

PRODUCT MONOGRAPH

PrTAFINLAR®

Dabrafenib (as dabrafenib mesylate)

Capsules, 50 mg and 75 mg

ATC Code: L01XE23
Protein Kinase Inhibitor

Protein Kinase Inhibitor (L01XE23)

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Date of Revision:
September 21, 2018

Submission Control No: 213581

TAFINLAR is a registered trademark

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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	<i>There are no clinically relevant nonmedicinal ingredients. For a complete listing of ingredients see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Unresectable or Metastatic Melanoma

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.

- 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 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 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).

Adjuvant treatment of melanoma

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

- The indication is based on relapse-free survival (RFS) demonstrated in a randomized, placebo-controlled Phase III trial. Overall survival (OS) benefit has not been confirmed (see CLINICAL TRIALS).
- Clinical data supporting the effectiveness of MEKINIST in combination with dabrafenib are limited to patients with BRAF V600E or BRAF V600K mutations. There are no clinical data for other less common BRAF V600 mutations.

Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAFINLAR (dabrafenib mesylate) in combination with trametinib is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

- TAFINLAR should not be used in patients with BRAF wild-type NSCLC (see WARNINGS AND PRECAUTIONS, General).
- Effectiveness is based on overall response rate (ORR). Prolongation of progression-free survival (PFS), overall survival (OS) and improvement in quality-of-life has not been demonstrated (see CLINICAL TRIALS).
- Clinical data supporting the effectiveness of TAFINLAR in combination with trametinib are limited to patients with a BRAF V600E mutation

A validated test is required to identify the BRAF V600 mutation status of melanoma and NSCLC tumours.

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

Geriatrics (≥ 65 years of age)

In clinical studies in unresectable or metastatic melanoma, 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 trametinib 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, Pregnant Women 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 Carcinogenesis and Mutagenesis 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

BRAFV600 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 or wild-type BRAF NSCLCs. New primary melanomas have been reported in patients taking TAFINLAR (see Carcinogenesis and Mutagenesis below). TAFINLAR should not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC 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. There is potential for loss of efficacy following co-administration of strong CYP3A4 and CYP2C8 inducers as they may decrease 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 in unresectable or metastatic melanoma 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 in unresectable or metastatic melanoma, 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). 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).

In a phase III trial in the adjuvant treatment of melanoma, the incidence and severity of pyrexia (*including influenza like illness, body temperature increased, hyperpyrexia and systemic inflammatory response syndrome*) were higher in the TAFINLAR in combination with trametinib arm (67% (292/435); 6% Grade 3/4) compared to the placebo arm (15% (66/432); <1% Grade 3). The median time to onset was 23 days with the combination, with a median duration of 3 days.

In the NSCLC phase II study, pyrexia occurred in 57% (53/93; 5% Grade 3) of patients. The median time to onset of first occurrence of fever was 22 days (range: 3 days to 416 days) and the median duration of fever was 3.5 days (range: 1 to 33 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 $\geq 38.5^{\circ}\text{C}$ 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 °C) 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).

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 °C). 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).

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 or NSCLC which has metastasized to the brain. Three patients who developed brain metastases while on treatment with TAFINLAR in combination with trametinib in melanoma phase III trials experienced fatal cerebral haemorrhage (see WARNINGS AND PRECAUTIONS, Haematologic).

Carcinogenesis and Mutagenesis

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 overall¹ TAFINLAR monotherapy population. In a pivotal phase III monotherapy study in unresectable or metastatic melanoma, 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 in unresectable or metastatic melanoma, 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.

In a phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving TAFINLAR in combination with trametinib developed cuSCC compared to 1% (5/432) of

¹ The overall monotherapy population includes integrated safety population of 586 patients with unresectable or metastatic melanoma and the monotherapy arm patients (N=211) of the phase III combination treatment study in unresectable or metastatic melanoma.

patients receiving placebo. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

In the NSCLC phase II study, 3% (3/93) of patients who received TAFINLAR in combination with trametinib developed cuSCC.

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 in unresectable or metastatic melanoma, 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 in unresectable or metastatic melanoma, 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. In the phase III clinical trial in the adjuvant treatment of melanoma, new primary melanomas occurred in <1% (1/435) of patients receiving the combination of TAFINLAR and trametinib as opposed to 1% (6/432) of patients receiving placebo.

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 in unresectable or metastatic melanoma. In the phase III combination study in unresectable or metastatic melanoma, 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. In the NSCLC phase II study, non-cutaneous malignancies were reported in 1% (1/93) of patients receiving the combination treatment with trametinib. In the phase III trial in the adjuvant treatment of melanoma comparing combination of TAFINLAR and trametinib to placebo, non-cutaneous secondary malignancies or recurrent malignancies were observed in 1% (5/435) of patients receiving active therapy compared to 1% (3/432) of patients receiving placebo.

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 \geq 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 msec. Particular care should be exercised when administering TAFINLAR to patients who are suspected to be at an increased risk of experiencing torsade de pointes (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology).

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

In a phase I/II study in unresectable or metastatic melanoma, 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 in unresectable or metastatic melanoma, DVT or PE occurred in 3% (6/209) of patients receiving combination therapy and in $< 1\%$ (2/211) of patients receiving TAFINLAR monotherapy. In the phase III study in the adjuvant treatment of melanoma, DVT and PE occurred in 2% (7/435) of patients receiving TAFINLAR and trametinib compared to 1% (5/432) of patients receiving placebo. In the NSCLC phase II study, PE occurred in 4% (4/93) of patients receiving TAFINLAR and trametinib.

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 a phase III combination study in patients with unresectable or metastatic melanoma, 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. 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 melanoma 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 of a patient and recurred following re-treatment at a reduced dose. In the phase I/II and phase III studies in unresectable or metastatic melanoma, pancreatitis has been reported in 2% (4/204) and < 1% (1/209), respectively, of patients treated with the combination of TAFINLAR and trametinib. In the adjuvant treatment of melanoma trial, pancreatitis was reported in 1% (6/435) of patients receiving TAFINLAR in combination with trametinib, and in < 1% (1/432) of patients receiving placebo.

In the NSCLC phase II study, acute pancreatitis has been reported in 1% (1/93) 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.

Haematologic

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 in unresectable or metastatic melanoma, 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 in unresectable or metastatic melanoma, 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 melanoma phase III trial in unresectable or metastatic melanoma, 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.

No fatal haemorrhagic events occurred in the phase III study in the adjuvant treatment of melanoma.

In the NSCLC phase II study, the incidence of haemorrhagic events in patients receiving TAFINLAR in combination with trametinib was 26% (24/93). Fatal haemorrhagic events occurred in 2% (2/93) of patients receiving TAFINLAR in combination with trametinib, one with retroperitoneal haemorrhage and one with subarachnoid haemorrhage.

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 in unresectable or metastatic melanoma, 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). In the adjuvant treatment of melanoma phase III combination study, 21% (91/435) of patients in the TAFINLAR and trametinib arm, including 7% with Grade 3 adverse events, and 3% (13/432) of patients in the placebo arm experienced hepatic events.

In the NSCLC phase II study, hepatic disorders were reported in 22% (20/93) of patients treated with TAFINLAR in combination with trametinib.

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 in unresectable or metastatic melanoma. 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 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 in unresectable or metastatic melanoma, 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 in unresectable or metastatic melanoma, 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. In the phase II NSCLC study, Grade 3 renal failure was reported in one patient and Grade 3 increased blood creatinine was reported in one patient. Granulomatous/tubulointerstitial nephritis has also been reported in clinical studies 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 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 alternative methods of contraception should be used (see DRUG INTERACTIONS, Drug-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 physal 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 in unresectable or metastatic melanoma 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.

Of the 435 patients who received TAFINLAR plus trametinib in the combination phase III study in the adjuvant treatment of melanoma, 85 patients (20%) were aged 65 years and older and 12 patients (3%) were aged 75 years and older. No overall differences in the effectiveness or safety of TAFINLAR plus trametinib were observed in elderly patients compared to younger patients.

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 was evaluated in an integrated safety population of 586 patients with BRAF V600-mutant unresectable 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 ($\geq 15\%$) of any grade for TAFINLAR in either the overall monotherapy safety population or the phase III pivotal study comparing TAFINLAR to dacarbazine in unresectable or metastatic melanoma, include hyperkeratosis, headache, pyrexia,

palmar-plantar erythrodysesthesia (PPE), arthralgia, fatigue, nausea, skin papilloma, alopecia, and rash.

The safety of TAFINLAR in combination with trametinib was evaluated in a multicentre, randomized phase III study (MEK115306) in a safety population of 209 patients with unresectable 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.

The safety of TAFINLAR in combination with trametinib has been evaluated in a phase III, randomized, double-blind study of TAFINLAR in combination with trametinib versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection. The median duration of exposure was 11 months for dabrafenib and trametinib and 10 months for the placebo arm. The majority of patients had > 6 to 12 months of exposure to dabrafenib (71%) and trametinib (72%), respectively.

In the TAFINLAR 150 mg twice daily and trametinib 2 mg once daily arm, the most common adverse reactions ($\geq 20\%$) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhoea, vomiting, arthralgia and myalgia. The most common serious adverse reactions ($\geq 1\%$) were pyrexia, chills, ejection fraction decreased, erysipelas, hypotension, cellulitis and chorioretinopathy.

Adverse reactions resulting in the permanent discontinuation of TAFINLAR in combination with trametinib occurred in 26% of patients. Adverse reactions leading to dose interruptions or reductions of TAFINLAR in combination with trametinib occurred in 66% and 38% of patients, respectively.

Female patients treated with combination therapy had higher incidences of treatment-related adverse events (95% vs. 88%) and treatment-related serious adverse events (31% vs. 24%), corresponding to more dose reductions (45% vs. 33%), dose interruptions (70% vs. 64%), and adverse events leading to discontinuation (32% vs. 22%) compared to male patients. No differences in the pattern of adverse events or the overall incidence of adverse events (females: 98% vs. males: 96%) were observed between genders.

The safety of TAFINLAR in combination with trametinib was also evaluated in a phase II, multi-centre, multi-cohort, non-randomised, open-label study of patients with BRAF V600E mutation positive metastatic NSCLC. Patients (N = 93) had a median exposure to TAFINLAR of 8.5 months (range: 0.3-31.6 months), with 62% of patients receiving treatment with TAFINLAR and trametinib for more than 6 months.

The most common adverse drug reactions ($\geq 20\%$) reported in patients with NSCLC who received TAFINLAR in combination with trametinib were pyrexia, asthenia, nausea, vomiting, oedema peripheral, diarrhoea, dry skin, rash decreased appetite, haemorrhage and chills.

The most common serious adverse drug reactions ($\geq 2\%$) reported in patients with NSCLC who received TAFINLAR in combination with trametinib were pyrexia, ejection fraction decreased, alanine aminotransferase increased, aspartate aminotransferase increased, hypotension, vomiting, anaemia, nausea, abdominal pain, asthenia, back pain, blood alkaline phosphatase increased, chills, confusional state, decreased appetite, dehydration, diarrhoea, dyspnoea, haemoptysis, hypercalcaemia, lung infection, pulmonary embolism, renal failure, respiratory distress, squamous cell carcinoma of skin and tubulointerstitial nephritis.

Twenty percent (20%) of NSCLC patients treated with the TAFINLAR and trametinib combination had AEs leading to permanent discontinuation of study treatment. The percentage of patients with AEs leading to dose interruptions and dose reductions was 67% and 35%, respectively.

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.

Unresectable or Metastatic Melanoma

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 unresectable or metastatic melanoma (BRF113683) and one phase II single-arm study in patients with melanoma metastatic to the brain (BRF113929) (see 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/m² every 3 weeks. In study BRF113929, TAFINLAR was administered as 150 mg orally twice daily in an open label fashion.

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 $\geq 10\%$ (All grades) or $\geq 2\%$ (Grades 3 or 4) of Patients in 2 Clinical Trials of TAFINLAR Monotherapy – Unresectable or Metastatic Melanoma Studies

	BRF113683: Treatment-Naïve Patients				BRF113929: Patients With Brain Metastases	
	TAFINLAR N = 187		DTIC N = 59		TAFINLAR N = 172	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Gastrointestinal disorders						
Nausea	27	< 1	53	0	26	2
Vomiting	18	1	25	0	20	1
Diarrhoea	14	< 1	12	0	13	< 1
Constipation	13	2	15	0	8	0
General disorders and administration site conditions						
Pyrexia	31	3	14	0	26	< 1
Fatigue	22	1	24	0	25	1
Asthenia	19	< 1	15	2	5	0
Chills	12	0	2	0	11	< 1
Infections and infestations						
Nasopharyngitis	16	0	7	0	6	0
Metabolism and nutritional disorders						
Decreased appetite	12	0	8	3	12	2
Hyperglycaemia	7	3	7	0	5	1
Hypophosphatemia	5	2	0	0	5	2
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
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
Nervous system disorders						
Headache	34	0	8	0	28	2

	BRF113683: Treatment-Naïve Patients				BRF113929: Patients With Brain Metastases	
	TAFINLAR N = 187		DTIC N = 59		TAFINLAR N = 172	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Respiratory, thoracic and mediastinal disorders						
Cough	14	0	7	0	10	0
Skin and subcutaneous disorders						
Hyperkeratosis	39	2	2	0	26	< 1
Alopecia	29	< 1	3	0	15	0
PPE ^c	20	2	2	0	15	2
Rash	18	0	0	0	17	0
Dry Skin	10	0	0	0	8	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 erythrodysesthesia 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%)

Abnormal Haematologic and Clinical Findings

Table 2 Laboratory Abnormalities Increased from Baseline in the Unresectable or Metastatic Melanoma 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 CLINICAL TRIALS). The common adverse reactions in Table 3 were reported in $\geq 10\%$ of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in $\geq 2\%$ of patients treated with the combination treatment.

Table 3 Adverse Reactions (%) Occurring in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grades 3 or 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the Unresectable or Metastatic Melanoma 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 (%)
Blood and lymphatic system disorders				
Neutropenia	10	3	2	< 1
Anaemia	6	3	9	4
Cardiac disorders				
Ejection fraction decreased	6	1	3	2
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
General disorders and administrative site conditions				

	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 (%)
Pyrexia	57	7	33	2
Fatigue	39	2	37	1
Chills	31	0	17	< 1
Oedema peripheral	21	< 1	9	< 1
Asthenia	12	1	14	< 1
Hepatobiliary disorders				
ALT increased	13	2	6	< 1
AST increased	13	3	4	< 1
Infections and infestations				
Nasopharyngitis	12	0	10	0
Urinary tract infection	11	2	3	< 1
Metabolism and nutritional disorders				
Decreased appetite	12	< 1	13	< 1
Hyperglycaemia ^a	7	3	3	< 1
Musculoskeletal, connective tissue and bone disorders				
Arthralgia	26	< 1	31	0
Pain in extremity	15	1	17	< 1
Myalgia	13	< 1	13	0
Neoplasms benign and malignant (including cysts and polyps)				
cuSCC ^{b,c}	3	3	10	10
Nervous system disorders				
Headache	33	< 1	30	1
Dizziness	14	0	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough	21	0	21	0
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
Vascular disorders				
Hypertension	25	6	16	6
Haemorrhage ^d	19	2	15	2
Hypotension	6	2	3	< 1

^a Includes hyperglycaemia, type 2 diabetes, diabetes mellitus, and blood glucose increase

^b Includes squamous cell carcinoma of skin, squamous cell carcinoma *in situ* (Bowen's disease) and keratoacanthoma

^c Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol

^d Includes intracranial and gastric haemorrhage

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 erythrodysesthesia syndrome (hand-foot syndrome) (5%), Actinic keratosis (5%), Urticaria (3%), Panniculitis, including erythema nodosum (3%), Skin fissures (2%), Photosensitivity (2%)

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

Abnormal Haematologic and Clinical Findings

Table 4 Laboratory Abnormalities Changed from Baseline in the Phase III Unresectable or Metastatic Melanoma Study MEK115306

Preferred Term	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	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

Adjuvant treatment of melanoma

TAFINLAR in Combination with Trametinib

Table 5 and Table 6 present adverse drug reactions and laboratory abnormalities, respectively, from the adjuvant treatment of melanoma phase III study (BRF115532) of TAFINLAR 150 mg given twice daily in combination with trametinib 2 mg given once daily (see CLINICAL TRIALS). The adverse drug reactions in Table 5 were reported in $\geq 10\%$ of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in $\geq 2\%$ of patients treated with the combination.

Table 5 Adverse Reactions (%) Occurring in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grades 3 and 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the Adjuvant Treatment of Melanoma Study BRF115532

	Study BRF115532			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 435)		Placebo (N = 432)	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Blood and lymphatic system disorders				
Neutropenia ¹	10	5	< 1	NR
Gastrointestinal disorders				
Nausea	40	< 1	20	NR
Diarrhoea	33	< 1	15	< 1
Vomiting	28	< 1	10	NR
Abdominal pain ²	16	< 1	11	< 1
Constipation	12	NR	6	NR
General disorders and administration site conditions				
Pyrexia ³	63	5	11	< 1
Fatigue ⁴	59	5	37	< 1
Chills	37	1	4	NR
Oedema peripheral ⁵	16	< 1	6	NR
Influenza-like illness	15	< 1	7	NR
Infections and infestations				
Nasopharyngitis ⁶	12	< 1	12	NR
Investigations				
Alanine aminotransferase increased ⁷	17	4	2	< 1
Aspartate aminotransferase increased ⁸	16	4	2	< 1
Metabolism and nutrition disorders				
Decreased appetite	11	< 1	6	NR
Musculoskeletal and connective tissue disorders				
Arthralgia	28	< 1	14	NR
Myalgia ⁹	20	< 1	14	NR
Pain in extremity	14	< 1	9	NR
Muscle spasms ¹⁰	11	NR	4	NR
Nervous system disorders				
Headache ¹¹	39	1	24	NR
Dizziness ¹²	11	< 1	10	NR

Respiratory, thoracic and mediastinal disorders				
Cough ¹³	17	NR	8	NR
Skin and subcutaneous tissue disorders				
Rash ¹⁴	37	< 1	16	< 1
Dry skin ¹⁵	14	NR	9	NR
Dermatitis acneiform	12	< 1	2	NR
Erythema ¹⁶	12	NR	3	NR
Pruritus ¹⁷	11	< 1	10	NR
Vascular disorders				
Haemorrhage ¹⁸	15	< 1	4	< 1
Hypertension ¹⁹	11	6	8	2
¹ Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia ² Abdominal pain also includes abdominal pain upper and abdominal pain lower ³ Pyrexia also includes hyperpyrexia ⁴ Fatigue also includes asthenia and malaise ⁵ Oedema peripheral also includes peripheral swelling ⁶ Nasopharyngitis also includes pharyngitis ⁷ Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia ⁸ Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia ⁹ Myalgia also includes musculoskeletal pain and musculoskeletal chest pain ¹⁰ Muscle spasms also includes musculoskeletal stiffness ¹¹ Headache also includes tension headache ¹² Dizziness also includes vertigo ¹³ Cough also includes productive cough ¹⁴ Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular ¹⁵ Dry skin also includes xerosis and xeroderma ¹⁶ Erythema also includes generalized erythema ¹⁷ Pruritus also includes pruritus generalized and pruritus genital ¹⁸ Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events. ¹⁹ Hypertension also includes hypertensive crisis NR: not reported				

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

Other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR in combination with trametinib in the safety population from the adjuvant treatment of melanoma phase III clinical trial include:

Eye disorders: Blurred vision (6%), Uveitis (1%), Chorioretinopathy* (1%), Retinal detachment** (1%)

Investigations: Alkaline phosphatase increased (7%), Ejection fraction decreased (5%)

Musculoskeletal and connective tissue disorders: Rhabdomyolysis (< 1%)

Renal and urinary disorders: Renal failure (< 1%)

Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysesthesia syndrome (6%)

* Chorioretinopathy also includes chorioretinal disorder.

** Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.

Table 6 Laboratory Abnormalities Changed from Baseline in the Phase III Adjuvant Treatment of Melanoma Study BRF115532

Test	TAFINLAR plus Trametinib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Haematology^a				
Neutropenia	47	6	12	<1
Leukopenia	43	3	10	<1
Lymphopenia	26	5	6	<1
Anaemia	25	<1	6	<1
Liver Function Tests				
Increased AST ^b	57	6	11	<1
Increased ALT ^c	48	5	18	<1
Increased blood alkaline phosphatase ^a	38	1	6	<1
Chemistry				
Hyperglycaemia ^d	63	3	47	<1
Hypophosphatemia ^e	42	7	10	<1
Hypoalbuminemia ^a	25	<1	<1	0
Hyponatraemia ^a	16	3	3	<1

^a For these laboratory tests the denominator is 431 for TAFINLAR plus Trametinib and 428 for Placebo

^b For these laboratory tests the denominator is 430 for TAFINLAR plus Trametinib and 426 for Placebo

^c For these laboratory tests the denominator is 429 for TAFINLAR plus Trametinib and 428 for Placebo

^d For these laboratory tests the denominator is 430 for TAFINLAR plus Trametinib and 427 for Placebo

^e For these laboratory tests the denominator is 431 for TAFINLAR plus Trametinib and 427 for Placebo.

Metastatic Non-Small Cell Lung Cancer

TAFINLAR in Combination with Trametinib

Table 57 and Table 8 present adverse drug reactions and laboratory abnormalities, respectively, from the NSCLC phase II study of TAFINLAR 150 mg given twice daily in combination with

trametinib 2 mg given once daily (see CLINICAL TRIALS). The common adverse drug reactions in Table 7 were reported in $\geq 10\%$ of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in $\geq 2\%$ of patients treated with the combination.

Table 7 Adverse Reactions (%) Occurring in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grades 3 or 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the NSCLC Study BRF113928

	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93)	
	All Grades (%)	Grades 3 and 4 (%)
Blood and lymphatic system disorders		
Anaemia	16	4
Neutropenia ¹	15	8
Leukopenia	6	2
Cardiac disorders		
Ejection fraction decreased	9	4
Gastrointestinal disorders		
Nausea	46	0
Vomiting	37	3
Diarrhoea	33	2
Decreased appetite	28	0
Constipation	16	0
General disorders and administration site disorders		
Pyrexia	55	5
Asthenia ²	47	6
Oedema peripheral	34	0
Chills	24	1
Investigations		
Weight decreased	13	1
Blood alkaline phosphatase increased	12	0
Aspartate aminotransferase increased	11	2
Alanine aminotransferase increased	10	4
Weight increased	10	3
Gamma-glutamyltransferase increased	2	2
Metabolism and nutrition disorders		
Hyponatraemia	14	9
Dehydration	8	3

	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93)	
	All Grades (%)	Grades 3 and 4 (%)
Hypercalcaemia	3	2
Musculoskeletal and connective tissue disorders		
Arthralgia	16	0
Myalgia	13	0
Muscle spasms	10	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Squamous cell carcinoma of skin	3	2
Nervous system disorders		
Headache	16	0
Dizziness	14	0
Renal and urinary disorders		
Tubulointerstitial nephritis	2	2
Respiratory, thoracic and mediastinal disorders		
Cough	23	0
Dyspnoea	15	2
Skin and subcutaneous tissue disorders		
Dry skin	32	1
Rash ³	31	3
Pruritus ⁴	15	2
Hyperkeratosis ⁵	13	1
Erythema	10	0
Vascular disorders		
Haemorrhage ⁶	26	3
Hypotension	15	2
Hypertension	8	6
Pulmonary embolism	4	2
¹ Neutropenia includes neutropenia and neutrophil count decreased. Neutrophil count decreased qualified as a neutropenia event. ² Asthenia also includes fatigue and malaise ³ Rash includes rash, rash generalized, rash papular, rash macular, rash maculo-papular and rash pustular ⁴ Pruritus includes pruritus, pruritus generalized and eye pruritus ⁵ Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis and keratosis pilaris ⁶ Haemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid haemorrhage, gastric haemorrhage, urinary bladder haemorrhage, contusion, haematochezia, injection site haemorrhage, melaena, pulmonary and retroperitoneal haemorrhage		

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

Other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR in combination with trametinib in the safety population from the NSCLC phase II clinical trial include:

Eye Disorders: Detachment of retina/retinal pigment epithelium (2%)

Gastrointestinal Disorders: Pancreatitis acute (1%)

Renal and Urinary Disorders: Renal failure (3%)

Abnormal Haematologic and Clinical Findings

Table 8 Laboratory Abnormalities Changed from Baseline in the Phase II Study BRF113928

Preferred Term	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93) ¹	
	All Grades (%)	Grades 3 and 4 ² (%)
Hyperglycaemia	71	9
Hyponatraemia	57	17
Hypophosphataemia	36	7
Creatinine	21	1
Increased alkaline phosphatase	64	0
Increased AST	61	4
Anaemia	46	10
Leukocytopenia	48	8
Neutropenia	44	8
Lymphocytopenia	42	14
Thrombocytopenia	16	1

¹ For these laboratory tests the denominator is n = 90, except for leukocytopenia, neutropenia, lymphocytopenia and thrombocytopenia (n = 91)

² Grade 4 adverse reactions limited to AST increased (n = 1), lymphocytopenia (n = 1), neutropenia (n = 1), hypophosphataemia (n = 1) and hyponatraemia (n = 1)

DRUG INTERACTIONS

Serious Drug Interaction

Dabrafenib is teratogenic and embryofetal 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 enzymes 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 meaningful change in the concentrations of the metabolites. Strong CYP3A4 inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir) or CYP2C8 inhibitors (e.g. gemfibrozil) should be avoided if possible and alternative agents should be considered during administration with TAFINLAR.

Pharmacokinetic data showed a decrease in repeat-dose dabrafenib C_{max} (27%) and AUC (34%) upon co-administration with rifampin (CYP3A4/CYP2C8 inducer). There was an increase in C_{max} (85%) and AUC (73%) for carboxy-dabrafenib and a decrease in C_{max} (39%) and AUC (30%) for desmethyl-dabrafenib; no relevant change in AUC was noted for hydroxy-dabrafenib. 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.

Co-administration of repeat dosing of dabrafenib 150 mg twice daily and a pH elevating agent, rabeprazole 40 mg once daily, resulted in a 3% increase in dabrafenib AUC and a 12% decrease in dabrafenib C_{max} . These changes in dabrafenib AUC and C_{max} are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Dabrafenib is a substrate of human P-glycoprotein (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-Lifestyle 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 trametinib 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.

Unresectable or metastatic melanoma and metastatic NSCLC

Treatment should continue until disease progression or the development of unacceptable toxicity (see Table 9).

Adjuvant treatment of melanoma

Treatment should continue for a period of 12 months, unless disease recurrence or unacceptable toxicity occurs (see Table 9).

Dose Modifications

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation of TAFINLAR (see Table 9 and Table 10).

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 9. Dose level reductions are listed in Table 10. 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 9 Recommended Dose Modifications for TAFINLAR Monotherapy and for TAFINLAR and Trametinib Combination Therapy

Adverse Reaction ^a	TAFINLAR
Cardiac	
<ul style="list-style-type: none"> • Symptomatic congestive heart failure 	<ul style="list-style-type: none"> • Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level
<ul style="list-style-type: none"> • Absolute decrease in LVEF of greater than 20% from baseline that is below LLN 	<ul style="list-style-type: none"> • Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level
Febrile Drug Reaction	
<ul style="list-style-type: none"> • Fever of 38.5 – 40 °C without complications 	<ul style="list-style-type: none"> • Withhold TAFINLAR until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level
<ul style="list-style-type: none"> • Fever > 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure 	<ul style="list-style-type: none"> • Discontinue treatment with TAFINLAR permanently, or withhold therapy until adverse reaction resolves. If resuming TAFINLAR therapy, administer at a reduced dose level.
Cutaneous	
<ul style="list-style-type: none"> • Intolerable Grade 2 rash or ≥ Grade 3 rash 	<ul style="list-style-type: none"> • Withhold TAFINLAR until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy
<ul style="list-style-type: none"> • Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks despite interruption of dosing 	<ul style="list-style-type: none"> • Permanently discontinue TAFINLAR
Ocular	
<ul style="list-style-type: none"> • Uveitis that responds to local ocular therapy 	<ul style="list-style-type: none"> • TAFINLAR may be continued at the same dose. Monitor as clinically indicated.
<ul style="list-style-type: none"> • Uveitis that does not improve despite ocular therapy 	<ul style="list-style-type: none"> • Withhold TAFINLAR until adverse reaction resolves and reduce by one dose level when resuming therapy

Adverse Reaction ^a	TAFINLAR
<i>Other</i>	
<ul style="list-style-type: none"> Grade 1 or Grade 2 (tolerable) 	<ul style="list-style-type: none"> TAFINLAR may be continued at the same dose. Monitor as clinically indicated.
<ul style="list-style-type: none"> Grade 2 (intolerable) OR Grade 3 adverse reaction 	<ul style="list-style-type: none"> Withhold TAFINLAR until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy
<ul style="list-style-type: none"> Grade 4 adverse reaction OR Grade 3 adverse reaction that does not improve to Grade 0-1 	<ul style="list-style-type: none"> Permanently discontinue TAFINLAR OR withhold therapy until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy

^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 10 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

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 is 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 of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations).

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on the oral clearance of dabrafenib 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 in patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on the oral clearance of dabrafenib 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 when used as either a monotherapy or in combination with trametinib.

Treatment

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

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 amino acid variants 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 in specific cancers, including approximately 50% of melanoma. 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 and V600E mutated non-small cell lung carcinoma (NSCLC) 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).

In a single-blind ECG assessment study in subjects with BRAF V600 mutation-positive tumours (N = 30), placebo was administered on Day -1 followed by a single dose of dabrafenib 300 mg on Day 1, dabrafenib 300 mg BID (twice the recommended dose) on Days 2 to 7, and a single dose of dabrafenib 300 mg on Day 8. ECG assessments performed on Days 1 and 8 showed an increase in heart rate, with statistically significant placebo-adjusted mean changes from baseline ranging from 3 to 12 bpm. No large changes in the mean QTc interval (i.e., > 20 ms) were detected.

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 mm Hg, 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 11.

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 (V_c/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 11 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: Based on the population pharmacokinetic analysis, oral dabrafenib clearance (CL/F) is similar in Asian and Caucasian cancer patients with similar liver function. There are insufficient data to evaluate the potential effect of other races/ethnicities on dabrafenib pharmacokinetics.

Hepatic Impairment: The pharmacokinetics of dabrafenib were 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 m²) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m²) 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.

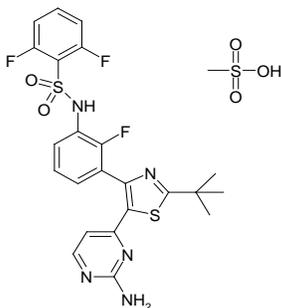
TAFINLAR hard capsules contain dabrafenib as dabrafenib mesylate, and the following non-medicinal ingredients: magnesium stearate, colloidal silicon dioxide, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172) and titanium dioxide (E171). Monogramming ink contains 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 ₃ N ₅ O ₂ S ₂ . CH ₄ O ₃ S
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 have 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 the phase III multi-centre, international clinical study MEK115306.

Screening for eligibility included central laboratory 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 efficacy and safety of TAFINLAR in combination with trametinib in the adjuvant treatment of patients with Stage III melanoma with a BRAF V600 mutation, following resection was studied in a phase III, multi-centre, randomized, double-blind, placebo-controlled study (BRF115532). Screening for the study included central laboratory testing of BRAF mutation (V600E or V600K) using a BRAF mutation assay conducted at baseline.

The efficacy and safety of TAFINLAR in combination with trametinib in the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation has been evaluated in the phase II multi-centre, international clinical study BRF113928. Screening for eligibility included local laboratory testing of BRAF V600E mutation conducted on tumour samples available mostly from the primary tumour.

Unresectable or Metastatic Melanoma

TAFINLAR Monotherapy

Phase III Pivotal Study BRF113683: Treatment-Naïve 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/m² 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

Table12).

Table 12 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)

ECOG = Eastern Cooperative Oncology Group; PS = performance status

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 (see Table13). 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 13 and Figure 1.

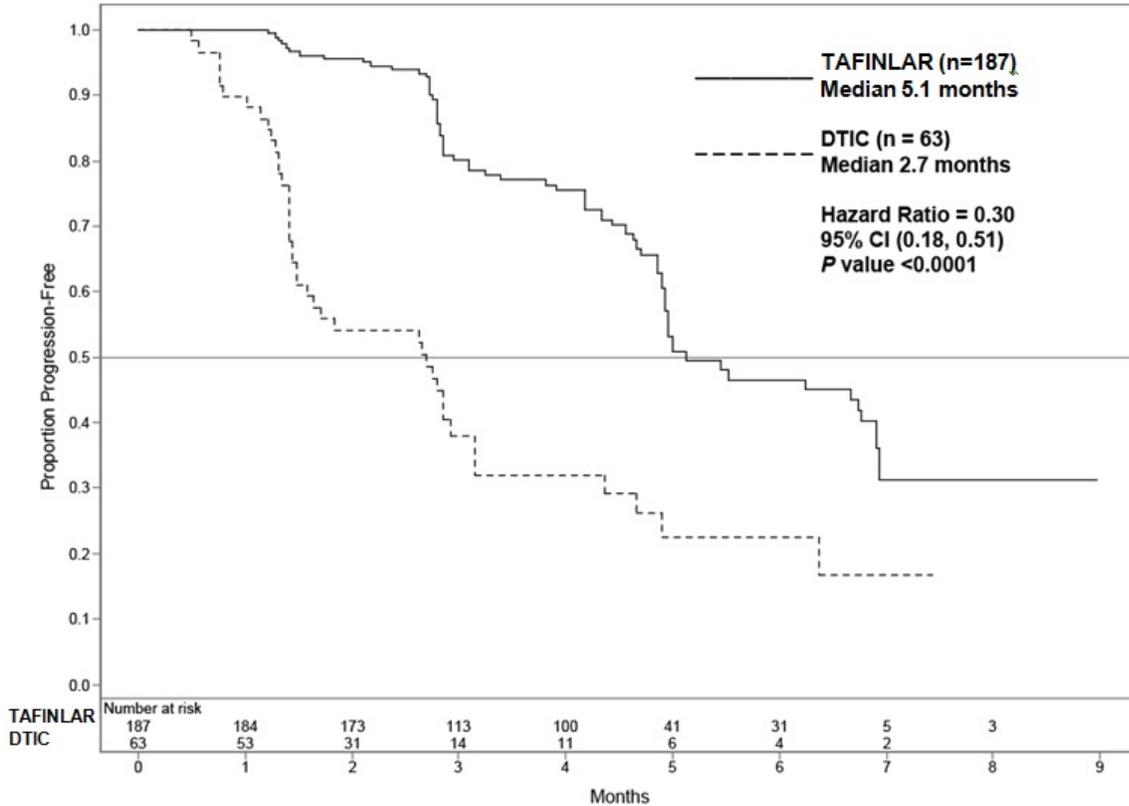
Table 13 Efficacy Results - Study BRF113683

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 (%) (95% CI)	99 (53) (45.5, 60.3)	12 (19) (10.2, 30.9)
Duration of Response Median, months (95% CI)	N = 99 5.6 (4.8, NR)	N = 12 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 14.

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 14 Efficacy Results in Patients with Brain Metastases - Study BRF113929

Endpoint	All Treated Patients			
	BRAF V600E		BRAF V600K	
	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 \leq 10% (based on historical results) in favour of the alternative hypothesis of OIRR \geq 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 unresectable 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 unresectable 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 data cut 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 \leq 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 15).

Table 15 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.

ECOG = Eastern Cooperative Oncology Group; PS = performance status

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 16 for details.

Efficacy results are presented in Table 16, Figure 2 and Figure 3.

Table 16 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 (%) (95% CI)	140 (67) (59.9, 73.0)	108 (51) (44.5, 58.4)	144 (69) (61.8, 74.8)	112 (53) (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 analysis 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

- Hazard ratio and log-rank p-value are adjusted for randomized strata: baseline LDH and BRAF mutation status
- 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
- 95% CI
- Includes only patients with measurable disease at baseline

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

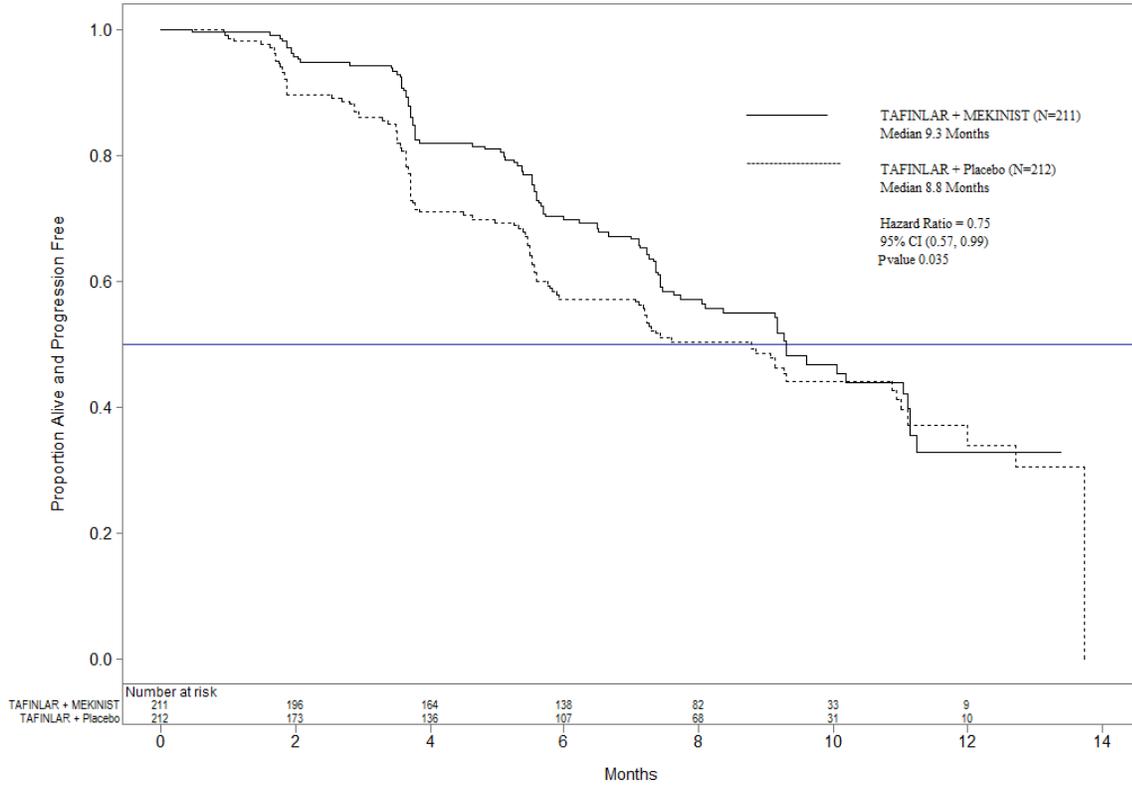
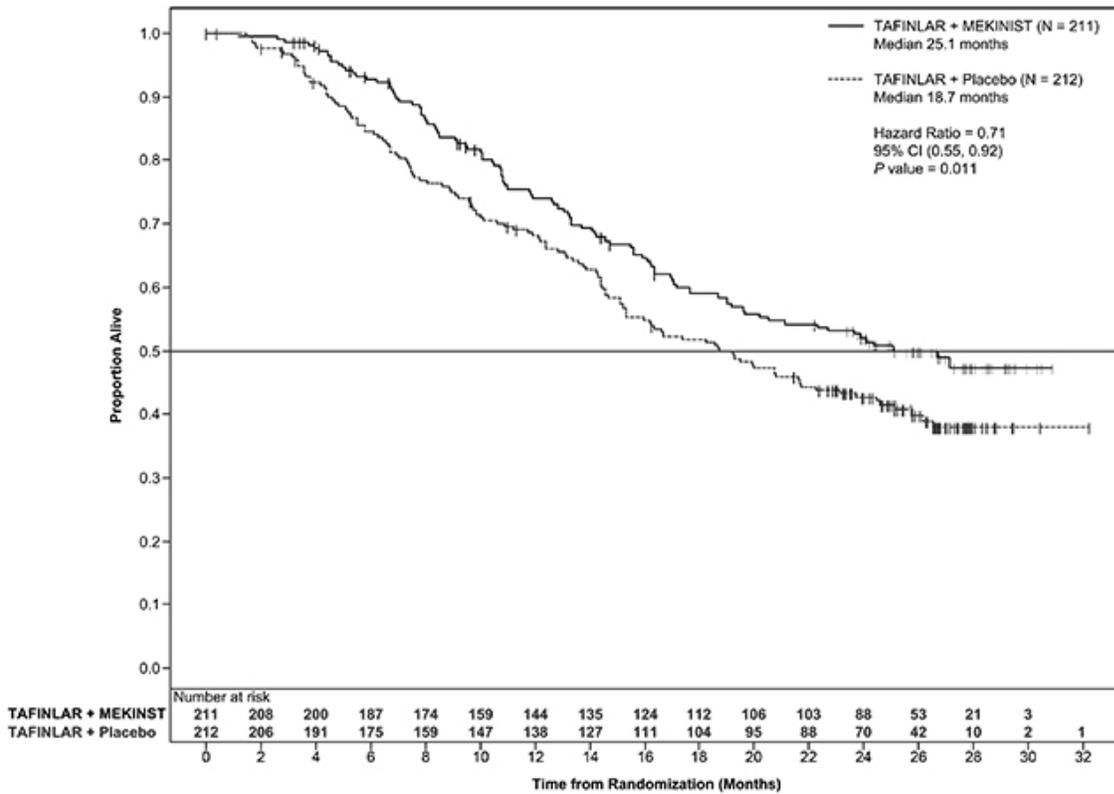


Figure 3 Kaplan-Meier Curves for Final OS (ITT population) - Study MEK115306



Adjuvant treatment of melanoma

TAFINLAR in Combination with Trametinib

Phase III Pivotal Study BRF115532

Trial Design

The efficacy and safety of TAFINLAR in combination with trametinib were studied in a phase III, multi-centre, randomized, double-blind, placebo-controlled study in patients with Stage III melanoma with a BRAF V600E or V600K mutation, following resection.

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (TAFINLAR 150 mg twice daily and trametinib 2 mg once daily) or two placebos for a period of 12 months. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. Any prior systemic anticancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease-free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time

from randomization to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. The key secondary endpoint was overall survival (OS). The median duration of follow-up (time from randomization to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Study Demographics and Baseline Characteristics

The baseline characteristics of the patients were well balanced in the two groups. In both groups 91% had a BRAF V600E mutation and 9% had a BRAF V600K mutation (Table 17).

Table 17 Demographic and Baseline Characteristics - Study BR115532

	TAFINLAR + Trametinib (N = 438)	Placebo (N = 432)
Age (years) Median (Min, Max)	50.0 (18,89)	51.0 (20,85)
Age Group, n (%) < 65	353 (81%)	359 (83%)
≥ 65	85 (19%)	73 (17%)
Sex, n (%) Female	195 (45%)	193 (45%)
Male	243 (55%)	239 (55%)
Race, n (%) White	432 (99%)	427 (99%)
Asian	6 (1%)	5 (1%)
Primary Tumour Type Melanoma	438 (100%)	432 (100%)
Time Since Initial Diagnosis (months) 1st Quartile	4	4
Median	5.0	6.0
3rd Quartile	19	20
Min. – Max.	1 - 306	0 - 351
Stage at Screening* IIIA	83 (19%)	71 (16%)
IIIB	169 (39%)	187 (43%)
IIIC	181 (41%)	166 (38%)
Unknown	5 (1%)	8 (2%)
Primary Tumour Ulceration Yes	179 (41%)	177 (41%)
No	253 (58%)	249 (58%)
Missing	6 (1%)	6 (1%)
In-transit Disease Yes	51 (12%)	36 (8%)
No	387 (88%)	395 (91%)
Missing	0	1 (<1%)
BRAF Mutation Status, n (%) V600E	400 (91%)	395 (91%)
V600K	38 (9%)	37 (9%)

* Per the American Joint Committee on Cancer (AJCC) – Melanoma of the Skin Staging – 7th Edition

Study Results

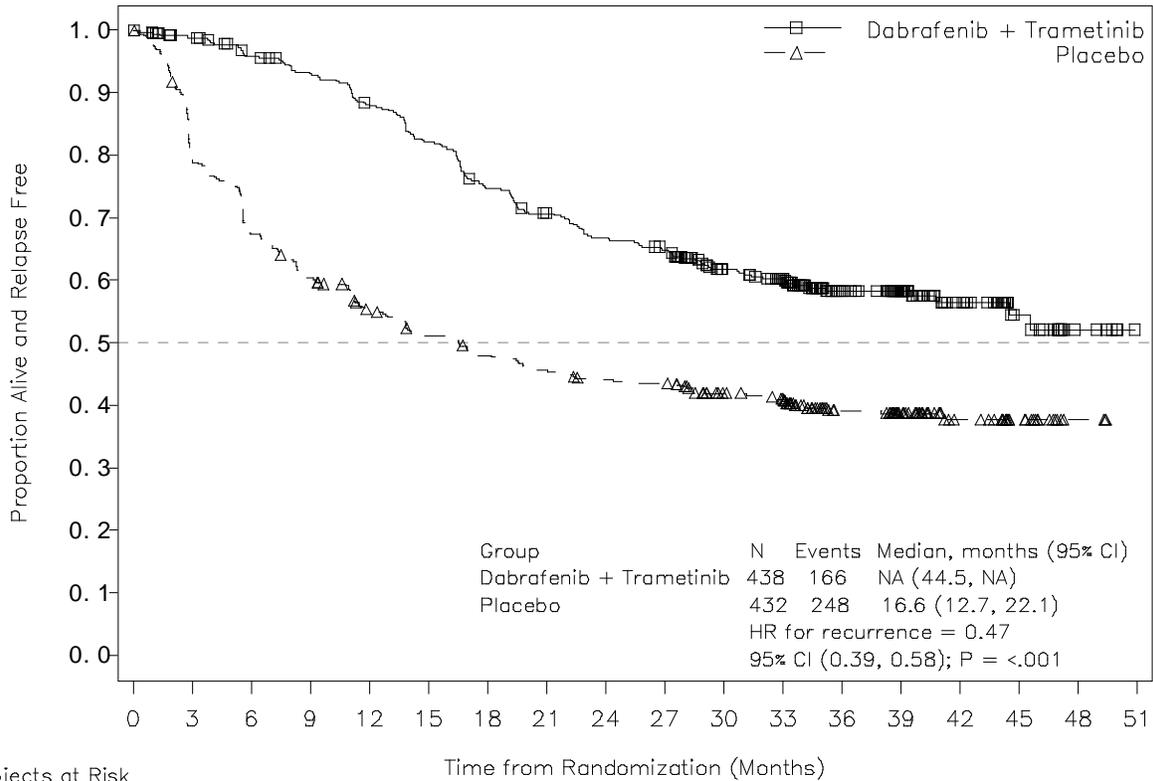
Results for the primary analysis of RFS are presented in Figure 4 and in Table 18. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm

compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; p=1.53×10⁻¹⁴). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and has not yet been reached for the combination arm.

Table 18 Relapse-Free Survival Results - Study BRF115532

	TAFINLAR + Trametinib (N = 438)	Placebo (N = 432)
RFS parameter		
Number of events, n (%)	166 (38%)	248 (57%)
Recurrence	163 (37%)	247 (57%)
Relapsed with distant metastasis	103 (24%)	133 (31%)
Death	3 (<1%)	1 (<1%)
Median (months) (95% CI)	NE (44.5, NE)	16.6 (12.7, 22.1)
Hazard ratio ^[1] (95% CI) p-value ^[2]	0.47 (0.39, 0.58) 1.53×10 ⁻¹⁴	
1-year rate (95% CI)	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)	0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)	0.39 (0.35, 0.44)
OS parameter		
Hazard ratio ^[1] (95% CI)	0.57 (0.42, 0.79)	
[1] Hazard ratio is obtained from the stratified Pike model. [2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K) NE = not estimable		

Figure 4 Relapse-free survival Kaplan-Meier curves (ITT population) – Study BRF115532



Subjects at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Dabrafenib + Trametinib	438	411	392	377	355	330	299	279	263	253	202	187	116	83	52	23	7	0
Placebo	432	335	280	250	219	199	185	176	168	166	141	132	87	62	33	16	3	0

Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79), which was not statistically significant. The overall survival data were not mature at the time of the study’s primary efficacy analysis.

Metastatic NSCLC

Phase II Pivotal Study BRF113928

Trial Design

BRF113928 was a Phase II, multi-centre, non-randomized and open-label study enrolling patients with metastatic BRAF V600E-mutant NSCLC. The study enrolled 93 patients; 57 patients whose disease progressed following 1 to 3 previous systemic treatments and 36 patients who received the study medication as first-line treatment for metastatic disease. All patients received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily.

The primary endpoint was the investigator-assessed ORR using the ‘Response Evaluation Criteria In Solid Tumors’ (RECIST), v1.1, and the secondary endpoint was Duration of Response

(DoR); both were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis. For those whose disease progressed following 1 to 3 previous systemic treatments, the null hypothesis was that the ORR is less than or equal to 30%. The alternative hypothesis was that the ORR is higher than or equal to 55%. For those who received the study medication as first line treatment for metastatic disease, the null hypothesis was that the ORR is less than or equal to 30%. The alternative hypothesis was that the ORR is higher than or equal to 60%.

Baseline characteristics are listed in Table 19 below.

Table 19 Demographic and Baseline Characteristics - Study BRF113928

	Previously treated TAFINLAR + Trametinib (N = 57)	Treatment-naïve TAFINLAR + Trametinib (N = 36)
Age (years) Median (Min, Max)	64 (41, 88)	67 (44, 91)
Age Group, n (%) < 65	29 (51)	14 (39)
≥ 65	28 (49)	22 (61)
Sex, n (%) Female	28 (49)	22 (61)
Male	29 (51)	14 (39)
Race, n (%) White	49 (86)	30 (83)
Asian	4 (7)	3 (8)
Black or African American	2 (4)	1 (3)
Other	2 (4)	2 (6)
ECOG PS at Baseline, n (%) 0	17 (30)	13 (36)
1	35 (61)	22 (61)
2	5 (9)	1 (3)
Histology, n (%) Squamous	0	1 (3)*
Non-squamous	57 (100)	35 (37)
Smoking History, n (%) Never smoked	16 (28)	10 (28)
Current smoker	6 (11)	5 (14)
Former smoker	35 (61)	21 (58)
Prior anti-cancer therapy for metastatic disease, n (%) 1	38 (67)	0 (0)
2	12 (21)	0 (0)
3	7 (12)	0 (0)

ECOG = Eastern Cooperative Oncology Group; PS = performance status

* 1 patient with adenosquamous carcinoma - predominately squamous histology. All histology was determined by local pathological report.

Study results

The ORR in the previously treated combination therapy population was 63.2% (95% CI, 49.3, 75.6) by investigator assessment and median DoR was 9.0 months (95% CI: 6.9, 18.3). The median duration of treatment was 10.6 months. The ORR in the treatment-naïve population was 61.1% (95% CI, 43.5, 76.9) and median DoR was not reached. The median duration of treatment was 8.21 months. The IRC-assessed efficacy results were consistent with the investigator assessments (see Table 20).

Table 20 Efficacy Results - Study BRF113928

Efficacy Endpoints [†]	Previously treated* N = 57		Treatment-naïve* N = 36	
	Investigator-Assessed	IRC-Assessed	Investigator-Assessed	IRC-Assessed
Primary Endpoint				
Overall Response Rate (ORR)				
ORR, % (95% CI)	63.2 (49.3, 75.6)	63.2 (49.3, 75.6)	61.1 (43.5, 76.9)	61.1 (43.5, 76.9)
CR, n (%)	2 (4)	0	2 (6)	1 (3)
PR, n (%)	34 (60)	36 (63)	20 (56)	21 (58)
Secondary endpoints				
Duration of response				
Median, months (95% CI)	9.0 (6.9, 18.3)	9.0 (5.8, 17.6)	NE (8.3, NE)	NE (6.9, NE)

* Primary analysis data cut-off dates: 07 October 2015 (previously treated), 08 August 2016 (treatment-naïve)

[†] CI = Confidence interval; CR = Complete response; IRC = Independent review committee; NE = Not evaluable; PR = Partial response

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, ¹⁴C-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 ¹⁸F-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 (IC₅₀) in *in vitro* kinase assay (see Table 21). The inhibitory activity of dabrafenib has not been determined for BRAF variants V600R, V600G and V600M.

Table 21 Inhibition of Different BRAF Variants by Dabrafenib

Kinase	IC₅₀ (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 (IC₅₀ < 1 µM) compared to melanoma cell lines expressing wild-type BRAF. In addition, dabrafenib inhibited growth in a BRAF V600E positive NSCLC cell line with an IC₅₀ value similar to those observed in BRAF mutation melanoma cell lines. Dabrafenib demonstrated suppression of phosphorylated ERK (pERK) in BRAF V600 mutant melanoma and BRAF V600E mutant NSCLC 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 IC₅₀ 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 IC₂₅ of 11.7 µM (6.1 µg/mL); however, its 3 active metabolites did not inhibit hERG (IC₅₀ > 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) and testicular toxicity (degeneration and tubular dilation) 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.

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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 can be taken **by itself or with trametinib**. When you take TAFINLAR with trametinib, read both leaflets.

TAFINLAR should only be used for people who have a cancer that has a certain change in a gene called "BRAF". Before taking TAFINLAR, you should have your cancer tested for this change. Your doctor will take a tumour tissue sample, to test whether TAFINLAR is suitable for you.

Taking TAFINLAR **by itself** is used for the following:

- to treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.

Taking TAFINLAR **with trametinib** is also used for the following:

- to treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.
- to help prevent melanoma from coming back. This is after the skin cancer was completely removed by surgery.
- to treat a type of lung cancer. This type of cancer is called non-small cell lung cancer. These drugs are used together when this cancer has spread to other parts of the body.

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.

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 and managed by a doctor who is experienced in the use of anti-cancer drugs. Serious side effects include:

- 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 secondary cancers

Other serious side effects when taking TAFINLAR with trametinib include:

- Serious bleeding
- Blood clots

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 trametinib. 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 trametinib, 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 trametinib, 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 trametinib, 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 trametinib, 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

trametinib 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 trametinib 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
- some medicines (called proton pump inhibitors) that reduce stomach acid (e.g. esomeprazole)
- 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.

Female patients compared to male patients who took combination therapy to help prevent melanoma from coming back after surgery had more side effects and serious side effects that caused:

- More dose decreases.
- More dose interruptions.
- More need to stop the drug treatment.

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 trametinib: the usual dose is two

75 mg capsules of TAFINLAR (150 mg) twice a day with 2 mg of trametinib once a day.

How to take TAFINLAR either by itself or with trametinib:

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 trametinib, take trametinib with either the morning or the evening dose of TAFINLAR. Take trametinib 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 trametinib 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 trametinib, call your doctor or poison control centre, or go to the nearest hospital emergency room right away. Take TAFINLAR capsules and trametinib 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 (*hyperkeratosis*)

- Skin effects such as rough scaly patches of skin (*actinic keratosis*), brown or yellow to red thickening of skin (*seborrhoeic keratosis*), skin tags (*acrochordon*), or redness of the skin (*erythema*)
- Skin effects such as rash, dryness, wart-like growths, or redness and/or swelling
- Possible peeling of the palms, fingers and soles of the feet which may be accompanied by tingling sensation and burning pain (*palmar-plantar erythrodysesthesia syndrome*)
- Papilloma (a type of harmless (*benign*) skin cancer)
- Headache
- Nausea, vomiting, or diarrhoea
- Decreased appetite
- Chills
- Feeling weak, sick and tired (*asthenia, including malaise and fatigue*)
- Lack of energy
- Fever (*pyrexia*)
- Joint pain (*arthralgia*), muscle pain (*myalgia*), or pain in the hands or feet (*pain in extremity*)
- Cough
- Unusual hair loss or thinning (*alopecia*)
- Itching (*pruritus*)
- Constipation
- Nasal inflammation (*nasopharyngitis*)
- Tiredness, chills, sore throat, joint or muscle aching (flu-like illness)

Common side effects - affects less than 1 in 10 but more than 1 in 100 people:

- Inflammation of the fatty layer underneath the skin (*panniculitis*)
- Increased sensitivity of the skin to sun (*photosensitivity*)
- Kidney disorder that may result in decreased urine output (*kidney failure*)
- Inflammation of the kidney (*nephritis*)

Common side effects that may show up in your blood tests:

- Low phosphorus (*hypophosphataemia*)
- Increase in sugar (*glucose*)

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

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

Very common side effects - these may affect more than 1 in 10 people:

- Swelling of the hands, ankles or feet (*oedema peripheral*)
- Stomach ache (*abdominal pain*)

- High blood pressure (*hypertension*)
- Urinary tract infections
- Rash, dry skin, itching, acne-like problem (*dermatitis acneiform*)
- Dizziness
- Bleeding (*haemorrhage*)
- Weight decreased
- Muscle spasms
- Low blood pressure (*hypotension*)

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*)
- Low sodium (*hyponatremia*)

Common side effects – affects less than 1 in 10 but more than 1 in 100 people:

- Night sweats
- Shortness of breath (*dyspnoea*)
- Tiredness, chest discomfort, light headedness, pain, palpitations (*ejection fraction decreased*)
- Slow heart rate (*bradychardia*)
- Eyesight problems
- Dry mouth
- Sore mouth or mouth ulcers (*stomatitis*)
- Inflammation of the mucous membranes
- Swelling of the face (*face oedema*), localized tissue swelling (*lymphoedema*)
- Low levels of water or fluid (*dehydration*)
- Infection of the skin (*cellulitis*)
- Inflammation of the follicles in the skin (*folliculitis*)
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles (*paronychia*)
- Skin rash with pus-filled blisters (*rash pustular*)
- Excessive sweating (*hyperhidrosis*)
- Skin cracking
- Weight increased
- Swelling in the eye caused by leaking fluid. This can cause blurred vision. (*chorioretinopathy*)

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) (*thrombocytopenia*)

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

- Lung inflammation (*pneumonitis*)

- Swelling around the eyes (*periorbital oedema*)
- Splitting of the light-sensitive membrane in the back of the eye from its supporting layers (*retinal detachment*)

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	Dermatitis acneiform: Skin rash, acne-like rash, redness of the face, dry or itching skin	✓	
	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		✓
	Uveitis (red, swollen eye): eye pain, burning or sensitive to light. Blurred vision. Headache.		✓
Very Common (when TAFINLAR is taken with trametinib)	Oedema: generalised swelling		✓
Common	New primary melanoma (mole which has irregular shape, border, or colour, is growing, or changing shape or colour, new skin lesion)	✓	

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
	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	✓	
	Tubulointerstitial nephritis: high or low urine output, drowsiness, confusion, nausea as a sign of an inflamed kidney		✓
Common (when TAFINLAR is taken with trametinib)	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		✓
	Pulmonary embolism (blood clot in the lung): sharp chest pain, coughing up blood, or sudden shortness of breath. Difficulty breathing, fainting, rapid heart rate, bluish skin.		✓
	Acute pancreatitis: acute, severe upper stomach pain		✓
Uncommon	Allergic Reactions: rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing		✓

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
	Pancreatitis (inflammation of the pancreas causing strong abdominal pain)	✓	

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 1908C
 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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This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: September 21, 2018

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