NOVARTIS

1 Tradename

TAFINLAR® 50 mg and 75 mg hard capsules.

2 Description and composition

Pharmaceutical form

50 mg hard capsules
Opaque, size 2 capsules composed of a dark red body and dark red cap containing a white to slightly coloured solid. Capsule shells imprinted with GS TEW and 50 mg.

75 mg hard capsules
Opaque, size 1 capsules composed of a dark pink body and dark pink cap containing a white to slightly coloured solid. Capsule shells imprinted with GS LHF and 75 mg.

Active substance

50 mg hard capsules
Each hard capsule contains dabrafenib mesilate equivalent to 50 mg of dabrafenib.

75 mg hard capsules
Each hard capsule contains dabrafenib mesilate equivalent to 75 mg of dabrafenib.

Excipients

Hard capsule: microcrystalline cellulose (cellulose, microcrystalline), magnesium stearate (vegetable source), colloidal silicon dioxide (silica, colloidal anhydrous).

Shell composition: red iron oxide, titanium dioxide, hypromellose.

Monogramming: black iron oxide, shellac, n-butyl alcohol, isopropyl alcohol, propylene glycol, ammonium hydroxide.

Pharmaceutical formulations may vary between countries.

Certain dosage strengths and forms may not be available in all countries.

3 Indications

Unresectable or metastatic melanoma
Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation *(see Section 12 Clinical Studies)*.

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

Advanced non-small cell lung cancer
Dabrafenib in combination with trametinib is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation (*see Section 12 Clinical Studies*).

Locally advanced or metastatic anaplastic thyroid cancer
Dabrafenib in combination with trametinib is indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAF V600 mutation and with no satisfactory locoregional treatment options *(see section 12 Clinical studies)*.

4 Dosage regimen and administration

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

Dosage regimen

General target population

Adults

The efficacy and safety of Tafinlar have not been established in patients with wild- type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC *(see section 12 Clinical Studies)*. Tafinlar should not be used in patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC.

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for treatment with Tafinlar as monotherapy and in combination with trametinib (*see section 12 Clinical Studies*).

When Tafinlar is used in combination with trametinib, please also refer to the full trametinib prescribing information.

Tafinlar should be taken either at least one hour before, or at least two hours after a meal (*see section 11 Clinical Pharmacology*), leaving an interval of approximately 12 hours between doses. 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.

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

Recommended Dosage for Unresectable or Metastatic Melanoma
The recommended dose of Tafinlar either as monotherapy or in combination with trametinib is 150 mg twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily. Treatment should continue until disease progression or the development of unacceptable toxicity *(see Table 4-2)*.

Recommended Dosage for the Adjuvant Treatment of Melanoma
The recommended dose of Tafinlar in combination with trametinib is 150 mg twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily until disease recurrence or unacceptable toxicity for up to 1 year.

Recommended Dosage for NSCLC
The recommended dose of Tafinlar in combination with trametinib is 150 mg twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily. Treatment should continue until disease progression or the development of unacceptable toxicity *(see Table 4-2)*.

Recommended Dosage for ATC
The recommended dose of Tafinlar in combination with trametinib is 150 mg twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily. Treatment should continue until disease recurrence or unacceptable toxicity.

Dose adjustments

Tafinlar as monotherapy and in combination with trametinib

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation.

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (*see section 6 Warnings and Precautions*).

For pyrexia management guidance see section below.

Recommended dose level reductions are provided in Table 4-1. Doses below 50 mg twice daily are not recommended.

Table 4-1 Recommended Tafinlar dose level reductions

Dose Level	Tafinlar Dose
Full dose	150 mg twice daily
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily

The recommended dose modification schedule is provided in Table 4-2. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The Tafinlar dose should not exceed 150 mg twice daily.

Table 4-2 Tafinlar dose modification schedule (excluding pyrexia)

Grade (CTC-AE)*	Dose Modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

** The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).*

Pyrexia management: Therapy should be interrupted (Tafinlar when used as monotherapy, and both Tafinlar and Mekinist when used in combination) if a patient's temperature is ≥38ºC (100.4°F). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia.Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. Patients should be evaluated for signs and symptoms of infection (*see section 6 Warnings and Precautions*).

Tafinlar, or both Tafinlar and Mekinist when used in combination, should be restarted if patient is symptom free for at least 24 hours either (1) at the same dose level or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. The use of oral corticosteroids should be considered in those instances in which anti- pyretics are insufficient.

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

Exceptions where dose modifications are necessary for Tafinlar only:

Uveitis management: No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold Tafinlar until resolution of ocular inflammation and then restart Tafinlar reduced by one dose level. No dose modification of trametinib is required when taken in combination with Tafinlar.

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 section 11 Clinical Pharmacology, Pharmacokinetics*). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined. Tafinlar should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on the oral clearance of dabrafenib or on the concentrations of its metabolites (*see section 11 Clinical Pharmacology, Pharmacokinetics*). There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be 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. Tafinlar should be used with caution in patients with moderate or severe hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Tafinlar in pediatric patients have not been established. Tafinlar is not recommended in this age group.

Geriatric patients (65 years or above)

No dosage adjustment is required in patients over 65 years of age *(see section Clinical 11 Pharmacology, Pharmacokinetics)*.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed.

6 Warnings and Precautions

When dabrafenib is used together with trametinib, the Package Insert of trametinib must be consulted prior to initiation of treatment. For additional information on warnings and precautions associated with trametinib treatment, please refer to the trametinib Package Insert.

BRAF V600 testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC therefore dabrafenib should not be used in patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC (see sections *Dosage Regimen and Administration* and *Clinical Studies*).

Dabrafenib in combination with trametinib in patients with melanoma who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section *Clinical Studies*). Therefore, other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

Dabrafenib in combination with trametinib in patients with brain metastases

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

New malignancies
New malignancies, cutaneous and non-cutaneous, can occur when dabrafenib is used as monotherapy or in combination with trametinib.

Pyrexia
Pyrexia was reported in clinical trials with Tafinlar monotherapy and in combination with trametinib (*see section 7 Adverse Drug Reactions*). In a Phase III clinical trial in patients with unresectable or metastatic melanoma, the incidence and severity of pyrexia were increased when Tafinlar was used in combination with trametinib (57% [119/209], 7% Grade 3) as compared to Tafinlar monotherapy (33% [69/211], 2% Grade 3). In a Phase III trial in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the Tafinlar in combination with Mekinist arm (67% [292/435]; 6% Grade 3/4) as compared to the placebo arm (15% [66/432]; <1% Grade 3). In a Phase II trial in patients with NSCLC the incidence and severity of pyrexia were increased slightly when Tafinlar was used in combination with trametinib (55% [51/93], 5% Grade 3) as compared to Tafinlar monotherapy (37% [31/84], 2% Grade 3). In a Phase II trial in patients with rare cancers including ATC, the incidence and severity of pyrexia was 35% (35/100), 4% Grade 3 or 4 across all cohorts. In patients with unresectable or metastatic melanoma who received the combination dose of Tafinlar 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored during and following severe events of pyrexia. Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both Tafinlar and Mekinist were interrupted, compared to when only Tafinlar was interrupted. Therefore, interruption of both Tafinlar and Mekinist is recommended if patient's temperature is ≥38oC (100.4°F), and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see sections 4 Dosage regimen and administration and 12 Clinical studies).

Cutaneous malignancies

Cutaneous Squamous Cell Carcinoma (cuSCC)
Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with Tafinlar as monotherapy and in combination with trametinib (*see section 7 Adverse Drug Reactions*). In a Phase III study in patients with unresectable or metastatic melanoma, 10% (22/211) of patients receiving Tafinlar monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 8 weeks. In patients who received Tafinlar in combination with trametinib, 3% (6/209) of patients developed cuSCC and events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on Tafinlar who developed cuSCC continued on treatment without dose modification. In a Phase II trial in patients with NSCLC, 18% (15/84) of patients receiving Tafinlar monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 11 weeks. In patients who received Tafinlar in combination with trametinib, 2% (2/93) of patients developed cuSCC. In a Phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving Tafinlar in combination with Mekinist as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

Skin examination should be performed prior to initiation of Tafinlar and during treatment with Tafinlar, every 2 months throughout therapy. Monitoring should continue every 2 to 3 months for 6 months following discontinuation of Tafinlar or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and Tafinlar treatment should 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 have been reported in patients treated with Tafinlar. In clinical trials in unresectable or metastatic melanoma these were identified within the first 5 months of therapy and did not require treatment modification other than excision. 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 Mekinist as opposed to 1% (6/432) of patients receiving placebo. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies
In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in

BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non- cutaneous malignancies, in patients treated with Tafinlar. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. In the Phase III trial in the adjuvant treatment of melanoma comparing combination of Tafinlar and Mekinist 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.

Patients should be monitored as clinically appropriate. In patients with a non-cutaneous malignancy that has a RAS mutation the benefits and risks should be considered before continuing treatment with Tafinlar. No dose modification of trametinib is required when taken in combination with Tafinlar.

Following discontinuation of Tafinlar, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

Pancreatitis
Pancreatitis has been reported in < 1 % of Tafinlar-treated patients in unresectable or metastatic melanoma clinical trials, and acute pancreatitis has been reported in 1% of Tafinlar-treated patients in the NSCLC trial. One of the events occurred on the first day of dosing of a metastatic melanoma patient and recurred following re-challenge at a reduced dose. In the adjuvant treatment of melanoma trial, pancreatitis was reported in 1% of patients receiving Tafinlar in combination with Mekinist, and in <1% of patients receiving placebo.

Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting Tafinlar after an episode of pancreatitis.

Uveitis
Treatment with Tafinlar has been associated with the development of uveitis (including iridocyclitis and iritis). Patients should be monitored during therapy for visual signs and symptoms (such as, change in vision, photophobia and eye pain) (*see section 4 Dosage regimen and administration*).

Hemorrhage
Hemorrhagic events, including major hemorrhagic events and fatal hemorrhages, have occurred in patients taking Tafinlar in combination with trametinib *(see section 7 Adverse Drug Reactions)*. Out of the 559 unresectable or metastatic melanoma patients treated with Tafinlar in combination with trametinib, there were seven fatal intracranial hemorrhagic cases (1%). Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). During the COMBI-v three year extended follow-up, one fatal intracranial hemorrhage occurred in one additional patient. No fatal hemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma Two out of 93 patients (2%) receiving Tafinlar in combination with trametinib in a Phase II trial in patients with metastatic NSCLC had fatal intracranial hemorrhagic events. If patients develop symptoms of hemorrhage they should immediately seek medical care.

Venous thromboembolism (VTE)

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur when Tafinlar is used in combination with trametinib. Patients should be advised to immediately seek medical care if they develop symptoms of VTE.

Skin toxicity

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with Tafinlar in combination with trametinib. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, Tafinlar and trametinib should be withdrawn.

Renal failure

Renal failure has been identified in < 1 % of patients treated with Tafinlar. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported. Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, Tafinlar may need to be interrupted as clinically appropriate. Tafinlar has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

QT prolongation

Worst-case QTc prolongation of > 60 millisecond (msec) was observed in 3 % of dabrafenib-treated subjects (One > 500 msec in the integrated safety population). Treatment with Tafinlar is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval.

Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored in all patients before treatment with Tafinlar, after one month of treatment and after dose modification. Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with Tafinlar is not recommended in patients with QTc > 500 msec. If during treatment the QTc exceeds 500 msec, Tafinlar treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 msec and at a lower dose as described in Table 4-2. Permanent discontinuation of Tafinlar treatment is recommended if the QTc increase meets values of both > 500 msec and > 60 msec change from pre-treatment values.

Non BRAF V600E mutation positive metastatic melanoma

Clinical data supporting the effectiveness of Tafinlar in patients with BRAF V600K mutations are limited, and phase 2 studies report fewer responses in BRAF V600K patients compared to BRAF V600E patients. There are no clinical data for other less common BRAF V600 mutations (*see Clinical Studies*).

7 Adverse Drug Reactions

Summary of the safety profile

The safety of dabrafenib monotherapy is based on the integrated safety population from five clinical studies BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680 including 578 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg twice daily. The most common adverse drug reactions (incidence ≥ 15 %) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

The safety of dabrafenib in combination with trametinib has been evaluated in the integrated safety population of 641 patients with BRAF V600 mutant unresectable or metastatic melanoma and advanced NSCLC treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 (see section *Clinical Studies*).

The most common adverse events (incidence ≥20%) for trametinib in combination with dabrafenib were: pyrexia, nausea, diarrhoea, fatigue, chills, headache, vomiting, arthralgia, hypertension, rash and cough.

The safety profile observed in study BRF117277/DRB436B2204 (COMBI-MB) in metastatic melanoma patients with brain metastases is consistent with the safety profile of Tafinlar in combination with Mekinist in unresectable or metastatic melanoma (see also section 12 Clinical studies).

Tabulated list of adverse reactions

Adverse drug reactions are listed below by MedDRA system organ class ranked by frequency using the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Table 7-1 Adverse reactions reported in the integrated safety population of dabrafenib monotherapy (n=578)

System Organ Class	Frequency category N=578	Adverse Reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma

		Seborrhoeic keratosis
		Acrochordon (skin tags)
		Basal cell carcinoma
	Uncommon	New primary melanoma
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Nausea
		Vomiting
		Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
		Alopecia
		Rash
		Palmar-plantar erythrodysaesthesia syndrome
	Common	Dry skin
		Pruritus
		Actinic keratosis
		Skin lesion
		Erythema
		Photosensitivity
	Uncommon	Panniculitis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute renal failure
		Tubulointerstitial nephritis
General disorders and administration site conditions	Very common	Pyrexia

		Fatigue
		Chills
		Asthenia
	Common	Influenza-like illness

Table 7-2 Unresectable or metastatic melanoma and Advanced NSCLC Adverse reactions reported in the integrated safety population of dabrafenib in combination with trametinib (n=641)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and infestations	Very common	Urinary tract infection
		Nasopharyngitis
	Common	Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[c]
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
	Uncommon	Chorioretinopathy
		Uveitis
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
	Uncommon	Bradycardia
	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[d]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
		Pneumonitis

Gastrointestinal disorders	Very common	Abdominal pain
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Gastrointestinal perforation
		Colitis
Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms
Renal and urinary disorders	Common	Renal failure
	Uncommon	Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
	Common	Mucosal inflammation
		Influenza-like illness
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased

[a] cu SCC: SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
[b] Papilloma, skin papilloma
[c] Includes drug hypersensitivity
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding

Description of selected adverse reactions

Cutaneous squamous cell carcinoma

For dabrafenib monotherapy in study MEK115306, cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 10% of patients and approximately 70% of the events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. In the integrated safety population for dabrafenib in combination with trametinib, 2% of patients developed cuS and the events occurred later than with dabrafenib monotherapy with a median time to onset of 31 weeks. All patients receiving dabrafenib as monotherapy or in combination with trametinib who developed cuSCC continued on treatment without dose modification.

New primary melanoma

New primary melanomas have been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib in melanoma studies. Cases were managed with excision and did not require treatment modification (see section 6 *Warnings and Precautions*). No new primary melanoma was reported from the Phase II NSCLC study (BRF113928).

Non-cutaneous malignancy

Activation of MAP-kinase signalling in BRAF wild type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations (see section *Warnings and Precautions*). Non-cutaneous malignancies were reported in 1% (6/586) of patients in the integrated safety population of dabrafenib monotherapy, and 1% (7/641) of patients in the integrated safety population of dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy and in combination with trametinib. Patients should be monitored as clinically appropriate.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking dabrafenib in combination with trametinib. Please refer to the trametinib Package Insert.

LVEF reduction/Left ventricular dysfunction

Decreased LVEF has been reported in 8% (54/641) of patients in the integrated safety population of dabrafenib in combination with trametinib. Most cases were asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function. Please refer to the trametinib Package Insert.

Pyrexia

Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib; the incidence and severity of pyrexia are increased with the combination

therapy (see section *Warnings and Precautions*). For patients who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events. In 1% of patients receiving dabrafenib as monotherapy in the integrated safety population, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care *(see sections 4 Dosage Regimen and Administration* and 6 *Warnings and Precautions*).

Hepatic events

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib Package Insert.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.

Arthralgia

Arthralgia was reported very commonly in the integrated safety population of dabrafenib monotherapy (25%) and dabrafenib in combination with trametinib (26%) although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%) and no Grade 4 occurrences being reported.

Hypophosphataemia

Hypophosphataemia has been reported commonly in the integrated safety population of dabrafenib monotherapy (7%) and of dabrafenib in combination with trametinib (4%). It should be noted that approximately half of these occurrences with dabrafenib monotherapy (4%) and 1% with dabrafenib in combination with trametinib were Grade 3 in severity.

Pancreatitis

Pancreatitis has been reported in dabrafenib monotherapy and in combination with trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis (see section 6 *Warnings and Precautions*).

Renal failure

Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon; however dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN). Caution should be used in this setting (see section 6 *Warnings and Precautions*).

Special populations

Elderly

Of the total number of patients in the integrated safety population of dabrafenib monotherapy (n=578), 22% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects.

In the integrated safety population of dabrafenib in combination with trametinib (n=641), 180 patients (28%) were ≥65 years of age, 50 patients (8%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

Adjuvant treatment of melanoma

Tafinlar in combination with Mekinist

The safety of Tafinlar in combination with Mekinist was evaluated in a Phase III, randomized, double-blind study of Tafinlar in combination with Mekinist versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection *(see section 12 Clinical studies)*.

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

Table 7-3 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥10% for all grade adverse reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the Tafinlar in combination with Mekinist arm.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-3 Adjuvant treatment of melanoma - Adverse drug reactions for Tafinlar in combination with Mekinist vs. placebo

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

Adverse drug reactions	Tafinlar in combination with Mekinist N=435		Placebo N=432		Frequency category (combination arm, all grades)
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %	
Pyrexia[17)]	63	5	11	<1	Very common
Fatigue[18)]	59	5	37	<1	Very common
Chills	37	1	4	NR	Very common
Oedema peripheral[19)]	16	<1	6	NR	Very common
Influenza-like illness	15	<1	7	NR	Very common
Investigations					
Alanine aminotransferase increased[20)]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21)]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	NR	2	<1	Common

1) Nasopharyngitis also includes pharyngitis.

2) Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.

3) Headache also includes tension headache.

4) Dizziness also includes vertigo.

5) Chorioretinopathy also includes chorioretinal disorder.

6) Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.

7) Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.

8) Hypertension also includes hypertensive crisis.

9) Cough also includes productive cough.

10) Abdominal pain also includes abdominal pain upper and abdominal pain lower.

11) Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.

12) Dry skin also includes xerosis and xeroderma.

13) Erythema also includes generalized erythema.

14) Pruritus also includes puritus generalized and pruritus genital.

15) Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.

16) Muscle spasms also includes musculoskeletal stiffness.

17) Pyrexia also includes hyperpyrexia.

18) Fatigue also includes asthenia and malaise.

19) Oedema peripheral also includes peripheral swelling.

20) Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

21) Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

NR: not reported

Locally advanced or metastatic anaplastic thyroid cancer

Tafinlar in combination with Mekinist:

The efficacy and safety of Tafinlar in combination with Mekinist was studied in a Phase II, nine-cohort, multicenter, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC.

The 'All Treated Subjects (ATS)' population was the primary safety population for the study and includes all patients who received at least one dose of Tafinlar or Mekinist from all the

histologic cohorts. The safety profiles in the ATS population and in the ATC cohort are consistent.

At the time of safety analysis, the most common adverse events (≥20%) reported for Tafinlar in combination with Mekinist in the ATS population were fatigue, pyrexia, rash, nausea, chills, vomiting, cough, and headache.

Table 7-4 lists the adverse drug reactions for Tafinlar in combination with Mekinist occurring at an incidence ≥10% for all grade adverse drug reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Study BRF117019.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-4 Anaplastic Thyroid Cancer - Adverse drug reactions for Tafinlar in combination with Mekinist in the ATS population

Adverse drug reactions	**Tafinlar in combination with Mekinist**		
	All grades n = 100 %	**Grades 3/4 n = 100 %**	**Frequency category**
Blood and lymphatic system disorders			
Neutropenia[1)]	15	6	Very common
Anaemia	14	2	Very common
Leukopenia[2)]	13	NR	Very common
Metabolism and nutrition disorders			
Hyperglycaemia	12	3	Very common
Decreased appetite	11	NR	Very common
Hypophosphataemia	6	3	Common
Hyponatremia	3	3	Common
Nervous system disorders			
Headache	20	2	Very common
Dizziness[3)]	13	NR	Very common
Eye disorders			
Detachment of retinal pigment epithelium	1	NR	Common
Vascular disorders			
Haemorrhage[4)]	16	NR	Very common
Hypertension	4	2	Common
Respiratory, thoracic and mediastinal disorders			
Cough[5)]	21	NR	Very common
Gastrointestinal disorders			
Nausea	31	1	Very common
Vomiting	22	1	Very common
Diarrhoea	17	1	Very common
Constipation	15	NR	Very common
Dry mouth	11	NR	Very common
Skin and subcutaneous tissue disorders			

Adverse drug reactions	Tafinlar in combination with Mekinist		
	All grades n = 100 %	**Grades 3/4 n = 100 %**	**Frequency category**
Rash[6)]	31	4	Very common
Musculoskeletal and connective tissue disorders			
Myalgia[7)]	11	1	Very common
Arthralgia	11	NR	Very common
Rhabdomyolysis	1	1	Common
General disorders and administration site conditions			
Fatigue[8)]	45	5	Very common
Pyrexia	35	4	Very common
Chills	25	1	Very common
Oedema[9)]	17	NR	Very common
Investigations			
Alanine aminotransferase increased	13	3	Very common
Aspartate aminotransferase increased	12	2	Very common
Blood alkaline phosphatase increased	11	3	Very common
Ejection fraction decreased	3	1	Common

[1)] Neutropenia includes neutropenia, neutrophil count decreased and febrile neutropenia. Neutrophil count decreased qualified as a neutropenia event.

[2)] Leukopenia includes leukopenia, white blood cell count decreased and lymphopenia.

[3)] Dizziness includes dizziness, vertigo and vertigo positional.

[4)] Haemorrhage includes haematuria, purpura, epistaxis, eye contusion, gingival bleeding, haemoptysis, melaena, petechiae, prothrombin time prolonged, rectal haemorrhage, retinal haemorrhage and vaginal haemorrhage.

[5)] Cough includes cough and productive cough.

[6)] Rash includes rash, rash maculo-papular, rash generalized and rash papular.

[7)] Myalgia includes myalgia and musculoskeletal pain.

[8)] Fatigue includes fatigue, asthenia and malaise.

[9.)] Oedema includes oedema and peripheral oedema.

NR: not reported

Adverse drug reactions (ADRs) from post-marketing experience and pooled clinical trials

The following ADRs have been derived from post-marketing experience including spontaneous case reports with Tafinlar in combination with trametinib. Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-5 ADRs from post-marketing experience and pooled clinical trials across indications

Adverse drug reaction	Frequency category
Immune system disorders	
Sarcoidosis	Uncommon
Vascular disorders	
Venous thrombo-embolism[1]	Common

[1)] VTE includes, pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.

8 Interactions

Effect of other drugs on Tafinlar

Based on *in vitro* studies, dabrafenib was shown to be primarily metabolized by cytochrome P450 (CYP) 2C8 and CYP3A4 *(see section 11 Clinical Pharmacology, Pharmacokinetics)*, while the active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are therefore likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with Tafinlar when possible. Use caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are coadministered with Tafinlar. Avoid coadministration of Tafinlar with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4.

Pharmacokinetic data showed an increase in repeat-dose dabrafenib C_{max} (33%) and AUC (71%) upon co-administration with ketoconazole (CYP3A4 inhibitor), and increases of 82% and 68% of hydroxy- and desmethyl-dabrafenib AUC, respectively. A decrease in AUC was noted for carboxy-dabrafenib (decrease of 16%).

Co-administration of dabrafenib and gemfibrozil (a CYP2C8 inhibitor) resulted in an increase in repeat-dose dabrafenib AUC (47%) and no meaningful change in the concentrations of the metabolites.

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

Drugs that affect gastric pH

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.

Effect of Tafinlar on other drugs

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 (see *section 11 Clinical Pharmacology, Pharmacokinetics*) and may increase the synthesis of transporters. This results in reduced plasma levels of medicinal products metabolised by these enzymes, and may affect some transported medicinal products. The reduction in plasma concentrations can lead to lost or reduced clinical effect of these medicinal products. There is also a risk of increased formation of active metabolites of these medicinal products. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGTs (glucuronide conjugating enzymes). The transport protein Pgp may also be induced as well as other transporters, e g MRP-2, BCRP and OATP1B1/1B3.

In vitro, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical study in 16 patients using a single-dose of midazolam, a CYP3A4 substrate, C_{max} and AUC were decreased by 47% and 65%, respectively with co-administration of repeat dose dabrafenib 150 mg twice daily. In a separate trial in 14 patients, 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 a small increase in C_{max} (18 and 19% respectively). Co-administration of Tafinlar and medicinal products which are affected by the induction of CYP3A4 or CYP2C9 such as hormonal contraceptives (see *section 9 Pregnancy, lactation, females and males of reproductive potential*), warfarin or dexamethasone may result in decreased concentrations and loss of efficacy. If co-administration of these medications is necessary, monitor patients for loss of efficacy or consider substitutions of these medicinal products.

Interactions with many medicinal products eliminated through metabolism or active transport is expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

The number of affected medicinal products is expected to be large; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, methadone)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin
- Antiepileptic (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with Tafinlar. Upon discontinuation of Tafinlar offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter substrates may increase and patients should be monitored for toxicity and dosage of these agents may need to be adjusted.

In vitro, dabrafenib is a mechanism based inhibitor of CYP3A4. Therefore, transient inhibition of CYP3A4 may be observed during the first few days of treatment.

Dabrafenib inhibits OATP1B1 and OATP1B3 (see section 11 C*linical Pharmacology, Pharmacokinetics*). Following co-administration of a single dose of rosuvastatin (OATP1B1 and OATP1B3 substrate) with repeat dose Tafinlar 150 mg twice daily in 16 patients, AUC was minimally changed (7% increase) and C_{max} was increased by 156%. Monitoring is recommended for adverse reactions if Tafinlar is coadministered with drugs that are OATP1B1 or OATP1B3 substrates with a narrow therapeutic index with regards to high peak concentrations.

Combination therapy and non-fixed dose combination therapy

Combination with trametinib:

Co-administration of repeat dosing of Tafinlar 150 mg twice daily and trametinib 2 mg once daily resulted in a 16% increase in dabrafenib C_{max} and a 23% increase in dabrafenib AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when Tafinlar is administered in combination with trametinib using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant. See the full prescribing information for trametinib for guidelines on drug interactions associated with trametinib monotherapy.

Effects of Tafinlar on substance transport systems

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

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of humanorganic 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 food on Tafinlar

Patients should take Tafinlar at least one hour prior to or two hours after a meal due to the effect of food on dabrafenib absorption (*see section pharmacokinetic*).

Paediatric population

Interaction studies have only been performed in adults.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Tafinlar can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Tafinlar in pregnant women. Reproductive studies in animals (rats) have demonstrated dabrafenib induced embryotoxicity and teratogenicity. Increased incidences of delays in skeletal development and reduced fetal body weight were observed following prenatal exposure to dabrafenib at concentrations 0.5 times the exposure in humans at the highest recommended dose of 150 mg twice daily. Embryo-lethality, ventricular septal defects, and variation in thymic shape were observed following prenatal exposure to dabrafenib at concentrations three times the exposure in humans at the highest recommended dose of 150 mg twice daily. Tafinlar should not be administered to pregnant women. If the patient becomes pregnant while taking Tafinlar, the patient should be advised of the potential risk to the fetus.

Animal data

In a combined embryo-fetal development study in rats, animals received oral doses of dabrafenib up to 300 mg/kg/day during the period of organogenesis. At ≥20 mg/kg/day, maternal systemic exposure (AUC) was 4.1 microgram*h/mL corresponding to approximately 0.5 times the human exposure at the highest recommended dose of 150 mg twice daily. Developmental toxicity consisted of delays in skeletal development and reduced fetal body weight. At a dose of 300 mg/kg/day maternal systemic exposure (AUC) was 22.6 microgram*h/mL corresponding to approximately three times the human exposure at the highest recommended dose of 150 mg twice daily. Developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape.

9.2 Lactation

Risk summary

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

9.3 Females and males of reproductive potential

Contraception

Females

Females of reproductive potential should be advised that animal studies have been performed showing Tafinlar to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when taking Tafinlar and for at least two weeks after stopping treatment with Tafinlar. If taking Tafinlar in combination with Mekinist, sexually-active females of reproductive potential are recommended to use effective contraception and

for at least 16 weeks after stopping treatment.

Tafinlar may decrease the efficacy of oral or any systemic hormonal contraceptives and an alternative method of contraception should be used *(see section 8 Interactions)*.

Males

Male patients (including those that have had a vasectomy) with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking Tafinlar monotherapy and for at least 2 weeks after stopping treatment with Tafinlar. If taking Tafinlar in combination with Mekinist, male patients should use condoms during sexual intercourse, and for at least 16 weeks after stopping treatment.

Infertility

There are no data in humans. Adverse effects on male and female reproductive organs have been seen in animals *(see section 13 Nonclinical Safety Data)*. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

10 Overdosage

There is currently very limited experience of overdosage with Tafinlar. The maximum dose of Tafinlar administered during clinical trials was 600 mg (300 mg twice daily).

There is no specific antidote for overdosage of Tafinlar. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, Tafinlar should be withheld and supportive care instituted. Further management should be as clinically indicated or as recommended by the national poisons center, where available.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

B-Raf serine-threonine kinase (BRAF) inhibitors. ATC code: L01EC02.

Mechanism of Action (MOA)

Tafinlar Monotherapy – Melanoma, NSCLC and ATC

Tafinlar (dabrafenib) is a potent, selective, ATP-competitive inhibitor of RAF kinases with IC_{50} values of 0.65, 0.5 and 1.84 nM for BRAF V600E, BRAF V600K and BRAF V600D enzymes, respectively. Oncogenic amino acid variants in BRAF at valine 600 (V600) lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumor cell growth. BRAF mutations have been identified in specific cancers, including approximately 50 % of melanoma and 1 to 3% of NSCLC. The most commonly observed BRAF mutation, (V600E) and the next most common (V600K) account for 95 % of the BRAF mutations found in all patients with cancer. A number of rare substitutions also occur including V600D, V600G and V600R. Dabrafenib also inhibits wild-type BRAF and CRAF enzymes with IC_{50} values of 3.2 and 5.0 nM, respectively in biochemical assays. Dabrafenib inhibits

BRAF V600 mutant melanoma, NSCLC and ATC cell line growth *in vitro* and melanoma xenograft models *in vivo*.

Tafinlar in combination with Mekinist –Melanoma, NSCLC and ATC

Mekinist (trametinib) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal- related kinase (ERK) pathway. Dabrafenib and trametinib inhibit two kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation positive melanoma, NSCLC and ATC cell lines in vitro and delays the emergence of resistance in vivo in BRAF V600 mutation positive melanoma xenografts.

Pharmacodynamics (PD)

Dabrafenib demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) in BRAF V600 mutant melanoma cell lines, *in vitro* and in animal models.

In patients with BRAF V600 mutant melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Cardiac electrophysiology

The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg Tafinlar twice daily was administered in 32 patients with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.

Pharmacokinetics (PK)

The pharmacokinetics 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 median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95 % (90 % CI: 81,110). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, $AUC0_{-\tau}$ and predose concentration ($C\tau$) were 1,478 ng/mL, 4,341 ng*hr/mL and 26 ng/mL, respectively. Administration of dabrafenib with food reduced the bioavailability (C_{max} and AUC decreased by 51 % and 31 % respectively) and delayed absorption of Tafinlar capsules when compared to the fasted state.

Distribution

Dabrafenib binds to human plasma protein and is 99.7 % bound. The steady-state volume of

distribution following intravenous microdose administration is 46 L.

Dabrafenib is a substrate of human P-glycoprotein (Pgp) and murine BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low. Dabrafenib is not an *in vitro* substrate of OATP1B1, OATP1B3 or OATP2B1 transporters.

Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of Pgp *in vitro*.

Biotransformation/metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised 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 (21to 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; while the activity of carboxy-dabrafenib is not likely to be significant.

Elimination

Terminal half-life following IV microdose is 2.6 hours. Dabrafenib terminal half-life is 8 hours due to a prolonged terminal phase after oral administration. IV plasma clearance is 12 L/hour. Fecal 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.

In Vitro evaluation of drug interaction potential

Effect of other drugs on Tafinlar:

In vitro results indicate that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Therefore, inhibitors or inducers of these enzymes have the potential to affect the PK of dabrafenib or its metabolites (see section 8 Interactions). Dabrafenib is a substrate of human Pgp and breast cancer resistance protein (BCRP) in vitro. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a drug-drug interaction is minimal.

Effect of Tafinlar on other drugs:

In human hepatocytes, dabrafenib produced concentration-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and clinical relevance cannot be excluded. Therefore, caution is recommended at co-administration of dabrafenib and OATP1B1 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 for OAT1, OAT3 and OCT2. For OATP1B1 and OATP1B3 the drug-drug interaction risk was assessed in a clinical study (see *section 8 Interactions*). Dabrafenib and desmethyl-dabrafenib were shown to be moderate inhibitors of human BCRP; however, based on clinical exposure, the risk of a drug-drug interaction is minimal. Neither dabrafenib nor its 3 metabolites were demonstrated to be inhibitors of Pgp *in vitro*.

Special populations

Pediatric population (below 18 years)

No studies have been conducted to investigate the pharmacokinetics of Tafinlar in pediatric patients.

Geriatric population (65 years or above)

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; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant.

Race/Ethnicity

The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. No dabrafenib dose adjustment is needed in Asian patients.

There are insufficient data to evaluate the potential effect of other race/ethnicties on dabrafenib pharmacokinetics.

Renal impairment

The pharmacokinetics of dabrafenib were characterised in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73m^2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73m^2) enrolled in clinical trials using a population analysis. The effect of mild or moderate renal impairment on dabrafenib oral clearance was small (< 6 % for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant effect on hydroxy-, carboxy-, and desmethyl-dabrafenib plasma concentrations. No data are available in patients with severe renal impairment *(see section 4 Dosage Regimen and Administration)*.

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. No data are available in patients with moderate to severe hepatic impairment (*see section 4 Dosage regimen and administration).*

12 Clinical Studies

Unresectable or metastatic melanoma

Tafinlar monotherapy

The efficacy and safety of Tafinlar in the treatment of adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma have been evaluated in 3 studies (BRF113683 [BREAK-3], BRF113929 [BREAK-MB], and BRF113710 [BREAK-2]) including patients with BRAF V600E and/or V600K mutations.

Included in these studies were in total 402 subjects with BRAF V600E and 49 subjects with BRAF V600K mutation. Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory trial and with respect to patients with the V600K mutation in single arm studies the activity appears lower than in V600E tumours.

No data is available in patients with melanoma harbouring BRAF V600 mutations other than V600E and V600K. Efficacy of dabrafenib in subjects previously treated with a protein kinase inhibitor has not been investigated.

Previously untreated patients

The efficacy and safety of Tafinlar were evaluated in a Phase III randomised, open- label study [BREAK-3] comparing Tafinlar to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Screening included central testing of BRAF mutation V600E using a BRAF mutation assay conducted on the most recent tumour sample available.

The trial enrolled 250 patients randomised 3:1 to receive either Tafinlar 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. The primary objective for this study was to evaluate the efficacy of Tafinlar compared to DTIC with respect to progression-free survival (PFS) for patients with BRAF V600E mutation positive unresectable or metastatic melanoma. Patients on the DTIC arm were allowed to receive Tafinlar after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6% were Caucasian; the median age was 52 years with 21 % of patients being ≥ 65 years, 98.4 % had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 97 % of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95 % Cl 0.18, 0.51; p < 0.0001) was achieved. Efficacy results from the primary analysis and a post-hoc analysis (25 June 2012) with 6-months additional follow up are summarized in Table 5. Overall survival data from a further post-hoc analysis based on a 31 January 2014 data cut are shown in Figure 1. The 12- and 24-month landmark OS rates for dabrafenib are 70% and 45%, respectively. Median OS at the 31 January 2014 data cutoff was 20.0 months (95% CI: 16.8-24.4).

Table 12-1 Efficacy in previously untreated patients (BREAK-3 Study, 25 June 2012)

	Data as of December 19, 2011		**Data as of June 25, 2012**	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival (Investigator assessed)				
Median, months (95 % CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.9 (5.2,9.0)	2.7 (1.5,3.2)
HR (95 % CI)	0.30 (0.18, 0.51) P < 0.0001		0.37 (0.24, 0.58) P < 0.0001	
Overall response[a]				
% (95 % CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95 % CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

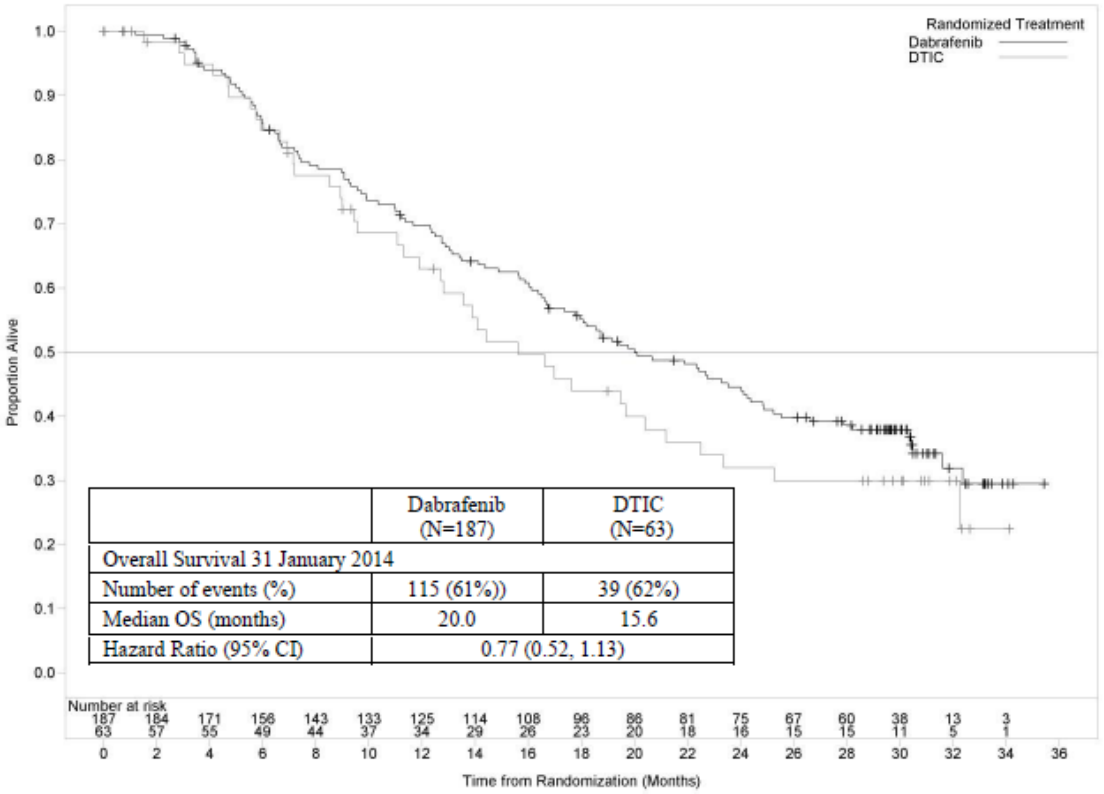
Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR-not reached

a. Defined as confirmed complete + partial response

Note: As of the 25 June 2012 cut-off, thirty-five subjects (55.6%) of the 63 randomized to DTIC had crossed over to dabrafenib. Median PFS after cross-over was 4.4 months.

As of the 25 June 2012 cut-off 63% of subjects randomized to dabrafenib and 79% of subjects randomized to DTIC had progressed or died.

Figure 12-1 Kaplan-Meier curves of overall survival (BREAK-3) (31 January 2014)

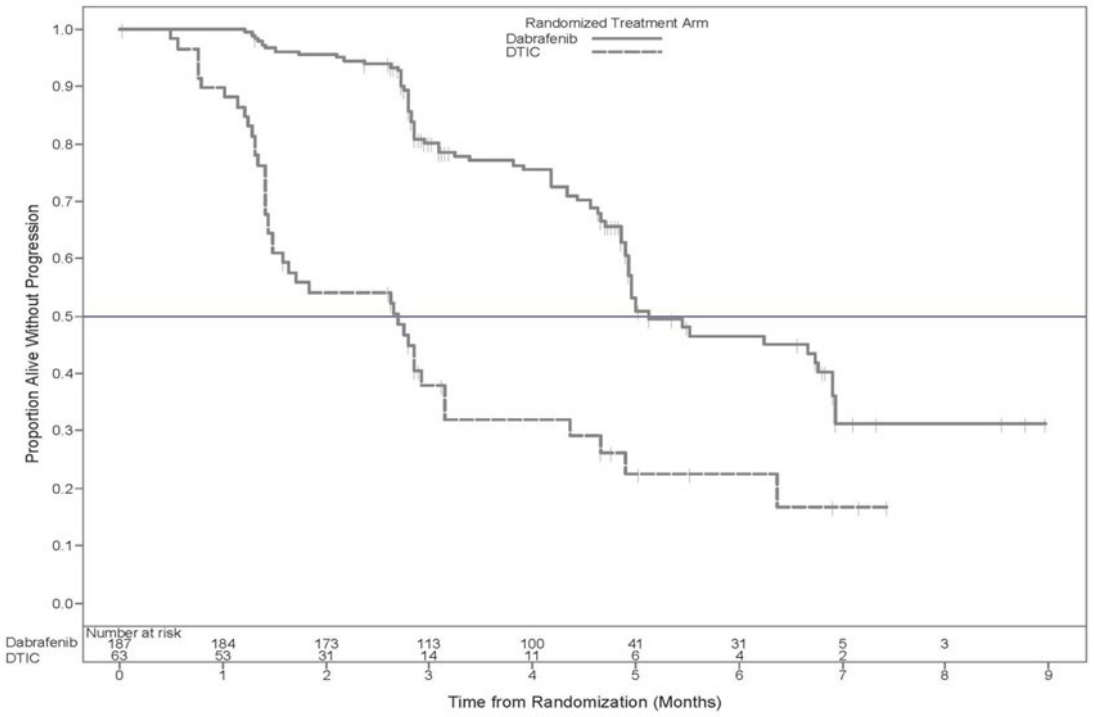


	Dabrafenib (N=187)	DTIC (N=63)
Overall Survival 31 January 2014		
Number of events (%)	115 (61%))	39 (62%)
Median OS (months)	20.0	15.6
Hazard Ratio (95% CI)	0.77 (0.52, 1.13)	

The primary analysis was based on a 118 events at the time of the data cut off. Efficacy results are summarized in Table 12-1 and Figure 12-1.

Twenty-eight patients (44 %) randomized to DTIC crossed over to Tafinlar following independently verified disease progression. Median time on Tafinlar after cross-over was 2.8 months and unconfirmed ORR was 46 %.

Figure 12-2 BREAK-3 Kaplan Meier investigator-assessed progression-free survival curves (ITT population)



Patients with brain metastases

BREAK-MB was a multi-center, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of Tafinlar in patients with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Patients were enrolled into Cohort A (patients with no prior local therapy for brain metastasis) or Cohort B (patients who received prior local therapy for brain metastasis). The results are summarized in Table 12-2.

Table 12-2 Efficacy data by investigator assessment from the BREAK-MB study

	All Treated Patients Population			
	BRAF V600E (Primary)		**BRAF V600K**	
Endpoints/ Assessment	**Cohort A N=74**	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate, % (95 % CI)[a]				
	39% (28.0, 51.2) P < 0.001[b]	31% (19.9, 43.4) P < 0.001[b]	7% (0.2, 31.9)	22% (6.4, 47.6)
Duration of intracranial response, median, months (95% CI)				
	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9 (NR, NR)	N=4 3.8 (NR, NR)
Overall response, % (95% CI)[a]				
	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
Duration of response, median, months (95% CI)				
	N=28	N=20	NA	N=5

	5.1 (3.7, NR)	4.6 (4.6, 6.5)		3.1 (2.8, NR)
Progression-free survival, median, months (95% CI)				
	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
Overall survival, median, months (95% CI)				
Median, months	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Abbreviations: CI: confidence interval; INV: investigator-assessed; NR: not reached; NA: not applicable
a - Confirmed response.
b –This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in BRAF V600E positive patients.

Patients who were previously untreated or failed at least one prior systemic therapy

BRF113710 (BREAK-2) was a multi-center, global, open-label, single-arm, Phase II study that enrolled 92 patients with histologically confirmed metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma. Patients were treatment-naïve (N = 15) or received prior treatment (N = 77) in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy.

The investigator assessed confirmed response rate in the primary efficacy population of patients with BRAF V600E metastatic melanoma (N=76) was 59 % (95% CI: 48.2, 70.3) including 7 % complete response. Median PFS was 6.3 months (95% CI: 4.6, 7.7) and the median duration of response was 5.2 months (95 % CI: 3.9, not calculable). Prior systemic therapy did not appear to significantly impact response. The investigator assessed confirmed response rate in a secondary efficacy population of patients with BRAF V600K mutation positive metastatic melanoma (N=16) was 13 % (95% CI: 0.0, 28.7) with a median duration of response of 5.3 months (95 % CI: 3.7, 6.8). There were no complete responses in the V600K patient population.

Tafinlar in combination with Mekinist

The efficacy and safety of the recommended dose of Tafinlar (150 mg twice daily) in combination with trametinib (2 mg once daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two pivotal Phase III studies.

MEK115306 (COMBI-d)

MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of Tafinlar and trametinib to Tafinlar and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was investigator assessed progression-free survival (PFS) with a key secondary endpoint of overall survival (OS). Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

A total of 423 patients were randomized 1:1 to either the combination therapy arm (Tafinlar 150 mg twice daily and trametinib 2 mg once daily) (N=211) or Tafinlar monotherapy arm (150 mg twice daily) (N=212). Baseline characteristics were balanced between treatment groups. Most patients were Caucasian (>99%) and male (53%), with a median age of 56

years (28% were ≥65 years). The majority of patients had Stage IVM1c disease (67%). Most patients had LDH ≤ULN (65%). ECOG performance status of 0 (72%), and visceral disease (73%) at baseline. Most patients had the BRAF V600E mutation (85 %); the remaining 15% of patients had the BRAF V600K mutation. Patients with brain metastases were not included in the trial.

Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 12-3. An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with dabrafenib monotherapy; the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5 year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 12-3, Figure 12-3). The Kaplan-Meier OS curve appears to stabilize from 3 to 5 years (see Figure 12-3). The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline

Table 12-3 Overall Survival results for Study MEK115306 (COMBI-d)

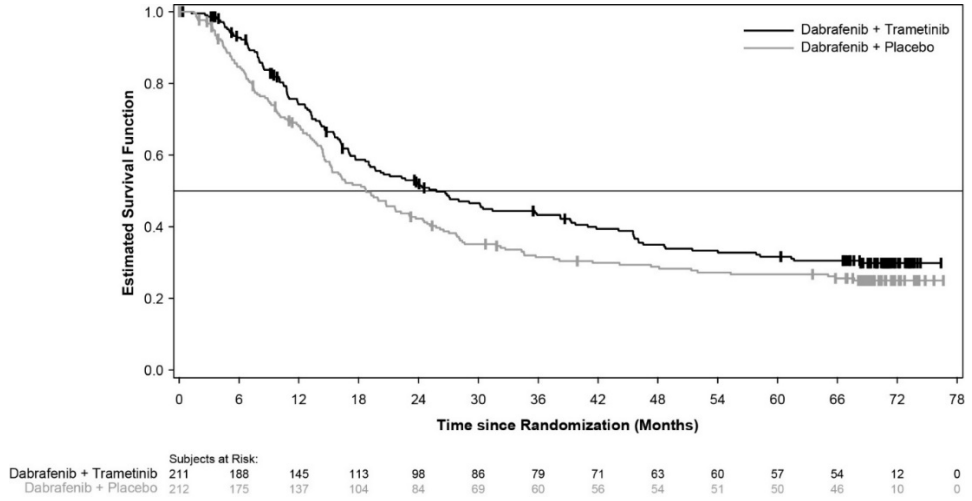
	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib Trametinib (n=211)**	**+Dabrafenib + Placebo (n=212)**	**Dabrafenib Trametinib (n=211)**	**+Dabrafenib + Placebo (n=212)**
Number of Patients						
Died (event), n (%)	99 (47)	123 (58)	114 (54)	139 (66)	135 (64)	151 (71)
Estimates of OS (months)						
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	26.7 (19.0, 38.2)	18.7 (15.2, 23.1)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.75 (0.58, 0.96)		0.80 (0.63, 1.01)	
p-value	0.011		NA		NA	

Overall survival Estimate, % (95% CI)	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + placebo (n=212)**
At 1 year	74 (66.8, 79.0)	68 (60.8, 73.5)
At 2 years	52 (44.7, 58.6)	42 (35.4, 48.9)
At 3 years	43 (36.2, 50.1)	31 (25.1, 37.9)
At 4 years	35 (28.2, 41.8)	29 (22.7, 35.2)
At 5 years	32 (25.1, 38.3)	27 (20.7, 33.0)

*OS analysis data cut-off: 12-Jan-2015, 3-year OS analysis data cut-off: 15-Feb-2016, 5-year OS analysis data cut-off: 10-Dec-2018

NR = Not reached, NA = Not applicable

Figure 12-3: COMBI-d-Kaplan-Meier overall survival curves (ITT Population)



Clinically meaningful improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 12-4).

Table 12-4 Investigator-assessed efficacy results for MEK115306 (COMBI-d) study (primary data cut and final data cut)

Endpoints	Primary Analysis*		Updated Analysis*		3 Year Analysis*		5 Year Analysis*	
	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)
Investigator Assessed PFS								
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	153 (73)	168[f] (79)	160 (76)	166[f] (78)
Median, months (95% CI[a])	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.0, 12.8)	7.6 (5.8, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.71 (0.57, 0.88)		0.73 (0.59, 0.91)	
P value (log-rank test)	0.035		<0.001		NA		NA	
Overall Response Rate[b] (%) 95% CI	67 (59.9, 73.0)	51 (44.5,58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	68 (61.5, 74.5)	55 (47.8, 61.5)	69 (62.5, 75.4)	54 (46.8, 60.6)
Difference in	15[d]		15[d]		NA		NA	

Endpoints	Primary Analysis*		Updated Analysis*		3 Year Analysis*		5 Year Analysis*	
	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)
response rate (CR[c] +PR[c]), % 95% CI for difference *P* value	5.9, 24.5 0.0015		6.0, 24.5 0.0014[g]					
Duration of Response (months)								
Median *(95% CI)*	9.2[e] (7.4, NR)	10.2[e] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1,13.8)	12.0 (9.3, 17.1)	10.6 (8.3, 12.9)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

**Primary analysis data cut-off: 26-Aug-2013, Final analysis data cut-off: 12-Jan-2015, 3 year analysis data cut-off: 15-Feb-2016, 5 year analysis data cut-off: 10-Dec-2018*
a- Confidence interval
b- Overall Response Rate = Complete Response + Partial Response
c- CR: Complete Response, PR: Partial Response
d- ORR difference calculated based on the ORR result not rounded
e- At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
f- Two patients were counted as progressed or died in the 3 year analysis but had an extended time without adequate assessment prior to the events, meaning they were censored in the 5-year analysis.
g - Updated analysis was not pre-planned and the p-value was not adjusted for multiple testing.
NR = Not reached
NA = Not applicable

MEK116513 (COMBI-v)

Study MEK116513 was a two-arm, randomized, open-label, Phase III study comparing Tafinlar and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was overall survival. Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

A total of 704 patients were randomized 1:1 to either the combination therapy arm (Tafinlar 150 mg twice daily and trametinib 2 mg once daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were Caucasians (>96%) and male (55%), with a median age of 55 years (24% were ≥ 65 years). The majority of patients had Stage IV M1c disease (61%). Most patients had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54% of patients had <3 disease sites at Baseline. The majority of patients had a BRAF V600E mutation (89%). Patients with brain metastases were not included in the trial.

An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with vemurafenib monotherapy; the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5 year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 12-5, Figure 12-4). The Kaplan-Meier OS curve appears to stabilize from 3 years to 5 years (see Figure 12-4). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an

elevated lactate dehydrogenase level at baseline.

Table 12-5 Overall Survival results for Study MEK116513 (COMBI-v)

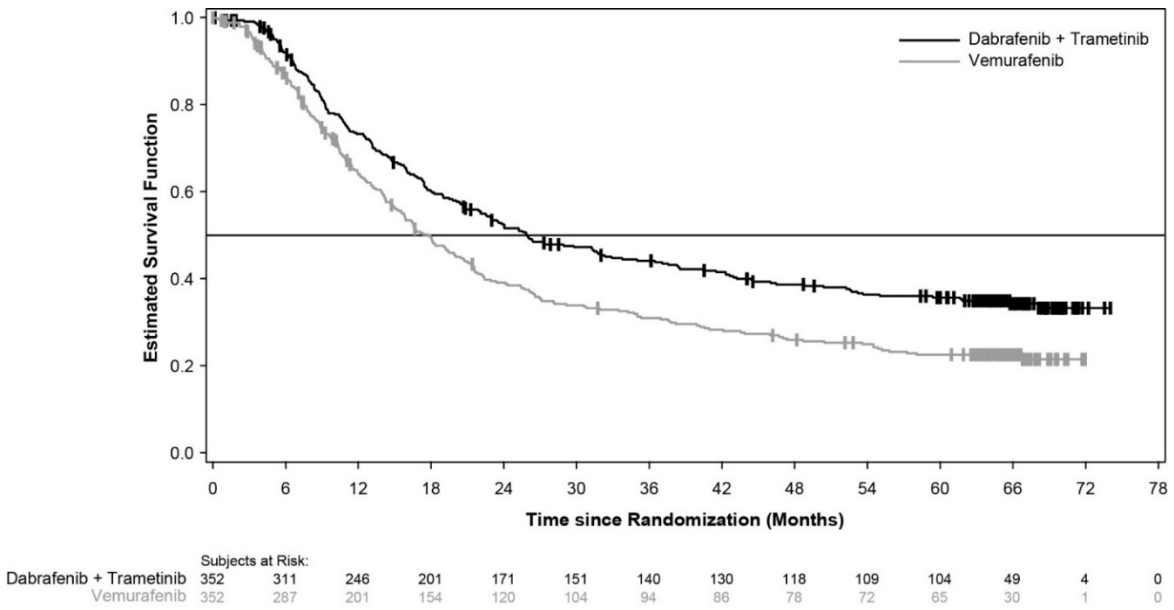
	OS analysis*		3-year OS analysis*		5-year OS analysis*	
	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)
Number of patients						
Died (event), n (%)	100 (28)	122 (35)	190 (54)	224 (64)	216 (61)	246 (70)
Estimates of OS (months)						
Median (95% CI)	NR (18.3, NR)	17.2 (16.4, NR)	26.1 (22.6, 35.1)	17.8 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.69 (0.53, 0.89)		0.68 (0.56, 0.83)		0.70 (0.58, 0.84)	
p-value	0.005		NA		NA	

Overall survival Estimate, % (95% CI)	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
At 1 year	72 (67, 77)	65 (59, 70)
At 2 years	53 (47.1, 57.8)	39 (33.8, 44.5)
At 3 years	44 (38.8, 49.4)	31 (25.9, 36.2)
At 4 years	39 (33.4, 44.0)	26 (21.3, 31.0)
At 5 years	36 (30.5, 40.9)	23 (18.1, 27.4)

NR = Not reached, NA = Not applicable

** Primary OS analysis data cut-off: 17-Apr-2014, 3 year OS analysis data cut-off: 15-Jul-2016, 5 year data cut-off: 8-Oct-2018.*

Figure 12-4 COMBI-v - Kaplan-Meier overall survival curves (ITT Population)



Clinically meaningful improvements for the secondary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to vemurafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to vemurafenib monotherapy (Table 12-6)

Table 12-6 Investigator-assessed efficacy results for MEK116513 (COMBI-v) study

Endpoint	Primary Analysis*		3-year analysis*		5-year analysis*	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Investigator Assessed PFS						
Progressive disease or death, n (%)	166 (47)	217 (62)	250 (71)	257 (73)	257 (73)	259 (74)
Median, months (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (5.7, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.61 (0.51, 0.73)		0.62 (0.52, 0.74)	
P value	<0.001		NA		NA	
Overall Response Rate 95% CI	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (61.9, 71.9)	53 (47.8, 58.4)	67 (62.2, 72.2)	53 (47.2, 57.9)
Difference in response rate (CR+PR), % 95% CI for difference	13 (5.7, 20.2)		NA		NA	
P value	0.0005		NA		NA	
Duration of Response (months)						
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)	13.8 (11.3, 17.7)	7.9 (7.4, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

Primary analysis data cut-off: 17-Apr-2014, 3-year analysis data cut-off: 15-Feb-2016, 5-year analysis data cut-off: 8-Oct -2018
PFS = Progression Free Survival; NR = Not reached

BRF117277 / DRB436B2204 (COMBI-MB)

The efficacy and safety of Tafinlar in combination with Mekinist in patients with BRAF mutant-positive melanoma that has metastasized to the brain was studied in a non-randomized, open-label, multi-center, Phase II study (COMBI-MB study).

A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.

- Cohort C: patients with BRAFV600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort D: patients with BRAFV600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 12-7. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 12-5. Due to small sample size reflected by wide 95% CIs, the results in cohorts B, C, and D should be interpreted with caution. BRAF V600K was the predominant mutation in cohort C and BRAF V600E was the predominant mutation in cohort D; and there were no BRAF V600D mutations observed.

Table 12-7 COMBI-MB - Efficacy data by investigator assessment

	All treated patients population			
Endpoints/ assessment	**Cohort A N=76**	**Cohort B N=16**	**Cohort C N=16**	**Cohort D N=17**
Intracranial response rate, % (95 % CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
Duration of intracranial response, median, months (95% CI)				
	6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
ORR, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
PFS, median, months (95% CI)				
	5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
OS, median, months (95% CI)				
Median, months	10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)
CI = Confidence Interval NR = Not Reported				

- In cohort A, 3 patients were found to have the BRAF V600K mutation upon central confirmation.
- In cohort C, 14 patients had the BRAF V600K mutation, and 2 patients had the BRAF V600R mutation.
- In cohort D, 15 patients had the BRAF V600E mutation, 1 patient had the BRAF V600K mutation and 1 patient had the BRAF V600R mutation.

Adjuvant treatment of melanoma

Study BRF115532 / CDRB436F2301 (COMBI-AD)

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

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (Tafinlar 150 mg twice daily and Mekinist 2 mg once daily) or two placebos for a period of 12 months. Enrollment 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 tumor 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 tumor assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint) and distant metastasis-free survival (DMFS).

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

Results for the primary analysis of RFS are presented in Figure 12-5 and in Table 12-8. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and has not yet been reached for the combination arm.

Figure 12-5 COMBI-AD - Relapse-free survival Kaplan-Meier curves (ITT population)

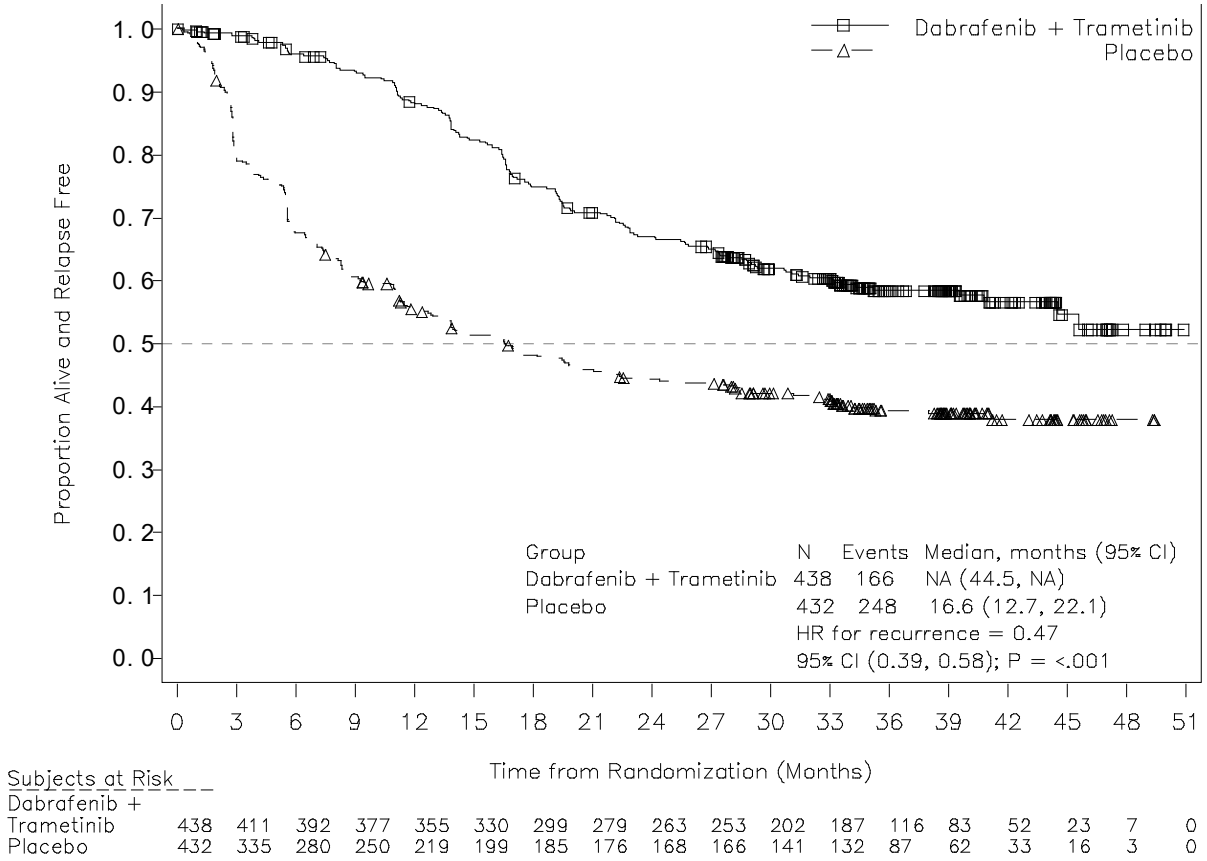


Table 12-8 COMBI-AD – Relapse-free survival results

	Dabrafenib + Trametinib	**Placebo**
RFS parameter	**N=438**	**N=432**
Number of events, n (%)	166 (38%)	248 (57%)
Recurrence	163 (37%)	247 (57%)
Relapsed with distant metastasis	103 (24%)	133 (31%)
Death	3 (<1%)	1 (<1%)
Median (months) (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)

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

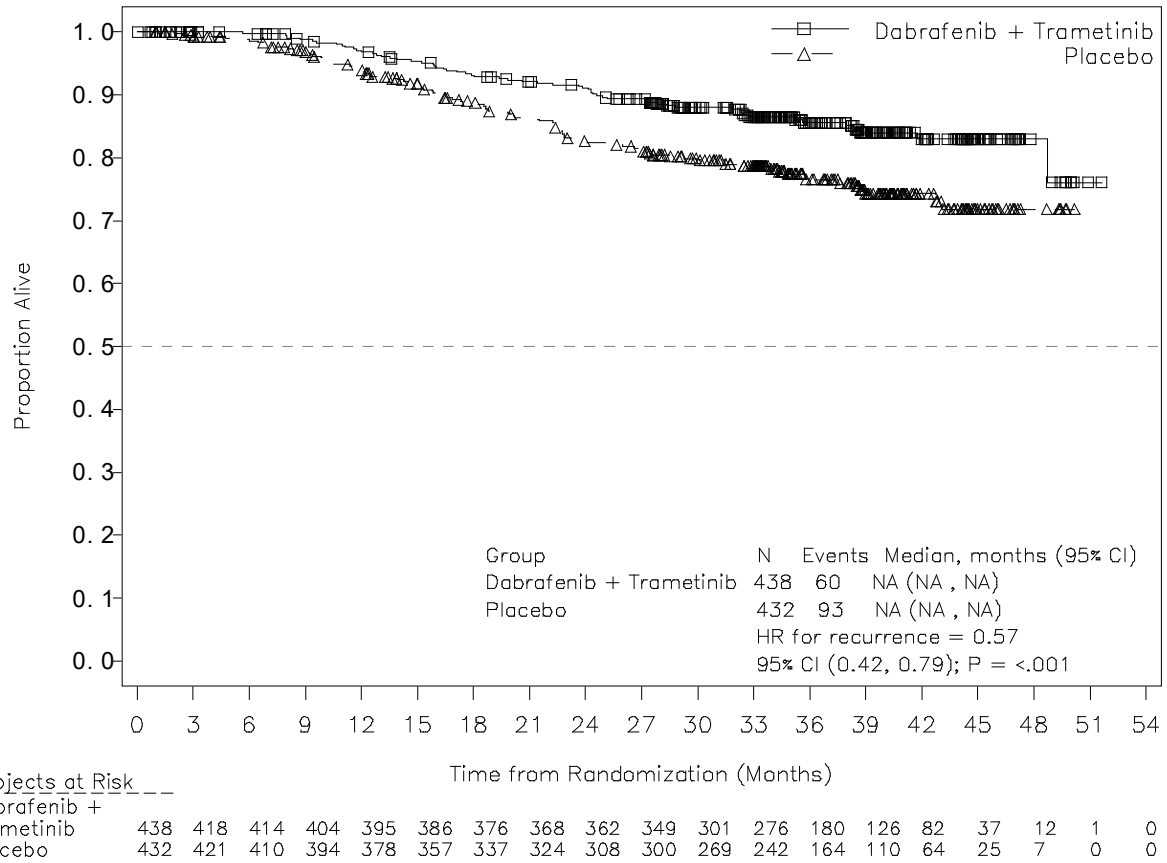
[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)

NE = not estimable

Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the

estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomization were 97% and 91% in the combination arm and 94% and 83% in the placebo arm, respectively. The Kaplan-Meier curve for this OS interim analysis is shown in Figure 12-6.

Figure 12-6 COMBI-AD – Overall survival Kaplan-Meier curves (ITT Population)



Prior BRAF inhibitor therapy

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

Part B of study BRF113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor (see section *Warnings and Precautions*). The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95 CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

Advanced NSCLC

Study E2201 (BRF113928)

The efficacy and safety of Tafinlar in combination with Mekinist was studied in a Phase II, three-cohort, multicenter, non-randomized, open-label study enrolling patients with Stage IV BRAF V600E mutant NSCLC.

The primary endpoint was the investigator-assessed overall response rate (ORR) using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (Tafinlar 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.

- Cohort B (n=57): Combination therapy (Tafinlar 150 mg twice daily and trametinib 2 mg once daily): 59 patients enrolled. 57 patients had previously received one to three lines of systemic treatment for their metastatic disease. Two patients did not have any previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.

- Cohort C (n=36): Combination therapy (Tafinlar 150 mg twice daily and Mekinist 2 mg once daily): 34 patients enrolled (note: the two patients from Cohort B that did not have any previous systemic treatment were included in the analysis for patients enrolled in Cohort C for a total of 36 patients). All patients received study medication as first line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy in Cohorts B and C most patients were Caucasians (n=79, 85%). There was a similar female to male ratio (54% vs 46%). The median age was 64 years in patients who had at least one prior therapy and 68 years in patients who were treatment naïve for their advanced disease. Most patients (n=87, 94%) enrolled in the combination therapy treated Cohorts had an ECOG performance status of 0 or 1. Twenty-six (26) patients (28%) had never smoked. Ninety-one 91 patients (97.8%) had a non-squamous histology. In the pre-treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

For the primary endpoint the investigator-assessed ORR, was 61.1% (95% CI, 43.5, 76.9) in the first-line population and 66.7% (95% CI, 52.9%, 78.6%) in the previously treated population. These results met the statistical significance to reject the null hypothesis that the ORR of Mekinist in combination with Tafinlar for both NSCLC population was less than or equal to 30%.

The ORR results assessed by IRC were consistent to the investigator assessment (Table 12-9).

The response was durable with median DoR in the previously treated population reaching 9.8 months (95% CI, 6.9, 16.0) by investigator assessment. For the first-line population, the

median DoR and PFS could not yet be estimated (Table 12-9), and 68% of patients with confirmed response were still ongoing in follow-up for duration of response.

The efficacy of the combination with trametinib was superior when indirectly compared to Tafinlar monotherapy in Cohort A.

Table 12-9 Efficacy Results in Patients with BRAF V600E NSCLC

Endpoint	Analysis	Combination First Line	Combination Second Line Plus
		N=36[1]	**N=57[1]**
Overall confirmed response n (%) (95% CI)	By Investigator	22 (61.1%) (43.5, 76.9)	38 (66.7%) (52.9, 78.6)
	By IRC	22 (61.1%) (43.5, 76.9)	36 (63.2%) (49.3, 75.6)
Median DoR, months (95% CI)	By Investigator	NE[2] (8.3, NE)	9.8 (6.9, 16.0)
	By IRC	NE (6.9, NE)	12.6 (5.8, NE)
Median PFS, months (95% CI)	By Investigator	NE (7.0, NE)	10.2 (6.9, 16.7)
	By IRC	NE (7.0, NE)	8.6 (5.2, 16.8)
Median OS, months (95% CI)	-	24.6 (11.7, NE)[3]	18.2 (14.3, NE)

[1] Data cut-off: 8-Aug-2016

[2] NE: Not Evaluable

[3] Event rate for OS calculation was 28% and hence the defined median value still needs to mature

Tafinlar Monotherapy:

At the time of the primary objective analysis for Cohort A, ORR as per investigator assessment was observed in 32.1% of second line plus all treated patients (95% CI: 21.9, 43.6). Partial response was the best response among all these patients. At a subsequent data cut for mature DoR, the estimated median DoR was 9.6 months (95% CI: 5.4, 15.2). The estimated median PFS was 5.5 months (95% CI: 3.4, 7.3). With an additional 18 months of follow-up from the primary objective analysis for Cohort A to determine a mature OS, the estimated median OS was 12.7 months (95% CI: 7.3, 16.3).

Locally advanced or metastatic anaplastic thyroid cancer

Study BRF117019 / CDRB436X2201

The efficacy and safety of Tafinlar in combination with Mekinist was studied in a Phase II, nine-cohort, multicenter, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic anaplastic thyroid cancer (ATC).

The study had pre-specified interim analyses that were performed approximately every 12 weeks. The primary endpoint was the investigator-assessed overall response rate (ORR) using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. ORR, DoR, and PFS were also assessed by an Independent Review Committee (IRC).

In the ATC cohort, patients received Tafinlar 150 mg twice daily and Mekinist 2 mg once daily. At the time of efficacy analysis, the ATC cohort had 26 patients enrolled, of which 23 patients were evaluable for response. There were 20 ATC patients who had a minimum of 6 months of follow-up after the first scheduled post-baseline assessment or discontinued study treatment prior to that.

Among the 26 patients enrolled, 13 (50%) were Caucasian and 12 (46%) were Asian. The female to male ratio was 1:1. The median age was 70 years. All patients (n=26, 100%) had an ECOG performance status of 0 or 1. Fourteen patients (54%) had a prior history of differentiated thyroid cancer. Prior anti-cancer treatments included surgery (n=24, 92%), external beam radiotherapy (n=21, 81%), and systemic therapy (n=14, 54%) for ATC. Central laboratory testing confirmed the BRAF V600E mutation in 23 patients (88%).

For the primary endpoint, the investigator-assessed ORR was 70% (95% CI: 47.1, 86.8) in the ATC cohort. The ORR results assessed by IRC and investigator-assessment were consistent (Table 12-8).

Responses were durable with a median DoR in the ATC cohort of 12.1 months (95% CI: 3.3, NE) by investigator assessment, and a median PFS of 13.8 months (95% CI: 4.7, NE).

For ATC subjects, the median OS was not yet reached at the time of data cut-off. Kaplan-Meier estimate of overall survival at 12 months for ATC patients was 63.8% (95% CI: 36.3, 82.0).

Table 12-10 Efficacy Results in Patients with BRAF V600E ATC

Endpoint	Analysis[1]	N=23[2]
Overall confirmed response n (%) (95% CI)	By Investigator	16 (70%) (47.1, 86.8)
	By IRC	14 (61%) (38.5, 80.3)
Median DoR, months (95% CI)	By Investigator	12.1 (3.3, NE[3])
	By IRC	12.0 (3.7, NE)
Median PFS, months (95% CI)	By Investigator	13.8 (4.7, NE)
	By IRC	10.8 (4.7, 20.1)
Median OS, months (95% CI)	-	NE (8.0, NE)

[1] Data cut-off: 24-May-2017

[2] 23 of 26 patients in the ATC cohort were evaluable for response

[3] NE: Not Estimable

Other Studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with Tafinlar and Mekinist combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only Tafinlar in case of pyrexia. In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both Tafinlar and Mekinist when patient's temperature was ≥38ºC (100.4°F) (COMBI-Aplus) or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia), resulted in improved pyrexia-related outcomes without impacting efficacy:

- Unresectable or metastatic melanoma setting (COMBI-d/v vs COMBI-i):
  - grade 3/4 pyrexia reduced from 6.6% to 3.4%
  - hospitalization due to pyrexia reduced from 12.3% to 6.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.4 % to 1.9%
  - treatment discontinuation rates due to pyrexia were comparable, 1.1% vs 1.9%
- Adjuvant melanoma setting (COMBI-AD vs COMBI-Aplus):
  - grade 3/4 pyrexia reduced from 5.7% to 4.3%
  - hospitalization due to pyrexia reduced from 11.0% to 5.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.0% to 2.2%
  - treatment discontinuation due to pyrexia reduced from 6.2% to 2.5%

13 Non-clinical safety data

Safety pharmacology and repeat dose toxicity

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 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 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 hematological 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).

Dabrafenib was phototoxic in an in vitro mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and in vivo at doses ≥ 100 mg/kg (> 44 times clinical exposure based on Cmax) in an oral phototoxicity study in hairless mice. Although dabrafenib was phototoxic in nonclinical studies, based on clinical safety data, there is low risk for phototoxicity to patients taking Tafinlar.

Carcinogenicity and mutagenicity
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.

Reproductive toxicity
Embryofetal development and fertility
In combined female fertility, early embryonic and embryofetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility. Developmental toxicity including embryo- lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC) *(see also section 9 Pregnancy, Lactation, Females And Males Of Reproductive Potential - Animal Data).*

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 rats and dogs were still present following a 4-week recovery period.

Juvenile animal studies
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).

Non-fixed dose combination therapy

Tafinlar in combination with Mekinist

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastro-intestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

14 Pharmaceutical information

Incompatibilities
Not applicable

Shelf-Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
See folding box.

Tafinlar should not be used after the date marked “EXP” on the pack.

Tafinlar must be kept out of the reach and sight of children.

Not all presentations are available in every country.

Do not store above 30ºC. Protect from light and moisture. Store in the original container. Do not remove the desiccant.

Nature and Contents of Container

50 mg capsule - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules. Each bottle contains a silica gel desiccant.

75 mg capsule- High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules. Each bottle contains a silica gel desiccant.

Not all presentations are available in every country.

Instructions for Use/Handling

There are no special requirements for use or handling of this product.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer

See folding box

Country Specific Package Leaflet

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