ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tafinlar 50 mg hard capsules

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

Tafinlar 75 mg hard capsules

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Tafinlar 50 mg hard capsules

Opaque dark red capsules, approximately 18 mm long, with capsule shell imprinted with “GS TEW” and “50 mg”.

Tafinlar 75 mg hard capsules

Opaque dark pink capsules, approximately 19 mm long, with capsule shell imprinted with “GS LHF” and “75 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Non-small cell lung cancer (NSCLC)

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

4.2 Posology and method of administration

Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anti-cancer medicinal products.

Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test.

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC. Dabrafenib should therefore not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see sections 4.4 and 5.1).

Posology

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) 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.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see Table 2). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

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

If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, the dose of trametinib should only be taken if it is more than 12 hours until the next scheduled dose.

Dose modification
Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage dose modification requirements.

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

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4).

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Tables 1 and 2, respectively.

Table 1 Recommended dose level reductions

Dose level	**Dabrafenib dose** Used as monotherapy or in combination with trametinib	**Trametinib dose*** Only when used in combination with dabrafenib
Starting dose	150 mg twice daily	2 mg once daily
1st dose reduction	100 mg twice daily	1.5 mg once daily
2nd dose reduction	75 mg twice daily	1 mg once daily
3rd dose reduction	50 mg twice daily	1 mg once daily
Dose adjustment for dabrafenib below 50 mg twice daily is not recommended, whether used as monotherapy or in combination with trametinib. Dose adjustment for trametinib below 1 mg once daily is not recommended, when used in combination with dabrafenib. *For dosing instructions for treatment with trametinib monotherapy, see trametinib SmPC, Posology and Method of administration.		

Table 2 Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTCAE)*	**Recommended dabrafenib dose modifications** Used as monotherapy or in combination with trametinib
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 reactions graded by the Common Terminology Criteria for Adverse Events (CTCAE)	

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 dabrafenib dose should not exceed 150 mg twice daily.

Pyrexia
If a patient's temperature is ≥38°C, therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination). 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. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and, if necessary, treated in line with local practice (see section 4.4). Dabrafenib, or both dabrafenib and trametinib when used in combination, should be restarted if the patient is symptom-free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation-positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Uveitis

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation, and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

RAS mutation-positive non-cutaneous malignancies

The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction

If dabrafenib is being used in combination with trametinib and an asymptomatic, absolute decrease of >10% in LVEF compared to baseline occurs, and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)

If patients report new visual disturbances such as diminished central vision, blurred vision or loss of vision at any time while on combination therapy with dabrafenib and trametinib, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for confirmed cases of RVO or RPED.

Interstitial lung disease (ILD)/Pneumonitis

In patients treated with dabrafenib in combination with trametinib with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

Special populations

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Dabrafenib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with trametinib.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined (see section 5.2). 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. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with trametinib.

Non-Caucasian patients

Limited safety and efficacy data have been collected on dabrafenib in non-Caucasian patients. 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.

Elderly
No adjustment of the initial dose is required in patients >65 years of age.

Paediatric population
The safety and efficacy of dabrafenib capsules in children and adolescents (<18 years) have not yet been established. No clinical data are available. Studies in juvenile animals have shown adverse effects of dabrafenib which had not been observed in adult animals (see section 5.3).

Method of administration

Tafinlar is for oral use. The capsules are to be swallowed whole with water. They should not be chewed or opened and should not be mixed with food or liquids due to chemical instability of dabrafenib.

It is recommended that the doses of dabrafenib be taken at similar times every day, leaving an interval of approximately 12 hours between doses. When dabrafenib 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 dabrafenib.

Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.

If a patient vomits after taking dabrafenib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to trametinib SmPC for information on method of administration when given in combination with dabrafenib.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When dabrafenib is given in combination with trametinib, the SmPC of trametinib must be consulted prior to intiation of combination treatment. For additional information on warnings and precautions associated with trametinib treatment, please refer to the trametinib SmPC.

BRAF V600 testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC therefore dabrafenib should not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see sections 4.2 and 5.1).

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 5.1). 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.

New malignancies

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

Cutaneous malignancies

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with dabrafenib alone and in combination with trametinib (see section 4.8). In the Phase III clinical trials MEK115306 and MEK116513 in patients with unresectable or metastatic melanoma, cuSCC occurred in 10% (22/211) of patients receiving dabrafenib as a monotherapy and in 18% (63/349) of patients receiving vemurafenib as a monotherapy, respectively. In the integrated safety population of patients with melanoma and advanced NSCLC, cuSCC occurred in 2% (19/1 076) of patients receiving dabrafenib in combination with trametinib. The median time to diagnosis of the first occurrence of cuSCC in study MEK115306 was 223 days (range 56 to 510 days) in the combination therapy arm and 60 days (range 9 to 653 days) in the dabrafenib monotherapy arm. In the Phase III study BRF115532 (COMBI-AD) in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving dabrafenib in combination with trametinib as compared to 1% (5/432) of patients receiving placebo had developed cuSCC at the time of the primary analysis. During the long-term (up to 10 years) off-treatment follow-up, 2 additional patients reported cuSCC in each treatment arm. Overall, the median time to onset of the first occurrence of cuSCC in the combination arm of the adjuvant treatment study was approximately 21 weeks and was 34 weeks in the placebo arm.

It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment or, if taken in combination, dabrafenib and trametinib 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 clinical trials in patients treated with dabrafenib. In clinical trials in unresectable or metastatic melanoma,these cases were identified within the first 5 months of dabrafenib as monotherapy. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies

In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAP kinase) signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to increased risk of non-cutaneous malignancies with dabrafenib exposure (see section 4.8) when RAS mutations are present. RAS-associated malignancies have been reported in clinical trials, both with another BRAF inhibitor (chronic myelomonocytic leukaemia and non-cutaneous SCC of the head and neck) as well as with dabrafenib monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with dabrafenib in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer).

Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen computerised tomography (CT) scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts and blood chemistry should be performed as clinically indicated.

The benefits and risks should be considered before administering dabrafenib in patients with a prior or concurrent cancer associated with RAS mutations. No dose modification of trametinib is required when taken in combination with dabrafenib.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Haemorrhage

Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking the combination of dabrafenib with trametinib (see section 4.8). Please refer to the trametinib SmPC (see section 4.4) for additional information.

Visual impairment

In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

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 dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada syndrome have been reported in patients treated with dabrafenib in combination with trametinib. Withhold dabrafenib until resolution of ocular inflammation and consider consulting an ophthalmologist. Systemic corticosteroid treatment may be necessary.

RPED and RVO may occur with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED.

Pyrexia

Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib (see section 4.8). In 1% of patients in clinical trials with dabrafenib monotherapy, serious non-infectious febrile events were identified (defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function) (see section 4.8). The onset of these serious non-infectious febrile events was typically within the first month of dabrafenib as monotherapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

The incidence and severity of pyrexia are increased with combination therapy. In the combination therapy arm of study MEK115306 in patients with unresectable or metastatic melanoma, pyrexia was reported in 57% (119/209) of patients with 7% Grade 3, as compared to the dabrafenib monotherapy arm with 33% (69/211) of patients reporting pyrexia, 2% Grade 3. In the Phase II study BRF113928 in patients with advanced NSCLC the incidence and severity of pyrexia were increased slightly when dabrafenib was used in combination with trametinib (48%, 3% Grade 3) as compared to dabrafenib monotherapy (39%, 2% Grade 3). In the Phase III study BRF115532 in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the dabrafenib in combination with trametinib arm (67%; 6% Grade 3/4) as compared to the placebo arm (15%; <1% Grade 3).

For patients with unresectable or metastatic melanoma 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.

Therapy (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) should be interrupted if the patient's temperature is ≥38ºC (see section 5.1). 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. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).

LVEF reduction/Left ventricular dysfunction

Dabrafenib in combination with trametinib has been reported to decrease LVEF (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib.

Renal failure

Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported (see section 4.8). Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting (see section 5.2).

Hepatic events

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib (see section 4.8). It is recommended that patients receiving treatment with dabrafenib in combination with trametinib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued thereafter as clinically indicated. Please refer to the trametinib SmPC for additional information.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8). Please refer to the trametinib SmPC for additional information.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC section 4.4 for additional information. If dabrafenib is being used in combination with trametinib then therapy with dabrafenib may be continued at the same dose.

Rash

Rash has been observed in about 24% of patients in clinical trials when dabrafenib is used in combination with trametinib (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions. Please refer to the trametinib SmPC section 4.4 for additional information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib SmPC section 4.4 for additional information.

Pancreatitis

Pancreatitis has been reported in <1% of patients treated with dabrafenib as monotherapy and in combination with trametinib in unresectable or metastatic melanoma clinical trials and about 4% of patients treated with dabrafenib in combination with trametinib in the NSCLC clinical trial. One of the events occurred on the first day of dabrafenib 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% (1/435) of patients receiving dabrafenib in combination with trametinib, and no patients receiving placebo. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when restarting dabrafenib after an episode of pancreatitis.

Deep vein thrombosis/Pulmonary embolism

Pulmonary embolism or deep vein thrombosis can occur when dabrafenib is used in combination with trametinib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

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 dabrafenib/trametinib combination therapy. 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, dabrafenib and trametinib should be withdrawn.

Gastrointestinal disorders

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4).

Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with dabrafenib in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with dabrafenib and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with dabrafenib in combination with trametinib. Caution should be taken when dabrafenib is administered in combination with trametinib. If HLH is confirmed, administration of dabrafenib and trametinib should be discontinued and treatment for HLH initiated.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of dabrafenib in combination with trametinib (see section 4.8). Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. Patients with risk factors for TLS should be closely monitored and prophylactic hydration should be considered. TLS should be treated promptly, as clinically indicated.

Effects of other medicinal products on dabrafenib

Dabrafenib is a substrate of CYP2C8 and CYP3A4. Potent inducers of these enzymes should be avoided when possible as these agents may decrease the efficacy of dabrafenib (see section 4.5).

Effects of dabrafenib on other medicinal products

Dabrafenib is an inducer of metabolising enzymes which may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A drug utilisation review (DUR) is therefore essential when initiating dabrafenib treatment. Concomitant use of dabrafenib with medicinal products that are sensitive substrates of certain metabolising enzymes or transporters (see section 4.5) should generally be avoided if monitoring for efficacy and dose adjustment is not possible.

Concomitant administration of dabrafenib with warfarin results in decreased warfarin exposure. Caution should be exercised and additional International Normalised Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin and at discontinuation of dabrafenib (see section 4.5).

Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure. Caution should be exercised and additional monitoring of digoxin is recommended when digoxin (a transporter substrate) is used concomitantly with dabrafenib and at discontinuation of dabrafenib (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on dabrafenib

Dabrafenib is a substrate for the metabolising enzymes CYP2C8 and CYP3A4, 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 dabrafenib when possible. Dabrafenib should be used with caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4 should be avoided.

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71% increase in dabrafenib AUC and a 33% increase in dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Co-administration resulted in increases in hydroxy- and desmethyl-dabrafenib AUC (increases of 82% and 68%, respectively). A decrease of 16% in AUC was noted for carboxy-dabrafenib.

Administration of gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily, with dabrafenib 75 mg twice daily, resulted in a 47% increase in dabrafenib AUC but did not alter dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤13%).

Administration of rifampin (a CYP3A4/CYP2C8 inducer) 600 mg once daily, with dabrafenib 150 mg twice daily, resulted in a decrease in repeat-dose dabrafenib C_{max} (27%) and AUC (34%). 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.

Co-administration of repeat doses of dabrafenib 150 mg twice daily and the pH-elevating agent rabeprazole 40 mg once daily resulted in a 3% increase in 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, H_2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Effect of dabrafenib on other medicinal products

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 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 P-gp may also be induced as well as other transporters, e.g. MRP-2. Induction of OATP1B1/1B3 and BCRP is not likely based on the observations from a clinical study with rosuvastatin.

In vitro, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical drug interaction study, C_{max} and AUC of oral midazolam (a CYP3A4 substrate) decreased by 47% and 65%, respectively with co-administration of repeat-dose dabrafenib.

Administration of dabrafenib 150 mg twice daily and warfarin resulted in a decrease in AUC of S- and R- warfarin of 37% and 33%, respectively, compared to administration of warfarin alone. C_{max} of S- and R-warfarin increased 18% and 19%.

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)
- Anti-cancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptics (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, see section 4.4)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives (see section 4.6)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Upon discontinuation of dabrafenib offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter

substrates (e.g. P-gp or MRP-2) may increase and patients should be monitored for toxicity and dose 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.

Effects of dabrafenib on substance transport systems

Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1), OATP1B3 and BCRP. Following co-administration of a single dose of rosuvastatin (OATP1B1, OATP1B3 and BCRP substrate) with repeat-dose dabrafenib 150 mg twice daily in 16 patients, C_{max} of rosuvastatin increased 2.6-fold whereas the AUC was only minimally changed (7% increase). The increased C_{max} of rosuvastatin is unlikely to have clinical relevance.

Combination with trametinib

Co-administration of repeat dosing of trametinib 2 mg once daily and dabrafenib 150 mg twice daily resulted in no clinically meaningful changes in trametinib or dabrafenib C_{max} and AUC with increases of 16 and 23%, respectively, in dabrafenib C_{max} and AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when trametinib is administered in combination with dabrafenib, a CYP3A4 inducer, using a population pharmacokinetic analysis.

When dabrafenib is used in combination with trametinib refer to the guidance for medicinal product interactions found in sections 4.4 and 4.5 of dabrafenib and trametinib SmPC.

Effect of food on dabrafenib

Patients should take dabrafenib as monotherapy or in combination with trametinib at least one hour prior to or two hours after a meal due to the effect of food on dabrafenib absorption (see section 5.2).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective methods of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and 16 weeks following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of oral or any systemic hormonal contraceptives and an effective alternative method of contraception should be used (see section 4.5).

Pregnancy

There are no data from the use of dabrafenib in pregnant women. Animal studies have shown reproductive toxicity and embryo-foetal developmental toxicities, including teratogenic effects (see section 5.3). Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the foetus. Please see trametinib SmPC (see section 4.6) when used in combination with trametinib.

Breast-feeding

It is not known whether dabrafenib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding child cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue dabrafenib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for dabrafenib as monotherapy or in combination with trametinib. Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals (see section 5.3). Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Please see trametinib SmPC (see section 4.6) when used in combination with trametinib.

4.7 Effects on ability to drive and use machines

Dabrafenib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of dabrafenib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be made aware of the potential for fatigue and eye problems to affect these activities.

4.8 Undesirable effects

Summary of the safety profile

The safety of dabrafenib monotherapy is based on the integrated safety population from five clinical trials, BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680, which included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg twice daily. The most common adverse 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 1 076 patients with BRAF V600 mutant unresectable or metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment) 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 clinical trials, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), 435 were treated with the combination in the adjuvant treatment of Stage III BRAF V600 mutant melanoma after complete resection in a randomised Phase III study BRF115532 (COMBI-AD) and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 (see section 5.1).

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

Tabulated list of adverse reactions

Adverse reactions associated with dabrafenib obtained from clinical studies and post-marketing surveillance are tabulated below for dabrafenib monotherapy (Table 3) and dabrafenib in combination with trametinib (Table 4). Adverse reactions are listed below by MedDRA system organ class and 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions with dabrafenib monotherapy

System organ class	Frequency (all grades)	Adverse reactions
Neoplasms benign, malignant and unspecified (incl 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
	Common	Peripheral neuropathy (including sensory and motor neuropathy)
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	Acute febrile neutrophilic dermatosis
		Panniculitis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute renal failure
		Nephritis
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
		Chills
		Asthenia
	Common	Influenza-like illness

Table 4 Adverse reactions with dabrafenib in combination with trametinib

System organ class	Frequency (all grades)	Adverse reactions
Infections and infestations	Very common	Nasopharyngitis
	Common	Urinary tract infection
		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[c]
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Common	Neutropenia
		Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[d]
		Sarcoidosis
	Rare	Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
	Not known	Tumour lysis syndrome
Nervous system disorders	Very common	Headache
		Dizziness
	Common	Peripheral neuropathy (including sensory and motor neuropathy)
Eye disorders	Common	Vision blurred
		Visual impairment
		Uveitis[e]
	Uncommon	Chorioretinopathy
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
		Atrioventricular block[f]
	Uncommon	Bradycardia
	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[g]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
	Uncommon	Pneumonitis

Gastrointestinal disorders	Very common	Abdominal pain[h]
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Colitis
	Rare	Gastrointestinal perforation
Skin and subcutaneous tissue disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema[i]
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
	Uncommon	Acute febrile neutrophilic dermatosis
	Not known	Stevens-Johnson syndrome
		Drug reaction with eosinophilia and systemic symptoms
		Dermatitis exfoliative generalised
		Tattoo-associated skin reactions
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms[j]
Renal and urinary disorders	Uncommon	Renal failure
		Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
		Influenza-like illness
	Common	Mucosal inflammation
		Face oedema

Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased
The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon); 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon). [a] Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma [b] Papilloma, skin papilloma [c] Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III [d] Includes drug hypersensitivity [e] Includes cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada syndrome [f] Atrioventricular block, atrioventricular block first degree, atrioventricular block second degree, atrioventricular block complete [g] Bleeding from various sites, including intracranial bleeding and fatal bleeding [h] Abdominal pain upper and abdominal pain lower [i] Erythema, generalised erythema [j] Muscle spasms, musculoskeletal stiffness		

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 cuSCC and the events occurred later than with dabrafenib monotherapy with a median time to onset of 18-31 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 4.4). 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 4.4). Non-cutaneous malignancies were reported in 1% (6/586) of patients in the integrated safety population of dabrafenib monotherapy, and <1% (8/1 076) of patients in the integrated safety population of dabrafenib in combination with trametinib. In the Phase III study BRF115532 (COMBI-AD) in the adjuvant treatment of melanoma, 1% (5/435) of patients receiving dabrafenib in combination with trametinib as compared to <1% (3/432) of patients receiving placebo developed non-cutaneous malignancies. During the long-term (up to 10 years) off-treatment follow-up, 9 additional patients reported non-cutaneous malignancies in the combination arm and 4 in in the placebo arm. 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 SmPC.

LVEF reduction/Left ventricular dysfunction
Decreased LVEF has been reported in 6% (65/1 076) 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 SmPC.

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 4.4). 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 4.2 and 4.4).

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

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 (25%) 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 4.4).

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 4.4).

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=1 076), 265 patients (25%) were ≥65 years of age, 62 patients (6%) 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 clinical trials. 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.

Dabrafenib in combination with trametinib in patients with brain metastases

The safety and efficacy of the combination of dabrafenib and trametinib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for an overdose of dabrafenib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, B-Raf serine-threonine kinase (BRAF) inhibitors, ATC code: L01EC02

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation is V600E which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.

Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations (Table 5).

Table 5 Kinase inhibitory activity of dabrafenib against RAF kinases

Kinase	Inhibitory concentration 50 (nM)
BRAF V600E	0.65
BRAF V600K	0.50
BRAF V600D	1.8
BRAF WT	3.2
CRAF WT	5.0

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

In subjects with BRAF V600 mutation-positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Combination with trametinib
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.

Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib has shown anti-tumour activity in BRAF V600 mutation-positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation-positive melanoma xenografts.

Determination of BRAF mutation status
Before taking dabrafenib or combination with trametinib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the Phase II and III clinical trials, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO). The IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with BRAF V600E or V600K mutation-positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the bioMerieux (bMx) THxID BRAF validated assay, which has CE marking. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical trials with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical trials (n=876) that were mutation-positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Clinical efficacy and safety

Unresectable or metastatic melanoma
- *Dabrafenib in combination with trametinib*

Treatment-naïve patients
The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic

melanoma with a BRAF V600 mutation was studied in two Phase III trials and one supportive Phase I/II study.

MEK115306 (COMBI-d):
MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Subjects 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 subjects were randomised 1:1 to either combination (N=211) or dabrafenib (N=212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the trial.

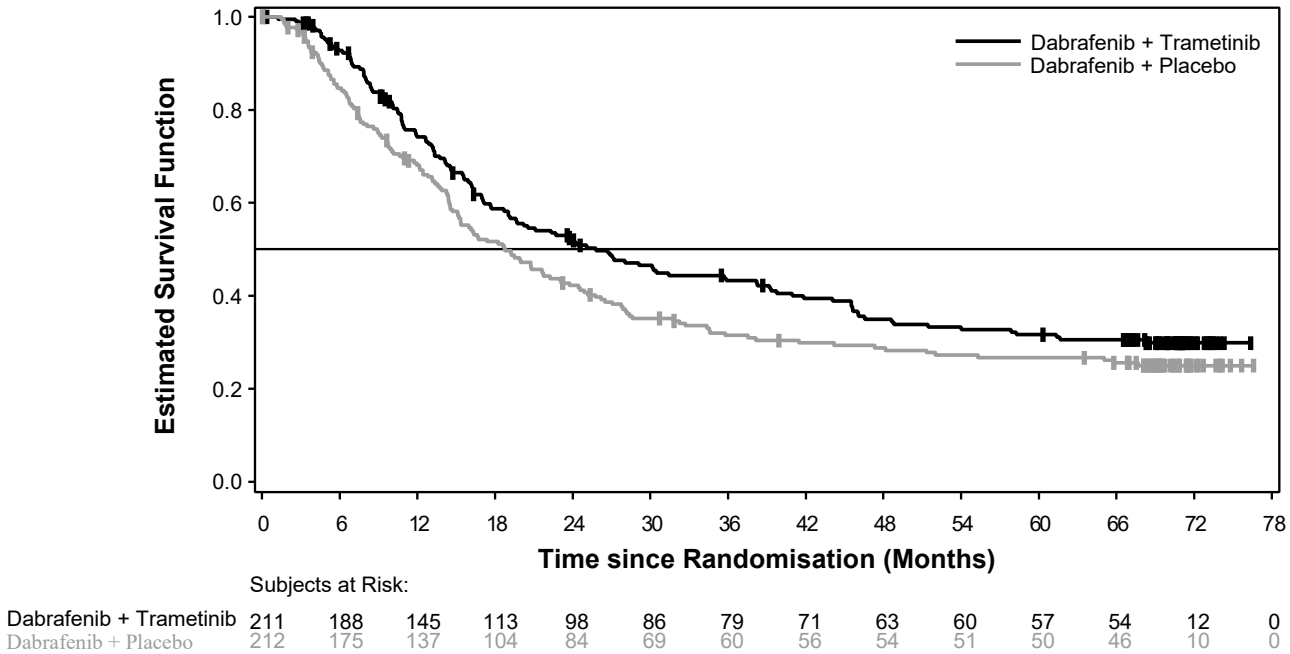
Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 6. From an OS analysis at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 6, Figure 1). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 1). 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 6 Overall Survival results for Study MEK115306 (COMBI-d)

	OS analysis (data cut-off: 12-Jan-2015)		**5-year OS analysis (data cut-off: 10-Dec-2018)**	
	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)	135 (64)	151 (71)
Estimates of OS (months)				
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.80 (0.63, 1.01)	
p-value	0.011		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)	

NR = Not reached, NA = Not applicable

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)



Improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. 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 7).

Table 7 Efficacy results for Study MEK115306 (COMBI-d)

	Primary analysis (data cut-off: 26-Aug-2013)		Updated analysis (data cut-off: 12-Jan-2015)		5-year analysis (data cut-off: 10-Dec-2018)	
Endpoint	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
PFS[a]						
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	160 (76)	166 (78)
Median PFS (months) (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	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)		0.73 (0.59, 0.91)	
P value	0.035		<0.001[f]		NA	
ORR[b] % (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	69 (62.5, 75.4)	54 (46.8, 60.6)
ORR difference (95% CI)	15[e] (5.9, 24.5)		15[e] (6.0, 24.5)		NA	
P value	0.0015		0.0014[f]		NA	
DoR[c] **(months)** Median (95% CI)	9.2[d] (7.4, NR)	10.2[d] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1, 13.8)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

[a] Progression-free survival (investigator assessed)
[b] Overall Response Rate = Complete Response + Partial Response
[c] Duration of response
[d] At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
[e] ORR difference calculated based on the ORR result not rounded
[f] 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 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS with a key secondary endpoint of PFS. Subjects 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 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at Baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

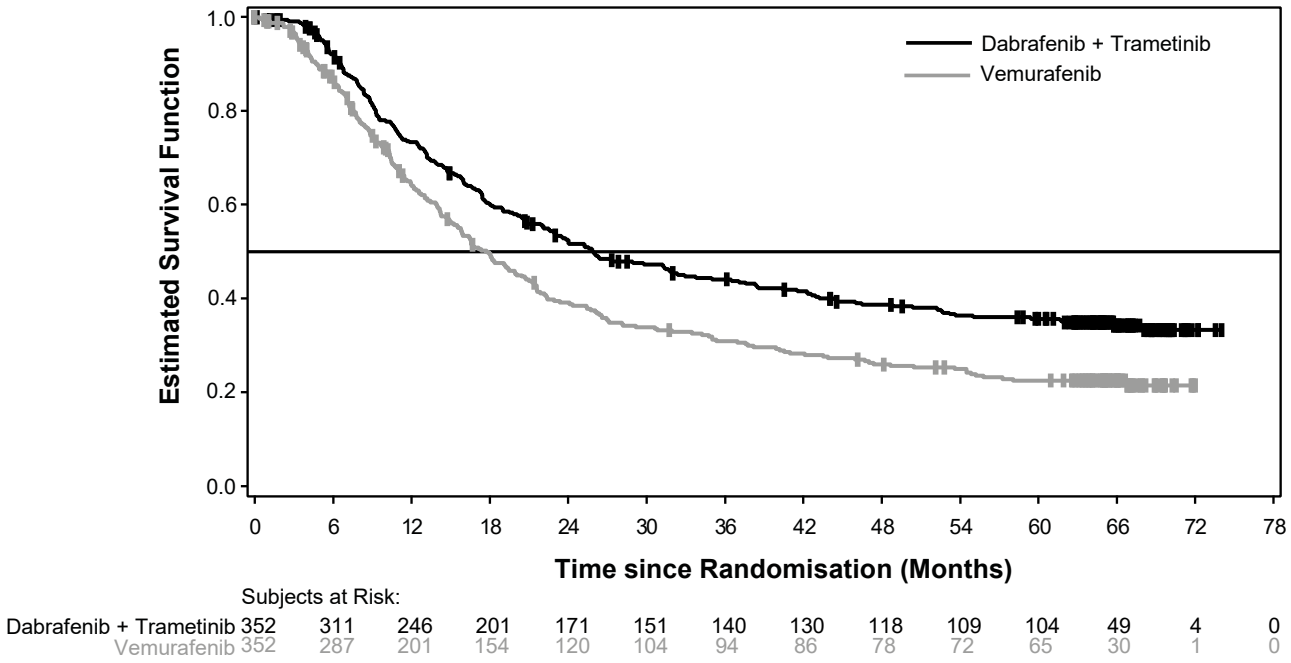
Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 8. From an OS analysis at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 8, Figure 2). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 2). 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 8 Overall Survival results for Study MEK116513 (COMBI-v)

	OS analysis data cut-off: 13-Mar-2015)		5-year OS analysis (data cut-off: 08-Oct-2018)	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of patients				
Died (event), n (%)	155 (44)	194 (55)	216 (61)	246 (70)
Estimates of OS (months)				
Median (95% CI)	25.6 (22.6, NR)	18.0 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.66 (0.53, 0.81)		0.70 (0.58, 0.84)	
p-value	<0.001		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

Figure 2 Kaplan-Meier overall survival curves for Study MEK116513



Improvements for the secondary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to vemurafenib monotherapy. Improvements were also observed for ORR

and a longer DoR was observed in the combination arm compared to vemurafenib monotherapy (Table 9).

Table 9 Efficacy results for Study MEK116513 (COMBI-v)

	Primary analysis (Data cut-off: 17-Apr-2014)		**5-year analysis (Data cut-off: 08-Oct-2018)**	
Endpoint	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
PFS[a]				
Progressive disease or death, n (%)	166 (47)	217 (62)	257 (73)	259 (74)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.62 (0.52, 0.74)	
P value	<0.001		NA	
ORR[b] % (95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (62.2, 72.2)	53 (47.2, 57.9)
ORR difference (95% CI)	13 (5.7, 20.2)		NA	
P value	0.0005		NA	
DoR[c] (months) Median (95% CI)	13.8[d] (11.0, NR)	7.5[d] (7.3, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

[a] Progression-free survival (investigator assessed)
[b] Overall Response Rate = Complete Response + Partial Response
[c] Duration of response
[d] At the time of the reporting the majority (59% of dabrafenib+trametinib and 42% of vemurafenib) of investigator-assessed responses were still ongoing
NR = Not reached
NA = Not applicable

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. 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).

Patients with brain metastases
The efficacy and safety of dabrafenib in combination with trametinib in patients with BRAF mutation-positive melanoma that has metastasised to the brain was studied in a non-randomised, open-label, multicentre, Phase II study (COMBI-MB study). A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.
- Cohort C: patients with BRAF V600D/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 BRAF V600D/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 Tumors (RECIST) version 1.1. Intracranial response assessed by the investigator in Cohorts B, C and D were secondary endpoints of the study. Due to small sample size reflected by wide 95% CIs, the results in Cohorts B, C, and D should be interpreted with caution. Efficacy results are summarised in Table 10.

Table 10 Efficacy data by investigator assessment from COMBI-MB study

	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)
Overall response rate, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
Progression-free survival, 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)
Overall survival, median, months (95% CI)				
	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 reached				

- *Dabrafenib monotherapy*

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

Included in these clinical trials 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 clinical trials the activity appears lower than in V600E tumours.

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

Previously untreated patients (results from the Phase III study [BREAK-3])
The efficacy and safety of dabrafenib were evaluated in a Phase III randomised, open-label study [BREAK 3] comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation-positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Patients with melanoma driven by BRAF mutations other than V600E were excluded.

The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to PFS per investigator assessment. Patients on the DTIC arm were allowed to cross over to dabrafenib 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 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 with 6-months additional follow up are summarised in Table 11. OS data from a further post-hoc analysis based on a 18 December 2012 data cut are shown in Figure 3.

Table 11 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				
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.

As of 25 June 2012 cut-off, thirty five subjects (55.6%) of the 63 randomised to DTIC had crossed over to dabrafenib and 63% of subjects randomised to dabrafenib and 79% of subjects randomised to DTIC had progressed or died. Median PFS after cross-over was 4.4 months.

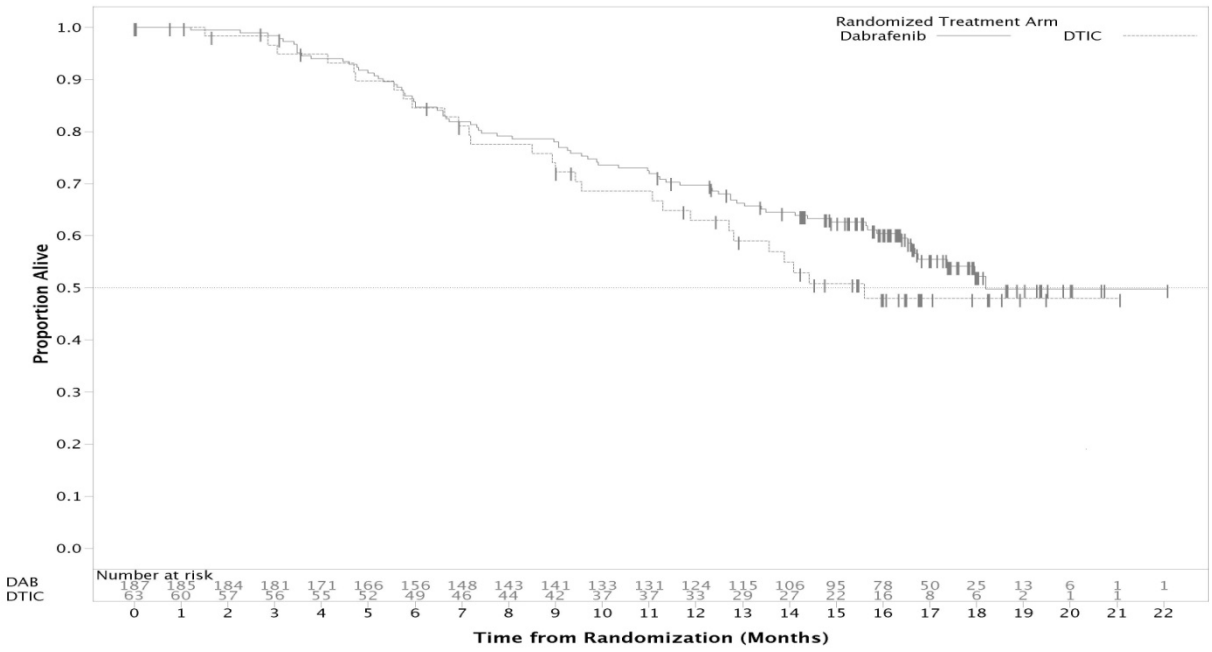
Table 12 Survival data from the primary analysis and post-hoc analyses

Cut-off date	**Treatment**	**Number of deaths (%)**	**Hazard ratio (95% CI)**
December 19, 2011	DTIC	9 (14%)	0.61 (0.25, 1.48) (a)
	dabrafenib	21 (11%)	
June 25, 2012	DTIC	21 (33%)	0.75 (0.44, 1.29) (a)
	dabrafenib	55 (29%)	
December 18, 2012	DTIC	28 (44%)	0.76 (0.48, 1.21) (a)
	dabrafenib	78 (42%)	

(a) Patients were not censored at the time of cross-over

OS data from a further post-hoc analysis based on the 18 December 2012 data cut demonstrated a 12-month OS rate of 63% and 70% for DTIC and dabrafenib treatments, respectively.

Figure 3 Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



Patients with brain metastases (results from the Phase II study (BREAK-MB)
BREAK-MB was a multicentre, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF mutation-positive (V600E or V600K) melanoma metastatic to the brain. Subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who received prior local therapy for brain metastasis).

The primary endpoint of the study was overall intracranial response rate (OIRR) in the V600E patient population, as assessed by investigators. The confirmed OIRR and other efficacy results per investigator assessment are presented in Table 13.

Table 13 Efficacy data in patients with brain metastases (BREAK-MB Study)

	All Treated Subjects Population			
	BRAF V600E (Primary)		BRAF V600K	
	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 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=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; 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 mutation-positive subjects.

Patients who were previously untreated or failed at least one prior systemic therapy (results from the Phase II [BREAK-2])
BRF113710 (BREAK-2) was a multicentre, single-arm study that enrolled 92 subjects with metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma.

The investigator assessed confirmed response rate in patients with BRAF V600E metastatic melanoma (n=76) was 59% (95% CI: 48.2, 70.3) and the median DoR was 5.2 months (95% CI: 3.9, not calculable) based on a median follow-up time of 6.5 months. In patients with BRAF V600K mutation-positive metastatic melanoma (n=16) the response rate was 13% (95% CI: 0.0, 28.7) with a median DoR of 5.3 months (95% CI: 3.7, 6.8). Although limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E mutation-positive tumours.

Adjuvant treatment of Stage III melanoma

BRF115532 (COMBI-AD)
The efficacy and safety of dabrafenib in combination with trametinib were studied in a Phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with Stage III (Stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC) cutaneous melanoma with a BRAF V600 E/K mutation, following complete resection.

Patients were randomised 1:1 to receive either combination therapy (dabrafenib 150 mg twice daily and trametinib 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 randomisation. Any prior systemic anti-cancer 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 versus V600K) and stage of disease prior to surgery using the American Joint Committee on Cancer (AJCC) 7th edition Melanoma Staging System (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour

assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint), freedom from relapse (FFR) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%).

The median duration of follow-up at the time of the primary analysis 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 Table 14. The study showed a statistically significant difference for the primary outcome of investigator-assessed RFS between treatment arms, with a median RFS of 16.6 months for the placebo arm and not yet reached for the combination arm (HR: 0.47; 95% confidence interval: (0.39, 0.58); $p=1.53\times10^{-14}$). The observed RFS benefit was consistently demonstrated across subgroups of patients including age, sex and race. Results were also consistent across stratification factors for disease stage and BRAF V600 mutation type.

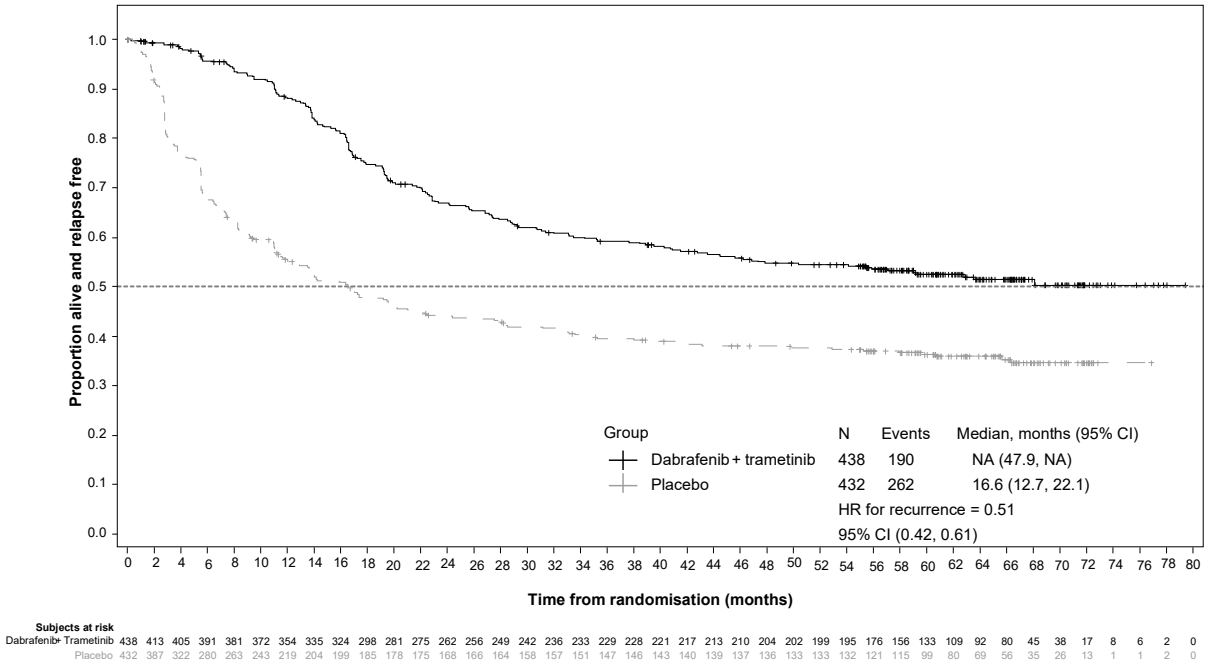
Table 14 Investigator-assessed RFS results for Study BRF115532 (COMBI-AD primary analysis)

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

[1] Hazard ratio is obtained from the stratified Pike model.
[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)
NE = not estimable

Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: 0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 4 Kaplan-Meier RFS curves for Study BRF115532 (ITT population, updated results)



At the time of the final OS analysis, the median duration of follow-up was 8.3 years in the combination arm and 6.9 years in the placebo arm. The observed difference in OS was not statistically significant (HR: 0.80; 95% CI: 0.62, 1.01) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year OS rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year OS rates were 66% in the combination arm and 63% in the placebo arm.

Non-small cell lung cancer

Study BRF113928

The efficacy and safety of dabrafenib in combination with trametinib was studied in a Phase II, three-cohort, multicentre, non-randomised and open-label study in which patients with stage IV BRAF V600E mutant NSCLC were enrolled. The primary endpoint was ORR using the RECIST 1.1 assessed by the investigator. Secondary endpoints included DoR, PFS, 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 (dabrafenib 150 mg twice daily), 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 59 patients enrolled. 57 patients had 1-3 lines of previous systemic treatment for their metastatic disease. 2 patients had no previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 34 patients. All patients received study medicinal product as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy cohorts B and C, most patients were Caucasian (>90%), and similar female versus male (54% versus 46%), with a median age of 64 years in second line or higher patients and 68 years in the first line patients. Most patients (94%) enrolled in the combination therapy treated cohorts had an ECOG performance status of 0 or 1. 26 (28%) had never smoked. The majority of patients had a non-squamous histology. In the previously

treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the primary endpoint of investigator-assessed ORR in the first line population was 61.1% (95% CI, 43.5%, 76.9%), and in the previously treated population was 66.7% (95% CI, 52.9%, 78.6%). These met the statistical significance to reject the null hypothesis that the ORR of dabrafenib in combination with trametinib for this NSCLC population was less than or equal to 30%. The ORR results assessed by IRC were consistent with the investigator assessment. The efficacy of the combination with trametinib was superior when indirectly compared to dabrafenib monotherapy in Cohort A. The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 15.

Table 15 Summary of efficacy in the combination treatment cohorts based on investigator and independent radiology review

Endpoint	Analysis	Combination 1st line N=36[1]	Combination 2nd line plus N=57[1]
Overall confirmed response n (%) (95% CI)	By Investigator	23 (63.9%) (46.2, 79.2)	39 (68.4%) (54.8, 80.1)
	By IRC	23 (63.9%) (46.2, 79.2)	36 (63.2%) (49.3, 75.6)
Median DoR Months (95% CI)	By Investigator	10.2 (8.3, 15.2)	9.8 (6.9, 18.3)
	By IRC	15.2 (7.8, 23.5)	12.6 (5.8, 26.2)
Median PFS Months (95% CI)	By Investigator	10.8 (7.0, 14.5)	10.2 (6.9, 16.7)
	By IRC	14.6 (7.0, 22.1)	8.6 (5.2, 16.8)
Median OS Months (95% CI)	-	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)

[1] Data cut-off: 7 January 2021

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). In the Phase III study MEK115306 no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to >500 msec; QTcB was increased more than 60 msec from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1%) treated with trametinib in combination with dabrafenib had a QTcB Grade 3 increase (>500 msec). Two of these patients had a QTcB Grade 3 increase (>500 msec) that was also an increase >60 msec from baseline.

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

Other studies - pyrexia management analysis
Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)
Pyrexia is observed in patients treated with dabrafenib and trametinib 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 dabrafenib in case of pyrexia (fever ≥38.5°C). 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 medicinal products when patient's temperature is ≥38°C (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of

grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with dabrafenib in one or more subsets of the paediatric population in melanoma and solid malignant tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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. A decrease in exposure was 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}, AUC(0-τ) and predose concentration (Cτ) 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 dabrafenib 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.

Biotransformation

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 metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hrs while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 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.

Medicinal product interactions

Effects of other medicinal products on dabrafenib
Dabrafenib is a substrate of human P-glycoprotein (P-gp) and human 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 P-gp or BCRP is low. Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of P-gp *in vitro*.

Effects of dabrafenib on other medicinial products
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*, and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro,* the risk of a drug-drug interaction at these transporters is minimal based on clinical exposure of dabrafenib and its metabolites.

Elimination

Terminal half-life of dabrafenib following an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after a single oral dose is 8 hours due to absorption-limited elimination after oral administration (flip-flop pharmacokinetics). IV plasma clearance is 12 l/hr.

After an oral dose, the major route of elimination of dabrafenib is metabolism, mediated via CYP3A4 and CYP2C8. Dabrafenib related material is excreted primarily in faeces, with 71% of an oral dose recovered in faeces; 23% of the dose was recovered in urine in the form of metabolites only.

Special patient populations

Hepatic impairment
A population pharmacokinetic analysis indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2).

Renal impairment
A population pharmacokinetic analysis suggests that mild renal impairment does not affect oral clearance of dabrafenib. Although data in moderate renal impairment are limited these data may indicate no clinically relevant effect. No data are available in subjects with severe renal impairment (see section 4.2).

Elderly
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 subjects ≥75 years of age, relative to subjects <75 years old.

Body weight and gender
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
The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. There are insufficient data to evaluate the potential effect of other races on dabrafenib pharmacokinetics.

Paediatric population
The pharmacokinetic exposures of dabrafenib at a weight-adjusted dosage in adolescent patients were within range of those observed in adults.

5.3 Preclinical safety data

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.

In combined female fertility, early embryonic and embryo-foetal 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 oestrous cycle, mating or fertility indices. 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).

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see section 4.6).

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

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

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 human clinical exposure based on AUC).

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 human clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.

Combination with trametinib

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastrointestinal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Magnesium stearate
Colloidal silicone dioxide

Capsule shell

Red iron oxide (E172)
Titanium dioxide (E171)
Hypromellose (E464)

Printing ink

Black iron oxide (E172)
Shellac
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque white high-density polyethylene (HDPE) bottle with polypropylene screw cap and a silica gel desiccant.

Each bottle contains either 28 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Tafinlar 50 mg hard capsules

EU/1/13/865/001
EU/1/13/865/002

Tafinlar 75 mg hard capsules

EU/1/13/865/003
EU/1/13/865/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 08 May 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Lek Pharmaceuticals d.d.
Verovškova ulica 57
1526, Ljubljana
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000, Ljubljana
Slovenia

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg hard capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/001 28 capsules
EU/1/13/865/002 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tafinlar 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/001 28 capsules
EU/1/13/865/002 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 75 mg hard capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/003 28 capsules
EU/1/13/865/004 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tafinlar 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 75 mg capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/003 28 capsules
EU/1/13/865/004 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules
dabrafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tafinlar is and what it is used for

Tafinlar is a medicine that contains the active substance dabrafenib. It is used either on its own or in combination with another medicine containing trametinib in adults to treat a type of skin cancer called melanoma that has spread to other parts of the body, or cannot be removed by surgery.

Tafinlar in combination with trametinib is also used to prevent melanoma from coming back after it has been removed by surgery.

Tafinlar in combination with trametinib is also used to treat a type of lung cancer called non-small cell lung cancer (NSCLC).

Both cancers have a particular change (mutation) in a gene called BRAF at the V600 position. This mutation in the gene may have caused the cancer to develop. Your medicine targets proteins made from this mutated gene and slows down or stops the development of your cancer.

2. What you need to know before you take Tafinlar

Tafinlar should only be used to treat melanomas and NSCLC with the BRAF mutation. Therefore before starting treatment your doctor will test for this mutation.

If your doctor decides that you will receive treatment with the combination of Tafinlar and trametinib, **read the trametinib leaflet carefully as well as this leaflet.**

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Do not take Tafinlar
- **if you are allergic** to dabrafenib or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Warnings and precautions
Talk to your doctor before taking Tafinlar. Your doctor needs to know if you:
- have any **liver problems.**
- have or have ever had any **kidney problems**.
  Your doctor may take blood samples to monitor your liver and kidney function while you are taking Tafinlar.
- **have had a different type of cancer other than melanoma or NSCLC**, as you may be at greater risk of developing other skin and non-skin cancers when taking Tafinlar.

Before you take Tafinlar in combination with trametinib your doctor also needs to know if you:
- have heart problems such as heart failure or problems with the way your heart beats.
- have eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid leakage (chorioretinopathy).
- have any lung or breathing problems, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue.
- have or have had any gastrointestinal problems such as diverticulitis (inflamed pouches in the colon) or metastases to the gastrointestinal tract.

Check with your doctor if you think any of these may apply to you.

Conditions you may need to look out for
Some people taking Tafinlar develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you're taking this medicine. Some of these symptoms (bleeding, fever, changes to your skin and eye problems) are briefly mentioned in this section, but more detailed information is found in section 4, "Possible side effects".

Bleeding
Taking Tafinlar in combination with trametinib can cause serious bleeding including in your brain, the digestive system (such as stomach, rectum or intestine), lungs, and other organs, and can lead to death. Symptoms may include:
- headaches, dizziness, or feeling weak
- passing blood in the stools or passing black stools
- passing blood in the urine
- stomach pain
- coughing / vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Fever
Taking Tafinlar or the combination of Tafinlar and trametinib may cause fever, although it is more likely if you are taking the combination treatment (see also section 4). In some cases, people with fever may develop low blood pressure, dizziness or other symptoms.

Tell your doctor immediately if you get a temperature above 38ºC or if you feel a fever coming on while you are taking this medicine.

Heart disorder
Tafinlar can cause heart problems, or make existing heart problems worse (see also "Heart conditions" in section 4), in people taking Tafinlar in combination with trametinib.

Tell your doctor if you have a heart disorder. Your doctor will run tests to check that your heart is working properly before and during your treatment with Tafinlar in combination with trametinib. Tell your doctor immediately if it feels like your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, light-headedness, shortness of breath or swelling in the legs. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Changes in your skin which may indicate new skin cancer
Your doctor will check your skin before you start taking this medicine and regularly while you are taking it. **Tell your doctor immediately** if you notice any changes to your skin while taking this medicine or after treatment (see also section 4).

Eye problems
You should have your eyes examined by your doctor while you are taking this medicine.
Tell your doctor immediately if you get eye redness and irritation, blurred vision, eye pain or other vision changes during your treatment (see also section 4).
Tafinlar when given in combination with trametinib can cause eye problems including blindness. Trametinib is not recommended if you have ever had blockage of the vein draining the eye (retinal vein occlusion). Tell your doctor immediately if you get the following symptoms of eye problems: blurred vision, loss of vision or other vision changes, coloured dots in your vision or halos (seeing blurred outline around objects) during your treatment. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

➔ **Read the information about fever, changes in your skin and eye problems in section 4 of this leaflet. Tell your doctor, pharmacist or nurse if you get any of the signs and symptoms listed.**

Liver problems
Tafinlar in combination with trametinib can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Tell your doctor as soon as possible if you get any of these symptoms

Muscle pain
Tafinlar in combination with trametinib can result in the breakdown of muscle (rhabdomyolysis). **Tell your doctor** as soon as possible if you get any of these symptoms.
- muscle pain
- dark urine due to kidney damage

If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Hole in the stomach or intestine (perforation)
Taking the combination of Tafinlar and trametinib may increase the risk of developing holes in the gut wall. **Tell your doctor** as soon as possible if you have severe abdominal pain.

Serious skin reactions
Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib. Tell your doctor immediately if you notice any changes to your skin (see section 4 for symptoms to be aware of).

Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes
An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin. Tell your doctor if you get any of these symptoms.

Immune system disorders
Tafinlar in combination with trametinib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis or HLH) in which the immune system makes too many infection-fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems. Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

Tumour lysis syndrome
If you experience the following symptoms, tell your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the breakdown products of dying cancer cells (tumour lysis syndrome or TLS) and can lead to changes in kidney function (see also section 4).

Children and adolescents
Tafinlar is not recommended for children and adolescents. The effects of Tafinlar in people younger than 18 years old are not known.

Other medicines and Tafinlar
Before starting treatment, tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

Some medicines may affect how Tafinlar works, or make it more likely that you will have side effects. Tafinlar can also affect how some other medicines work. These include:
- **birth control medicines** (*contraceptives)* containing hormones, such as pills, injections, or patches
- warfarin and acenocoumarol, medicines used to **thin the blood**
- digoxin, used to treat **heart conditions**
- medicines to treat **fungal infections**, such as ketoconazole, itraconazole, voriconazole and posaconazole
- some calcium channel blockers, used to treat **high blood pressure**, such as diltiazem, felodipine, nicardipine, nifedipine or verapamil
- medicines to treat **cancer,** such as cabazitaxel
- some medicines to **lower fat (lipids)** in the blood stream, such as gemfibrozil
- some medicines used to treat certain **psychiatric conditions**, such as haloperidol
- some **antibiotics**, such as clarithromycin, doxycyline and telithromycin
- some medicines **for tuberculosis** (TB), such as rifampicin
- some medicines that reduce **cholesterol** levels, such as atorvastatin and simvastatin
- some **immunosuppressants**, such as cyclosporin, tacrolimus and sirolimus
- some **anti-inflammatory** medicines, such as dexamethasone and methylprednisolone
- some medicines to treat **HIV**, such as ritonavir, amprenavir, indinavir, darunavir, delavirdine, efavirenz, fosamprenavir, lopinavir, nelfinavir, tipranavir, saquinavir and atazanavir
- some medicines used for **pain relief**, such as fentanyl and methadone
- medicines to treat seizures (**epilepsy**), such as phenytoin, phenobarbital, primidone, valproic acid or carbamazepine
- **antidepressant** medicines such as nefazodone and the herbal medicine St John's wort (*Hypericum perforatum)*

➔ **Tell your doctor, pharmacist or nurse** if you are taking any of these (or if you are not sure). Your doctor may decide to adjust your dose.

Keep a list of the medicines you take, so you can show it to your doctor, pharmacist or nurse.

Pregnancy, breast-feeding and fertility
Tafinlar is not recommended during pregnancy.

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine. Tafinlar is not recommended during pregnancy, since it may potentially harm an unborn baby.
- If you are a woman who could become pregnant you must use a reliable birth control method while you are taking Tafinlar and for at least 2 weeks after you stop taking it and for at least 16 weeks following the last dose of trametinib when given in combination with Tafinlar.
- Birth control medicines containing hormones (such as pills, injections or patches) may not work as well while you are taking Tafinlar or combination treatment (Tafinlar as well as trametinib). You need to use another effective method of birth control so you do not become pregnant while you are taking this medicine. Ask your doctor, pharmacist or nurse for advice.
- If you do become pregnant while you are taking this medicine, tell your doctor immediately.

Tafinlar is not recommended while breast-feeding.
It is not known whether the ingredients of this medicine can pass into breast milk.
If you are breast-feeding, or planning to breast-feed, you must tell your doctor. You and your doctor will decide if you will take this medicine or breast-feed.

Fertility – both men and women
Animal studies have shown that the active substance dabrafenib may permanently reduce male fertility. In addition, men who are taking Tafinlar may have a reduced sperm count and their sperm count may not return to normal levels after they stop taking this medicine.

Prior to starting treatment with Tafinlar, talk to your doctor about options to improve your chances to have children in the future.

Taking Tafinlar with trametinib: trametinib may impair fertility in both men and women.

If you have any further questions on the effect of this medicine on sperm count, ask your doctor, pharmacist or nurse.

Driving and using machines
Tafinlar can have side effects that may affect your ability to drive or use machines.
Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.
Descriptions of these effects can be found in sections 2 and 4.
Discuss with your doctor, pharmacist or nurse if you are unsure about anything. Even your disease, symptoms and treatment situation may affect your ability to drive or use machines.

3. How to take Tafinlar

Always take this medicine exactly as your doctor, pharmacist or nurse has told you to. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
The usual dose of Tafinlar either used alone or in combination with trametinib is two 75 mg capsules twice a day (corresponding to a daily dose of 300 mg). The recommended dose of trametinib, when used in combination with Tafinlar, is 2 mg once a day.

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

Tafinlar are also available as 50 mg capsules if a dose reduction is recommended.

Don’t take more Tafinlar than your doctor has recommended, since this may increase the risk of side effects.

How to take it
Swallow the capsules whole with water, one after the other.

Don’t chew or crush the capsules, since they will otherwise lose their effect.

Take Tafinlar twice a day, on an empty stomach. This means that
- after taking Tafinlar, you must wait **at least 1 hour** before eating.
- after eating, you must wait **at least 2 hours** before taking Tafinlar.

Take Tafinlar in the morning and evening, about 12 hours apart. Take your morning and evening doses of Tafinlar at the same times every day. This will increase the chance of remembering to take the capsules.

Don’t take the morning and evening doses of Tafinlar at the same time.

If you take more Tafinlar than you should
If you take too many capsules of Tafinlar, **contact your doctor, pharmacist or nurse for advice.** If possible, show them the Tafinlar pack with this leaflet.

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

If you stop taking Tafinlar
Take Tafinlar for as long as your doctor recommends. Do not stop unless your doctor, pharmacist or nurse advises you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

How should you take Tafinlar in combination with trametinib
- Take Tafinlar in combination with trametinib exactly as your doctor, pharmacist or nurse tells you. Do not change your dose or stop Tafinlar or trametinib unless your doctor, pharmacist or nurse tells you to.
- Take **Tafinlar twice daily** and take **trametinib once daily**. It may be good for you to get into the habit of taking both medicines at the same times each day. The Tafinlar doses should be about 12 hours apart. Trametinib when given in combination with Tafinlar should be taken with **either** the morning dose of Tafinlar **or** the evening dose of Tafinlar.
- Take Tafinlar and trametinib on an empty stomach, at least one hour before or two hours after a meal. Take whole with a full glass of water.
- If you miss a dose of Tafinlar or trametinib, take it as soon as you remember. Do not make up for missed doses and just take your next dose at your regular time:
    - If it is less than 6 hours to your next scheduled dose of Tafinlar, which is taken twice daily.
    - If it is less than 12 hours to your next scheduled dose of trametinib, which is taken once daily.
- If you take too much Tafinlar or trametinib, immediately contact your doctor, pharmacist or nurse. Take Tafinlar capsules and trametinib tablets with you when possible. If possible, show them the Tafinlar and trametinib pack with each leaflet.
- If you get side effects your doctor may decide that you should take lower doses of Tafinlar and / or trametinib. Take the doses of Tafinlar and trametinib exactly as your doctor, pharmacist or nurse tells you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects
Bleeding problems
Tafinlar can cause serious bleeding problems, especially in your brain when taken in combination with trametinib. Call your doctor or nurse and get medical help right away if you have any unusual signs of bleeding, including:
- headaches, dizziness, or weakness
- coughing up of blood or blood clots
- vomit containing blood or that looks like "coffee grounds"
- red or black stools that look like tar

Fever
Taking Tafinlar may cause fever in more than 1 in 10 people. **Tell your doctor, pharmacist or nurse immediately if you get a fever (temperature 38ºC or above) or if you feel a fever coming on while you are taking this medicine**. They will carry out tests to find out if there are other causes for the fever and treat the problem.

In some cases, people with fever may develop low blood pressure and dizziness. If the fever is severe, your doctor may recommend that you stop taking Tafinlar, or Tafinlar and trametinib, while they treat the fever with other medicines. Once the fever is controlled, your doctor may recommend that you start taking Tafinlar again.

Heart conditions
Tafinlar can affect how well your heart pumps blood when taken in combination with trametinib. It is more likely to affect people who have an existing heart problem. You will be checked for any heart problems while you are taking Tafinlar in combination with trametinib. Signs and symptoms of heart problems include:
- feeling like your heart is pounding, racing, or beating irregularly
- dizziness
- tiredness
- feeling lightheaded
- shortness of breath
- swelling in the legs

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

Changes in your skin
Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib (frequency not known). If you notice any of the following:
- reddish patches on the trunk that are circular or target-shaped, with central blisters. Skin peeling. Ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).
- widespread rash, fever, and enlarged lymph nodes (DRESS-syndrome or drug hypersensitivity syndrome).

➔ **stop using the medicine and seek medical attention immediately.**

Patients taking Tafinlar may commonly (may affect up to 1 in 10 people) develop a different type of skin cancer called *cutaneous squamous cell carcinoma (cuSCC)*. Others may develop a type of skin cancer called *basal cell carcinoma (BCC)*. Usually, these skin changes remain local and can be removed with surgery and treatment with Tafinlar can be continued without interruption.

Some people taking Tafinlar may also notice that new melanomas have appeared. These melanomas are usually removed by surgery and treatment with Tafinlar can be continued without interruption.

Your doctor will check your skin before you start taking Tafinlar, then check it again every month while you are taking this medicine and for 6 months after you stop taking it. This is to look for any new skin cancers.

Your doctor will also check your head, your neck, your mouth, your lymph glands and you will have scans of your chest and stomach area (called CT scans) regularly. You may also have blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

Check your skin regularly whilst taking Tafinlar
If you notice any of the following:
- new wart
- skin sore or reddish bump that bleeds or does not heal
- change of a mole in size or colour
    - ➔ **Tell your doctor, pharmacist or nurse as soon as possible** if you get any of these symptoms - either for the first time or if they get worse.

Skin reactions (rash) can happen while taking Tafinlar in combination with trametinib. **Talk to your doctor** if you get a skin rash while taking Tafinlar in combination with trametinib.

Eye problems
Patients taking Tafinlar alone can uncommonly (may affect up to 1 in 100 people) develop an eye problem called uveitis, which could damage your vision if it is not treated. This may occur commonly (may affect up to 1 in 10 people) in patients taking Tafinlar in combination with trametinib.

Uveitis may develop rapidly and the symptoms include:
- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots before the eyes
    - ➔ **Contact your doctor, pharmacist or nurse immediately** if you get these symptoms.

Tafinlar can cause eye problems when taken in combination with trametinib. Trametinib is not recommended if you have ever had a blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye examination before you take Tafinlar in combination with trametinib and while you are taking it. Your doctor may ask you to stop taking trametinib or refer you to a specialist, if you develop signs and symptoms in your vision that include:
- loss of vision
- eye redness and irritation
- coloured dots in your vision
- halo (seeing a blurred outline around objects)
- blurred vision
    - ➔ **Contact your doctor, pharmacist or nurse immediately if you get these symptoms.**

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

Immune system disorders
If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. These may be signs of a condition where the immune system

makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

Tumour lysis syndrome
Tell your doctor immediately if you experience the following symptoms: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be signs of a condition resulting from a rapid breakdown of cancer cells which in some people may be fatal (tumour lysis syndrome or TLS), see section 2 (frequency not known).

Possible side effects in patients taking Tafinlar alone

The side effects that you may see when you take Tafinlar alone are as follows:

Very common side effects (may affect more than 1 in 10 people)
- Papilloma (a type of skin tumour which is usually not harmful)
- Decreased appetite
- Headache
- Cough
- Feeling sick (nausea), being sick (vomiting)
- Diarrhoea
- Thickening of the outer layers of the skin
- Unusual hair loss or thinning
- Rash
- Reddening and swelling of the palms, fingers and soles of the feet (see "Changes in your skin" earlier in section 4)
- Joint pain, muscle pain, or pain in the hands or feet
- Fever (see "Fever" earlier in section 4)
- Lack of energy
- Chills
- Feeling weak

Common side effects (may affect up to 1 in 10 people)
- Skin effects including cutaneous squamous cell carcinoma (a type of skin cancer), wart-like growths, skin tags, uncontrolled skin growths or lesions (basal cell carcinoma), dry skin, itching or redness of skin, patches of thick, scaly, or crusty skin (actinic keratosis), skin lesions, skin reddening, increased sensitivity of the skin to sun
- Constipation
- Flu-like illness
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)

Common side effects that may show up in your blood tests
- Low levels of phosphate (hypophosphataemia) in the blood
- Increase in blood sugar level (hyperglycaemia)

Uncommon side effects (may affect up to 1 in 100 people)
- New melanoma
- Allergic reaction (hypersensitivity)
- Inflammation of the eye (uveitis, see "Eye problems" earlier in section 4))
- Inflammation of the pancreas (causing strong abdominal pain)
- Inflammation of the fatty layer under the skin (panniculitis)
- Kidney problems, kidney failure
- Inflammation of kidneys
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Possible side effects when Tafinlar and trametinib are taken together

When you take Tafinlar and trametinib together you may get any of the side effects given in the lists above, although the frequency may change (increase or decrease).

You may also get **additional side effects due to taking trametinib** at the same time as Tafinlar.

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

Please also read the trametinib package leaflet for details of the side effects you may get with trametinib.

The side effects that you may see when you take Tafinlar in combination with trametinib are as follows:

Very common side effects (may affect more than 1 in 10 people)
- Nasal and throat inflammation
- Decreased appetite
- Headache
- Dizziness
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious (haemorrhage)
- Cough
- Stomach ache
- Constipation
- Diarrhoea
- Feeling sick (nausea), being sick (vomiting)
- Rash, dry skin, itching, skin reddening
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Lack of energy, feeling weak
- Chills
- Swelling of the hands or feet (oedema peripheral)
- Fever
- Flu-like illness

Very common side effects that may show up in your blood tests
- Abnormal blood test results related to the liver

Common side effects (may affect up to 1 in 10 people)
- Infection of the urinary system
- Skin effects including infection of the skin (cellulitis), inflammation of hair follicles in the skin, nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles, skin rash with pus-filled blisters, cutaneous squamous cell carcinoma (a type of skin cancer), papilloma (a type of skin tumour which is usually not harmful), wart-like growths, increased sensitivity of the skin to sun (see also “Changes in your skin” earlier in section 4)
- Dehydration (low levels of water or fluid)
- Blurred vision, eyesight problems, inflammation of the eye (uveitis)
- Heart pumping less efficiently
- Low blood pressure (hypotension)
- Localised tissue swelling
- Shortness of breath
- Dry mouth

- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Acne-like problems
- Thickening of the outer layer of the skin (hyperkeratosis), patches of thick, scaly, or crusty skin (actinic keratosis), chapping or cracking of the skin
- Increased sweating, night sweats
- Unusual hair loss or thinning
- Red, painful hands and feet
- Inflammation of the fatty layer under the skin (panniculitis)
- Inflammation of the mucosa
- Swelling of the face
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)
- Irregular heartbeat (atrioventricular block)

Common side effects that may show up in your blood tests
- Low levels of white blood cells
- Decrease in number of red blood cells (anaemia), blood platelets (cells that help blood to clot), and a type of white blood cells (leukopenia)
- Low levels of sodium (hyponatraemia) or phosphate (hypophosphataemia) in the blood
- Increase in blood sugar level
- Increase in creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Increase in some substances (enzymes) produced by the liver

Uncommon side effects (may affect up to 1 in 100 people)
- Appearance of new skin cancer (melanoma)
- Skin tags
- Allergic reactions (hypersensitivity)
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) and swelling around the eyes
- Heart rate that is lower than the normal range and/or a decrease in heart rate
- Inflammation of the lung (pneumonitis)
- Inflammation of pancreas
- Inflammation of the intestines (colitis)
- Kidney failure
- Inflammation of the kidneys
- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Rare side effects (may affect up to 1 in 1 000 people)
- A hole (perforation) in the stomach or intestines

Not known (frequency cannot be estimated from the available data)
- Inflammation of the heart muscle (myocarditis) which can result in breathlessness, fever, palpitations and chest pain
- Inflamed, flaky skin (exfoliative dermatitis)
- Skin reactions localised in tattoos

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tafinlar

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

Do not use this medicine after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tafinlar contains
- The active substance is dabrafenib. Each hard capsule contains dabrafenib mesilate equivalent to 50 mg or 75 mg of dabrafenib.
- The other ingredients are: microcrystalline cellulose, magnesium stearate, colloidal silicone dioxide, red iron oxide (E172), titanium dioxide (E171), and hypromellose (E464). Further, the capsules are printed with black ink that contains black iron oxide (E172) shellac and propylene glycol.

What Tafinlar looks like and contents of the pack
Tafinlar 50 mg hard capsules are opaque dark red and imprinted with “GS TEW” and “50 mg”.
Tafinlar 75 mg hard capsules are opaque dark pink and imprinted with “GS LHF” and “75 mg”.

The bottles are opaque white plastic with threaded plastic closures.

The bottles also include a silica gel desiccant in a small cylinder-shaped container. The desiccant must be kept inside the bottle and must not be eaten.

Tafinlar 50 mg and 75 mg hard capsules are available in packs containing 28 or 120 capsules. Not all pack sizes may be marketed in your country.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.