were evaluated in a two-cohort phase II study (BRF113929) in patients with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Patients enrolled had no prior local therapy for brain metastases (Cohort A) or had received prior local therapy for brain metastases (Cohort B). Prior treatment for patients in Cohort B included brain surgery, whole-brain radiation therapy and stereotactic radiosurgery. The study employed modified RECIST criteria. Smaller lesions were allowed (≥ 5 mm) and up to 5 target lesions in the brain could be used.

In both cohorts, the majority of patients were male (70%), all were Caucasian, and the median age was 52.5 years. All patients had ECOG status of 0 or 1, all patients had measurable intracranial disease at baseline (100% M1c), and 89% also had measurable extracranial disease.

Study results

Investigator and independent-radiologist assessed overall intracranial response rates (OIRR) for Cohorts A and B are presented by BRAF mutation status (V600E and V600K) in Table 10.

In both cohorts, patients with BRAF V600E-mutation positive melanoma had better overall intracranial responses than patients with BRAF V600K-mutation positive melanoma. Overall intracranial response rates were higher by investigator-assessments compared to independent-radiologist assessments.

Table 10 Efficacy Results in Patients with Brain Metastases, Study BRF113929

	All Treated Patients			
	BRAF V600E		BRAF V600K	
Endpoint	**Cohort A N = 74**	**Cohort B N = 65**	**Cohort A N = 15**	**Cohort B N = 18**
Investigator-assessed OIRR				
%	39	31	7	22
(95% CI)	(28.0, 51.2)[a]	(19.9, 43.4)[a]	(0.2, 31.9)	(6.4, 47.6)
CR	3	0	0	0
PR	36	31	7	22
Independent radiologist-assessed OIRR				
%	20	18	0	11
(95% CI)	(11.8, 31.2)	(9.9, 30.0)	(0.0, 21.8)	(1.4, 34.7)
CR	1	0	0	0
PR	19	18	0	11

Cohort A: patients with no prior local therapy for brain metastasis
Cohort B: patients who received prior local therapy for brain metastasis
CR = Complete Response; PR = Partial Response
[a] $p < 0.001$. This study was designed to support or reject the null hypothesis of OIRR ≤ 10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in BRAF V600E positive subjects

Study BRF113710: Patients Who Were Previously Untreated or Failed at Least One Prior Systemic Therapy

Trial design, Demographics and Baseline Characteristics

The efficacy and safety of TAFINLAR were evaluated in a phase II study (BRF113710) of patients with BRAF (V600E or V600K) mutation-positive metastatic melanoma (Stage IV). The majority (80%) had received prior chemotherapy (cytotoxic/non cytotoxic) in the advanced or metastatic setting, while the remainder were considered treatment naïve for systemic therapy (20%). In this study, 53% of patients were male and 99% were Caucasian; the median age was 55.5 years. Patients were either ECOG status 0 (55%) or

ECOG status 1 (45%); 63% had M1c disease stage; and 62% had baseline LDH equal to or below ULN.

Study results

Confirmed ORR for patients with BRAF V600E metastatic melanoma (n = 76) and V600K (n = 16) metastatic melanoma were reported by both investigator and independent radiologist assessments. There were greater numbers of overall responses for V600E patients of 59 % and 41% by investigator and independent-radiologist reviews, respectively compared to V600K patients (ORR of 13% and 25% by investigator and independent radiologist reviews, respectively). Complete responses (CR) were only reported for the V600E patient population (7% and 3% by investigator and independent radiologist assessments, respectively).

TAFINLAR in Combination with Trametinib

Phase III Pivotal Study MEK115306

Trial design

MEK115306 was a phase III, randomized, double-blind study comparing the combination of TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.

Patients were not allowed to have prior systemic anti-cancer treatment in the advanced or metastatic setting, although prior systemic treatment in the adjuvant setting was allowed. The primary endpoint was investigator-assessed PFS, which was to be assessed after 193 events (progression or death) were observed (Primary PFS Analysis); upon formal declaration of a datacut based on the 193 known events, an additional 18 progressions were discovered during the data retrieval and cleaning process. Secondary endpoints ORR and duration of response were reported at the time of this primary PFS analysis. The secondary endpoint OS analysis was to be performed when 220 events (death) had occurred (Final OS Analysis).

Patients were stratified by lactate dehydrogenase (LDH) level (above the upper limit of normal [ULN] versus ≤ ULN) and BRAF mutation (V600E versus V600K). Crossover was not allowed.

TAFINLAR and trametinib were administered at their recommended monotherapy doses of 150 mg twice daily and 2 mg once daily, respectively.

Study Demographics and Baseline Characteristics

Study demographics were balanced between treatment arms. Baseline disease characteristics and prognostic factors were well balanced between the treatment arms,

with the exception of the occurrence of visceral disease, which was higher in the combination therapy arm compared with the TAFINLAR monotherapy arm (see Table 11).

Table 11 Demographic and Baseline Characteristics, Study MEK115306

	TAFINLAR + Trametinib (N = 211)	**TAFINLAR + Placebo (N = 212)**
Age (years)		
Median (Min, Max)	55.1 (22, 89)	56.5 (22, 86)
Age Group, n (%)		
< 65	154 (73)	151 (71)
≥ 65	57 (27)	61 (29)
Sex, n (%)		
Female	100 (47)	98 (46)
Male	111 (53)	114 (54)
ECOG PS at Baseline, n (%)		
0	155 (73)	150 (71)
1	55 (26)	61 (29)
Baseline LDH, n (%)		
≤ ULN	133 (63)	140 (66)
> ULN	77 (36)	71 (33)
Visceral Disease at Baseline, n (%)		
Yes	165 (78)	145 (68)
No	46 (22)	66 (31)
BRAF Mutation Status, n (%)		
V600E	179 (85)	181 (85)
V600K[a]	32 (15)	30 (14)
(M stage) at Screening, n (%)		
M0	5 (2)	10 (5)
M1a	19 (9)	31 (15)
M1b	45 (21)	32 (15)
M1c	142 (67)	138 (65)

[a] One subject was both BRAF V600E and BRAF V600K mutation positive and is included in the V600K subset in this display.

Study results

Treatment with the combination therapy resulted in a statistically significant improvement in investigator-assessed PFS compared with TAFINLAR monotherapy treatment (HR 0.75; 95% CI: 0.57, 0.99; p = 0.035). This represents a 25% reduction in risk of tumour progression or death in the combination therapy arm compared with TAFINLAR monotherapy. Median PFS for the combination therapy arm was 9.3 months compared with 8.8 months for the TAFINLAR monotherapy arm. Independent reviewer assessed PFS results were not statistically significant (HR 0.78; 95% CI: 0.59, 1.04).

The secondary endpoints, including ORR and OS, are supportive of the TAFINLAR combination with trametinib PFS benefit. See Table 12 for details.

Efficacy results are presented in, Figure 2 and Figure 3.

Table 12 Efficacy Results, Study MEK115306

	Primary Analysis*		**Updated Analysis***	
	TAFINLAR + Trametinib	**TAFINLAR + Placebo**	**TAFINLAR + Trametinib**	**TAFINLAR + Placebo**
Primary endpoint				
PFS	**(N = 211)**	**(N = 212)**	**(N = 211)**	**(N = 212)**
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)
HR (95% CI) and log-rank p-value[a]	0.75 (0.57, 0.99) p = 0.035		0.67 (0.53, 0.84) p < 0.001	
Secondary endpoints				
ORR[d]	N = 210	N = 210	N = 210	N = 210
CR, n (%)	22 (10)	18 (9)	33 (16)	28 (13)
PR, n (%)	118 (56)	90 (43)	111 (53)	84 (40)
ORR (CR+PR), n (%)	140 (67)	108 (51)	144 (69)	112 (53)
(95% CI)	(59.9, 73.0)	(44.5, 58.4)	(61.8, 74.8)	(46.3, 60.2)
Duration of Response	N = 140	N = 109	N = 144	N = 113
Median, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)	12.9 (9.4, 19.5)	10.6 (9.1, 13.8)
	Interim Analysis		**Final Analysis**	
OS	**(N = 211)**	**(N = 212)**	**(N = 211)**	**(N = 212)**
Died (%)	40 (19)	55 (26)	99 (47)	123 (58)
HR (CI) and log-rank p-value[a]	0.63 (0.30, 1.32)[b]		0.71 (0.55, 0.92)[c] p = 0.011	
Median, months (95% CI)	NR		25.1 (19.2, NR)	18.7 (15.2, 23.7)

*****Primary data cut: 26 August 2013, Final OS data cut: 12 January 2015
PFS = Progression-Free Survival; CI = Confidence Interval; HR = Hazard Ratio; CR = Complete Response; ORR = Overall response rate; PR = Partial Response; NR = Not Reached

a. Hazard ratio and log-rank p-value are adjusted for randomized strata: baseline LDH and BRAF mutation status
b. The stopping boundary for overall survival (one-sided alpha) for this interim analysis is based on the available information (95 events), and is 0.00014. Confidence interval is based on the allocated alpha. The results were not statistically significant
c. 95% CI
d. Includes only patients with measurable disease at baseline

Figure 2 **Kaplan-Meier Curves for PFS Primary Analysis (ITT Population), Study MEK115306**

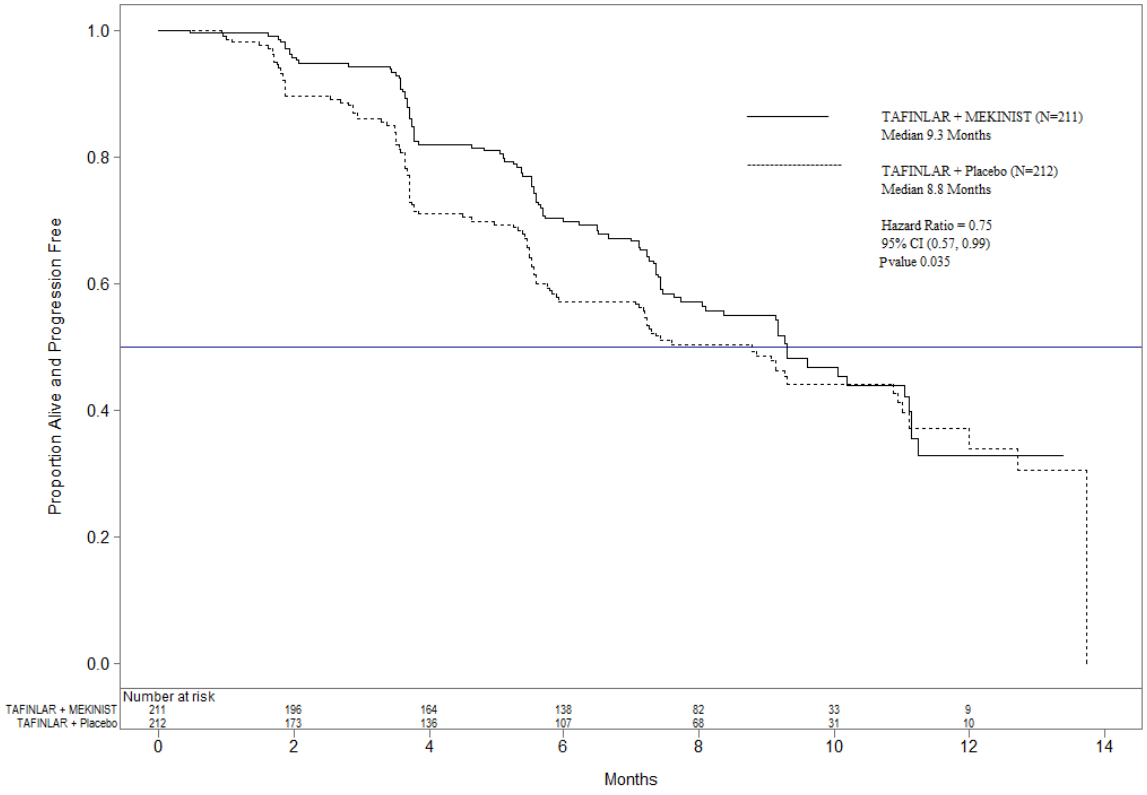
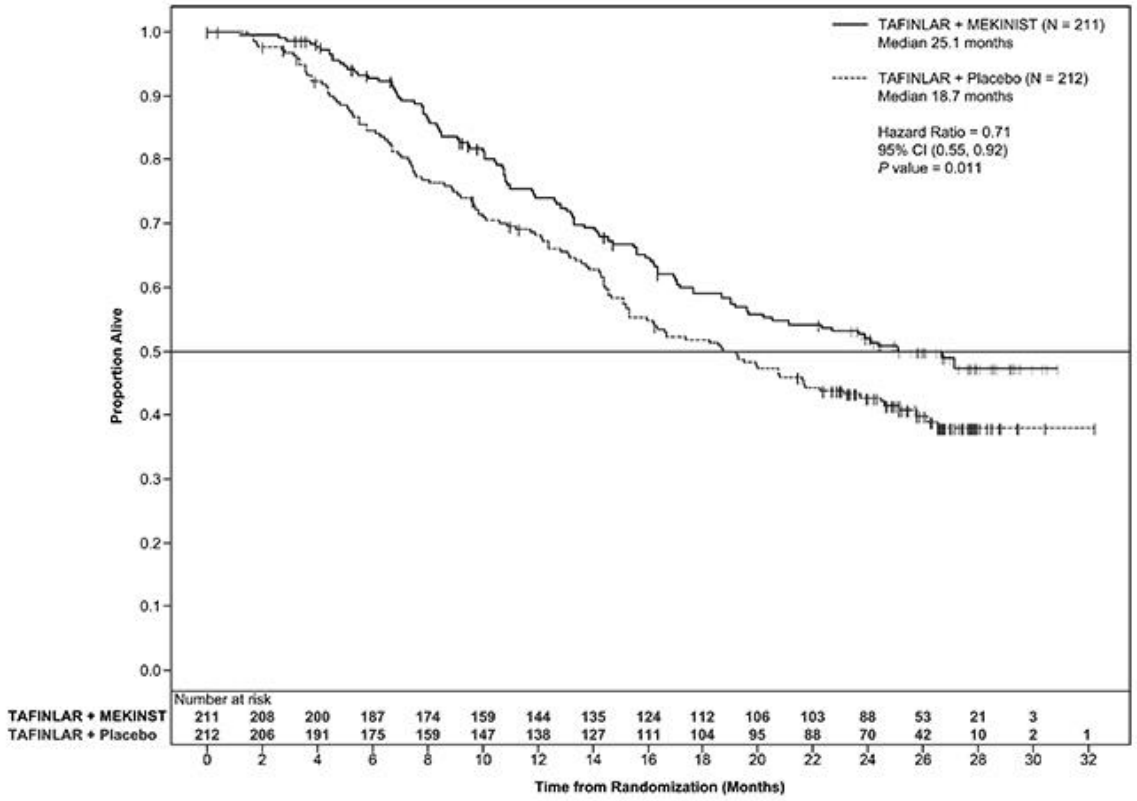


Figure 3 Kaplan-Meier Curves for Final OS (ITT population), Study MEK115306



DETAILED PHARMACOLOGY

Non-clinical Pharmacokinetics

Active dabrafenib metabolites (hydroxy-, carboxy- and desmethyl-dabrafenib) were found to circulate in plasma of mice, rats and dogs upon oral administration of dabrafenib. Following up to 13 weeks of repeat oral administration of dabrafenib, gender averaged mean systemic exposure in rats and dogs to hydroxy-dabrafenib was greater than clinical exposure in humans, but less than clinical exposures for carboxy- and desmethyl-dabrafenib.

In a single dose quantitative whole body autoradiography study in partially pigmented rats, ^{14}C-dabrafenib-associated radioactivity was widely distributed into tissues, and most tissue concentrations were lower than those observed in blood. There was no selective association or retention of radioactivity with melanin-containing tissues of the eye (uveal tract) or skin. Radioactivity in the brain was below the limit of quantitation at all time points assessed.

Brain penetration of dabrafenib and metabolites was also evaluated in a positron emission tomography study in the pig following a single dose of ^{18}F-dabrafenib. There was no

evidence for brain penetration of dabrafenib or circulating metabolites, hydroxy- and carboxy-dabrafenib, in this study.

Primary Pharmacodynamics

Dabrafenib is a selective, ATP-competitive inhibitor of RAF kinases requiring low concentrations to inhibit 50% of enzyme activity (IC_{50}) in *in vitro* kinase assay (Table13). The inhibitory activity of dabrafenib has not been determined for BRAF variants V600R, V600G and V600M.

Table13 Inhibition of Different BRAF Variants by Dabrafenib

Kinase	IC_{50} (nM)
BRAF_wild-type	3.2
BRAF_V600E	0.65
BRAF_V600D	1.84
BRAF_V600K	0.5

The results from the *in vitro* kinase assays were consistent with the inhibition of proliferation of melanoma cell lines. Melanoma cell lines harbouring V600E, V600K or V600D mutations were sensitive to cell growth inhibition by dabrafenib (IC_{50} < 1 μM) compared to melanoma cell lines expressing wild-type BRAF. Dabrafenib demonstrated suppression of phosphorylated ERK (pERK) in tumour cell lines and achieved biomarker suppression and tumour regression in BRAF V600E human melanoma mouse xenografts. Suppression of pERK and tumour regression in BRAF V600K human melanoma mouse xenografts by dabrafenib has not been evaluated.

Dabrafenib showed good selectivity for BRAF V600E in panels of > 270 protein and lipid kinases. Dabrafenib demonstrated weak inhibition for most kinases screened; however, inhibition was noted for 1 kinase with potential physiological impact. Dabrafenib inhibits LIM kinase 1 (LIMK1) with an IC_{50} value of 11 nM. Literature studies have also demonstrated that LIMK1 knockout (-/-) mice have reduced bone mass and that LIMK1 is required for normal osteoblast differentiation.

In patients with BRAF V600E mutation-positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Safety Pharmacology

Dabrafenib inhibited hERG repolarization with an estimated IC_{25} of 11.7 μM (6.1 μg/mL); however, its 3 active metabolites did not inhibit hERG (IC_{50} > 30 μM). In an ex-vivo rabbit left ventricular wedge assay, dabrafenib caused QT interval shortening (29.7% at 30 μM) with no significant changes in QRS interval and no torsadogenic potential. In rats, a single oral dose of dabrafenib of ≥ 5 mg/kg caused a dose-dependent, mild to moderate increase in heart rate (9 to 48 beats/minute or up to 18%). In dogs, a

single oral dose of 50 mg/kg dabrafenib produced a mild increase in heart rate (28%) along with a mild decrease in PR interval (7%) that reversed by 24 hours post dose.

TOXICOLOGY

General Animal Toxicology

Adverse cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation were seen in dogs (≥ 2 times human clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥ 0.5 and 0.6 times human clinical exposure for rats and mice respectively). Hepatic effects, including hepatocellular necrosis and inflammation were observed in mice (≥ 0.6 times clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥ 20 mg/kg/day (≥ 9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Reversible haematological effects have been observed in dogs and rats given dabrafenib. In studies of up to 13 weeks, decreases in reticulocyte counts and/or red cell mass were observed in dogs and rats (≥ 10 and 1.4 times clinical exposure, respectively).

Dogs given dabrafenib and trametinib in combination for 4 weeks demonstrated decreased serum albumin concentrations consistent with an acute phase response secondary to mild granulomatous changes in the stomach and mesenteric lymph node. Decreases in serum albumin have also been reported in patients receiving combination therapy as compared to those receiving dabrafenib monotherapy in the phase III combination study (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Table 4).

Dogs given dabrafenib and trametinib in combination for 4 weeks also demonstrated decreased lymphoid cellularity of the thymus at a lower dose than in a 3-week dog study in which single agent trametinib was administered.

Reproductive and Developmental Toxicity

Dabrafenib is embryo-foetal toxic and teratogenic in animals at doses similar to human clinical exposures. In combined female fertility, early embryonic and embryo-foetal development studies in rats, a reduction in fertility was observed at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC). There was also delayed skeletal development and reduced foetal body weight at doses ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC). The numbers of ovarian *corpora lutea* were reduced in pregnant females at 300 mg/kg/day. Developmental toxicity including embryo-lethality and ventricular septal defects were also seen at 300 mg/kg/day.

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see WARNINGS AND PRECAUTIONS, Reproduction).

Juvenile Toxicity

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations), testicular toxicity (degeneration and tubular dilation) and earlier vaginal opening (with no associated effects on ovarian weights or morphologic changes in female reproductive tissues) were observed (≥ 0.2 times adult human clinical exposure based on AUC). Renal toxicity, which had not been observed in adult animals, was primarily observed in rats given dabrafenib pre-weaning (< 22 days old).

Carcinogenesis and Mutagenesis

Carcinogenicity studies with dabrafenib have not been conducted. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Phototoxicity

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at single doses ≥ 100 mg/kg (> 44 times clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.

REFERENCES

1. Ascierto PA, Minor D, Ribas A, Lebbe C, Siegfried A, Arya N, et al. 113710 A Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol. 2013; 31(26): 3205-11.
2. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumors: a phase 1 dose-escalation trial. Lancet. 2012; 379(9829): 1893–901.
3. Hauschild A, Grob, J-J, Demidov LV, Jouary T, Gutzmer R, Millward M et al. Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 2012 Jul 28; 380(9839):358-65.
4. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov; 13(11):1087-95.
5. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. N. Engl. J. Med. 2014; 371: 1877-1888.
6. Product Monograph MEKINIST (trametinib) 0.5 mg, 1.0 mg, 2.0 mg. Novartis Pharmaceuticals Canada Inc.

PART III: CONSUMER INFORMATION

PrTAFINLAR®

Dabrafenib (as dabrafenib mesylate) Capsules

This leaflet is part III of a three-part "Product Monograph" published when TAFINLAR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TAFINLAR. Contact your doctor or pharmacist if you have any further questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TAFINLAR is a medicine to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery.

TAFINLAR should only be used for people whose cancer has a particular change (mutation) in a gene called BRAF. You should have your cancer tested for this mutation in the BRAF gene before starting treatment with TAFINLAR.

Your doctor may decide that your melanoma will be treated with TAFINLAR in combination with MEKINIST®. If you are taking these two medicines together, read the MEKINIST leaflet carefully as well as this leaflet.

What it does:
TAFINLAR targets proteins made from the changed (mutated) BRAF gene. This slows down or stops growth of cancer cells.

When it should not be used:
Do not use TAFINLAR if you are allergic to dabrafenib mesylate, or any of the other ingredients in TAFINLAR (see 'What the important non-medicinal ingredients are').

You should not use TAFINLAR if you do not have a particular change (mutation) in a gene called BRAF or if the mutation in BRAF is not known.

What the medicinal ingredient is:
Dabrafenib mesylate

What the important nonmedicinal ingredients are:
Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose.
Capsule shell: hypromellose, red iron oxide, titanium dioxide.
Printing ink: black iron oxide, shellac, propylene glycol.

What dosage forms it comes in:
TAFINLAR is available as 50 mg and 75 mg hard capsules.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TAFINLAR should only be prescribed by a doctor who is experienced in the use of anti-cancer drugs.

- Taking TAFINLAR may cause severe fever
- TAFINLAR can harm an unborn baby
- Birth control using hormones (pills, injections, or patches) may not work as well while you are taking TAFINLAR
- TAFINLAR has not been studied in patients with moderate or severe liver problems
- Patients taking TAFINLAR have reported second cancers

TAFINLAR in combination with MEKINIST
In addition to the above events,

- Serious bleeding
- Blood clots

TAFINLAR should only be used to treat melanomas with a change (mutation) in the BRAF gene. Your doctor will take a tumour tissue sample, to test whether TAFINLAR is suitable for you.

TAFINLAR is not recommended for children and adolescents (< 18 years of age).

Fever (high temperature > 38.5°C): **Taking TAFINLAR may cause fever. Fever may happen more often or may be more severe when TAFINLAR is taken with MEKINIST. Stop taking TAFINLAR and tell your doctor immediately if you get a fever**. In some cases, people with fever may develop chills, low blood pressure, dizziness and kidney problems. If the fever is severe, your doctor may recommend that you stop taking TAFINLAR while they treat the fever with other medicines. Once the fever is controlled, your doctor may recommend that you start taking TAFINLAR again.

Bleeding problems: **TAFINLAR, when taken with MEKINIST, can cause serious bleeding problems**, including in your brain, stomach, or bowel, and can lead to death. Call your doctor and get medical help right away if you have any unusual signs of bleeding including:

- headaches, dizziness, or feeling weak
- coughing up blood or blood clots
- vomiting blood or your vomit looks like "coffee grounds"
- red or black stools that look like tar

Blood Clots: **TAFINLAR, when taken with MEKINIST, can cause blood clots in your arms and legs**, which can travel to your lungs and can lead to death. Get medical help right away if you have any of the following symptoms:

- chest pain
- sudden shortness of breath or trouble breathing
- pain in your legs with or without swelling
- swelling in your arms or legs, especially one larger than the other
- a cool or pale arm or leg

Changes in your skin: **If you notice any skin lesions while taking this medicine, talk to your doctor as soon as possible.**

Up to 1 in 10 people taking TAFINLAR may develop a different type of skin cancer called *cutaneous squamous cell carcinoma*. Usually, this remains local and can be removed with surgery and people can continue treatment.
Some people taking TAFINLAR also may notice that new melanomas have appeared. These are usually removed by surgery and people can continue treatment.

Your doctor will check your skin for any new cancers before you start taking TAFINLAR, and every 2 months while you take TAFINLAR. Your doctor will check your skin again every 2 or 3 months for 6 months after you stop taking TAFINLAR.

Check your skin regularly while taking TAFINLAR for any of the following:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or colour of a mole

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

Eye Problems: **TAFINLAR can cause an eye problem called uveitis which could damage your vision if it is not treated. Uveitis may develop rapidly; symptoms include:**

- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots in front of your eyes

Contact your doctor immediately if you get these symptoms. **It is very important to tell your doctor immediately if you develop these symptoms**, especially if you have a painful, red eye that does not clear up quickly. They may arrange for you to see a specialist eye doctor for a complete eye examination.

Liver problems: **TAFINLAR, when taken with MEKINIST, can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal**. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:

- Loss of appetite
- Feeling sick (nausea)
- Being sick (vomiting)
- Pain in your stomach (abdomen)
- Yellowing of your skin or the whites of your eyes (jaundice)
- Dark-coloured urine
- Itching of your skin

Decrease in white blood cells (neutropenia): **TAFINLAR, when taken with MEKINIST, can cause a decrease in a certain kind of white blood cells that may lead to infection which can be life-threatening, or to unexpected bruising or bleeding**. Your doctor will monitor you periodically. Signs that certain white cell counts are low may include:

- Symptoms of infection (fever, chills, sore throat)
- Bruise or bleed easily
- Cold

Non-Skin Cancers: Have been reported in patients receiving TAFINLAR. Your doctor will monitor you periodically.

Heart Problems: TAFINLAR has an effect on the electrical activity of the heart known as QT prolongation.

Diabetes: TAFINLAR may cause an elevation in blood sugars or worsening of diabetes. If you are diabetic your blood sugar may be monitored more frequently while on TAFINLAR.

Driving and using machines: TAFINLAR can have side effects that may affect your ability to drive or use machines.

Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.

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

BEFORE you use TAFINLAR either by itself or with MEKINIST talk to your doctor if you:

- are pregnant, think you may be pregnant or are planning to become pregnant. You must use reliable non-hormonal birth control while receiving TAFINLAR and for 4 weeks after you stop the treatment. Pills, patches and injections are not effective in preventing pregnancies because they may not work as well while you are taking TAFINLAR; therefore you should use an alternative method. You must make sure that you do not get pregnant while receiving

TAFINLAR, but if you do, inform your doctor immediately. TAFINLAR can harm an unborn baby.
- are breastfeeding. Do not breastfeed if you are taking TAFINLAR. If you wish to restart breastfeeding after TAFINLAR treatment, you must discuss this with your doctor, who will tell you when it is safe to do so.
- are a male. Men who take TAFINLAR may have a reduced count of sperm that may not return to normal levels after you stop taking TAFINLAR.
- have or have had a heart rhythm disorder such as irregular heartbeat, prolongation of the QT interval or any risk factors for Torsade de Pointes (dangerous rapid fluttering of the heart) such as diabetes, low potassium, magnesium or calcium levels, or a history of low heart rate, fainting, or loss of consciousness.
- have heart valve problems.
- have elevated blood sugar levels (diabetes).
- have any liver problems. Your doctor may take blood samples to monitor your liver function while you are taking TAFINLAR.
- have or have ever had any kidney problems.
- plan to have surgery, dental or other medical procedures.
- have any other medical conditions.

BEFORE you use TAFINLAR with MEKINIST also talk to your doctor if you have:

- had bleeding problems or blood clots.
- heart problems such as heart failure or problems with the way your heart beats.
- eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid leakage.
- any skin problems including rash or acne-like rash.
- high blood pressure (hypertension).
- a low number of white blood cells (neutropenia).
- any lung or breathing problems, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue (pneumonitis).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor, nurse or pharmacist about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Do not start, stop or change any medicine without talking to
your doctor, nurse or pharmacist first.

Some medicines may affect how TAFINLAR works, or make it more likely that you will have side effects.
TAFINLAR can also affect how some other medicines work. These include:

- birth control using hormones such as pills, injections, or patches
- warfarin, to thin the blood
- medicines to treat fungal infections, such as ketoconazole
- some antibiotic medicines, such as clarithromycin or rifampin
- dexamethasone
- some medicines to treat HIV, such as ritonavir
- medicines to treat seizures, such as phenytoin, phenobarbital, or carbamazepine
- the anti-depressant medicine nefazodone
- the lipid lowering medicine gemfibrozil
- medicines that reduce stomach acid (e.g. esomeprazole, ranitidine, magnesium hydroxide)
- the herbal product, St John's wort
- medicines known to cause heart rhythm changes

Tell your doctor if you are taking any of these. Your doctor may decide to adjust your dose. Keep a list of the medicines you take, so you can show it to your doctor when you get a new medicine.

It is important to take TAFINLAR on an empty stomach, because food may affect the way TAFINLAR is absorbed into your body and how effective it works.

PROPER USE OF THIS MEDICATION

Always take TAFINLAR exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

Usual Dose:
Taking TAFINLAR by itself: the usual dose of TAFINLAR is two 75 mg capsules (150 mg), twice a day (a total of four capsules equalling 300 mg).

Taking TAFINLAR with MEKINIST: the usual dose is two 75 mg capsules of TAFINLAR (150 mg) twice a day with 2 mg of MEKINIST once a day.

How to take TAFINLAR either by itself or with MEKINIST:

Take TAFINLAR on an empty stomach at least one hour before or at least two hours after food.

Swallow the TAFINLAR capsules whole with a full glass of water, one after the other.

Take TAFINLAR at about the same time two times each day.

If you take TAFINLAR with MEKINIST, take MEKINIST with either the morning or the evening dose of TAFINLAR. Take MEKINIST at about the same time each day.

Your doctor may decide that you should take a lower dose if you get side effects.

Take TAFINLAR for as long as your doctor recommends.

Do not take the morning and evening doses of TAFINLAR at the same time, and do not take more than one dose of MEKINIST a day.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you take too much TAFINLAR or MEKINIST, call your doctor or poison control centre, or go to the nearest hospital emergency room right away. Take TAFINLAR capsules and MEKINIST tablets with you when possible.

Missed Dose:

If the missed dose is less than 6 hours late, take it as soon as you remember. If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time. Then continue to take your capsules at regular times as usual. **Do not take a double dose to make up for a missed dose.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects that can occur when you take TAFINLAR are:

Very common side effects - these may affect more than 1 in 10 people:
- Thickening of the outer layers of the skin
- Skin effects such as rash, dryness, wart-like growths, or redness and swelling of the palms, fingers and soles of the feet
- Headache
- Nausea, vomiting, or diarrhoea
- Decreased appetite
- Chills
- Feeling weak
- Lack of energy
- Fever
- Joint pain, muscle pain, or pain in the hands or feet
- Cough
- Unusual hair loss or thinning
- Itching
- Constipation
- Nasal inflammation

Common side effects - affects less than 1 in 10 but more than 1 in 100 people:
- Flu-like illness
- Skin effects including rough scaly patches of skin, brown or yellowish thickening of the skin, skin tags, or redness of the skin
- Inflammation of the fatty layer underneath the skin (*panniculitis*)

Common side effects that may show up in your blood tests:
- Low phosphorus
- Increase in sugar (glucose)

Uncommon side effects - affects less than 1 in 100 but more than 1 in 1000 people:
- Inflammation of the eye (uveitis)
- Inflammation of the kidney (nephritis)
- Kidney disorder that may result in decreased urine output (kidney failure)

Refer to the MEKINIST Consumer Information leaflet for possible side effects when TAFINLAR is taken with MEKINIST including heart problems, eye problems and rash.

In addition to the above, other side effects that can occur when you take TAFINLAR with MEKINIST are:

Very common side effects - these may affect more than 1 in 10 people:
- Swelling of the hands or feet
- Stomach ache
- High blood pressure
- Urinary tract infections
- Acne-like problem
- Dizziness
- Bleeding (haemorrhage)

Very common side effects that may show up in your blood tests
- Abnormal blood test results related to the liver
- Low levels of a type of white blood cells (*neutropenia*)

Common side effects – affects less than 1 in 10 but more than 1 in 100 people:
- Night sweats
- Shortness of breath
- Muscle spasms
- Heart pumping less efficiently
- Low blood pressure (*hypotension*)
- Slow heart rate
- Eyesight problems
- Dry mouth
- Sore mouth or mouth ulcers
- Inflammation of the mucous membranes
- Swelling of the face, localized tissue swelling
- Low levels of water or fluid (*dehydration*)

- Infection of the skin (*cellulitis*)
- Papilloma (a type of skin cancer)
- Inflammation of the follicles in the skin
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Skin rash with pus-filled blisters
- Excessive sweating (*hyperhidrosis*)
- Skin cracking

Common side effects that may show up in your blood tests

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

Uncommon side effects – affects less than 1 in 100 but more than 1 in 1000 people:

- Lung inflammation (*pneumonitis*)
- Swelling around the eyes
- Swelling in the eye cause by fluid leakage (*chorioretinopathy*)
- Separation or tear of the lining of the back part of the eye (*retinal detachment or tear*)

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. Tell your doctor if you have any side effect that bothers you or that does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist
Very Common	**Fever** (high temperature > 38.5°C) that may be accompanied by rigors, chills, low blood pressure or kidney problems		✓
	Serious bleeding problems: headaches, dizziness or feeling weak, coughing up blood or blood clots, vomiting blood or vomit looking like "coffee grounds", red or black stools that look like tar		✓
Common (when TAFINLAR is taken alone)	**New primary melanoma** (mole which has irregular shape, border, or colour, is growing, or changing shape or colour)	✓	
Common	**Cutaneous squamous cell cancer including keratoacanthomas** (skin sore, wart, or reddish bump that bleeds or does not heal)	✓	
	Eye problems (redness, pain, blurred vision, floating spots, light sensitivity)	✓	
Common (when TAFINLAR is taken with MEKINIST)	**Blood clots:** chest pain, sudden shortness of breath or trouble breathing, pain in your legs with or without swelling, swelling in your arms and legs, a cool or pale arm or leg		✓
Uncommon	**Allergic Reactions** (rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing)		✓
	Pancreatitis (inflammation of the pancreas causing strong abdominal pain**)**	✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist
Uncommon (when TAFINLAR is taken with MEKINIST)	**New primary melanoma** (mole which has irregular shape, border, or colour, is growing, or changing shape or colour)	✓	

This is not a complete list of side effects. For any unexpected effects while taking TAFINLAR, contact your doctor or pharmacist.

HOW TO STORE IT

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

Store TAFINLAR between 15°C to 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

www.novartis.ca or by contacting the sponsor,

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