ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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).

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 anticancer 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 therefore dabrafenib should 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).

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).

Therapy should be interrupted if the patient's temperature is ≥38.5ºC. Patients should be evaluated for signs and symptoms of infection (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.		
*Please refer to the trametinib SmPC, Posology and method of administration, for dosing instructions for treatment with trametinib monotherapy.		

Table 2 Dose modification schedule based on the grade of any Adverse Events (AE)

Grade (CTC-AE)*	**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 events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0	

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.

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 pyrexia, 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

Pyrexia
When dabrafenib is used alone and in combination with trametinib, therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5°C (please refer to Table 2 for dose modification guidance). Trametinib should be continued at the same dose. 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).

Upon resolution of pyrexia dabrafenib should be restarted with appropriate anti-pyretic prophylaxis, 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.

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 absolute decrease of >10% in LVEF compared to baseline 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.

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 have not yet been established in children and adolescents (<18 years). 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

The dabrafenib capsules are to be swallowed whole with water. The capsules 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.

Trametinib in combination with dabrafenib in patients with brain metastases

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

New malignancies

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

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 studies MEK115306 and MEK116513 in patients with metastatic melanoma, cuSCC occurred in 10% (22/211) of patients receiving dabrafenib as a single agent and in 18% (63/349) of patients receiving vemurafenib as a single agent, respectively. In the integrated safety population of patients with metastatic melanoma and advanced NSCLC, cuSCC occurred in 2% (13/641) 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.

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 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 malignancy

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 (for women) are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts 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 for additional information (see section 4.4).

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.

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 subjects 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 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).

For patients with 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 with dabrafenib should be interrupted if the patient's temperature is ≥38.5ºC (please refer to Table 2 for dose modification guidance). Patients should be evaluated for signs and symptoms of infection. Dabrafenib can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. If fever is associated with other severe signs or symptoms, dabrafenib should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2). No dose modification of trametinib is required when taken in combination with dabrafenib.

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 25% of patients in clincial studies when dabrafenib is used in combination with trametinib. 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 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 melanoma patient and recurred following re-challenge at a reduced dose. 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.

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

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.

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).

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).

Agents that increase gastric pH might decrease the bioavailability of dabrafenib and should be avoided when possible (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 Normalized 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. Use caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Avoid co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4.

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 Pgp may also be induced as well as other transporters, e.g. MRP-2, BCRP and OATP1B1/1B3.

In vitro, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical drug interaction study, C_{max} and AUC of oral midazolam (a CYP3A4 substrate) decreased by 61% and 74%, respectively with co-administration of repeat-dose dabrafenib using a formulation with lower bioavailability than dabrafenib formulation.

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)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptic (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin, 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 may increase and patients should be monitored for toxicity and dosage of these agents may need to be adjusted.

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

Effects of dabrafenib on substance transport systems

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

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 PK 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 4 weeks following discontinuation of dabrafenib and 4 months following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as a barrier method, 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.

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 studies including 578 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg twice daily. The most common adverse drug reactions (ADRs) (incidence ≥15%) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

The safety of dabrafenib in combination with trametinib has been evaluated in the integrated safety population of 641 patients with BRAF V600 mutant unresectable or metastatic melanoma and

advanced NSCLC treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 (see section 5.1).

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

Tabulated summary of adverse reactions

ADRs which were reported are listed below by MedDRA body system organ class and by frequency. The following convention has been utilised for the classification of frequency:

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
Not known	(cannot be estimated from the available data)

Table 3 Adverse reactions reported in the integrated safety population of dabrafenib monotherapy (n=578)

System Organ Class	Frequency (all grades)	Adverse Reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma
		Seborrhoeic keratosis
		Acrochordon (skin tags)
		Basal cell carcinoma
	Uncommon	New primary melanoma
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Nausea
		Vomiting
		Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
		Alopecia
		Rash
		Palmar-plantar erythrodysaesthesia syndrome
	Common	Dry skin
		Pruritus
		Actinic keratosis
		Skin lesion
		Erythema
		Photosensitivity reaction

	Uncommon	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 reported in the integrated safety population of dabrafenib in combination with trametinib (n=641)

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

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

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

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.

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 cuCSS and the events occurred later than with dabrafenib monotherapy with a median time to onset of 31 weeks. All patients receiving dabrafenib as monotherapy or in combination with trametinib who developed cuSCC continued on treatment without dose modification.

New primary melanoma

New primary melanomas have been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib in melanoma studies. Cases were managed with excision and did not require treatment modification (see section 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% (7/641) of patients in the integrated safety population of dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy and in combination with trametinib. Patients should be monitored as clinically appropriate.

Haemorrhage

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

LVEF reduction/Left ventricular dysfunction

Decreased LVEF has been reported in 8% (54/641) of patients in the integrated safety population of dabrafenib in combination with trametinib. Most cases were asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function. Please refer to the trametinib 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 (26%) although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%) and no Grade 4 occurrences being reported.

Hypophosphataemia

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

Pancreatitis

Pancreatitis has been reported in dabrafenib monotherapy and in combination with trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis (see section 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=641), 180 patients (28%) were ≥65 years of age, 50 patients (8%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

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 inhibitor, ATC code: L01XE23

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 studies 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 studies (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

Melanoma

- *Dabrafenib in combination with trametinib*

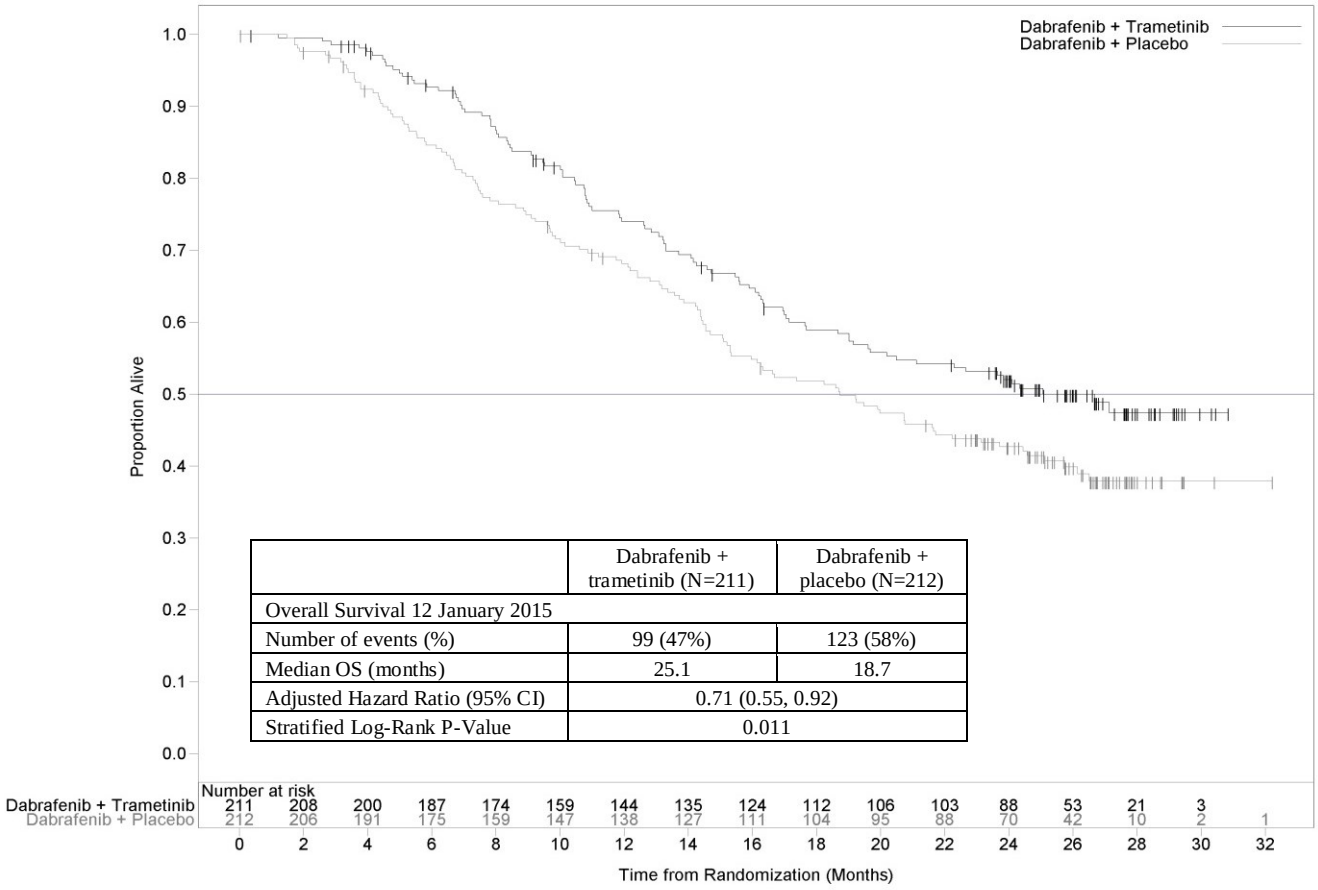
Treatment-naïve patients
The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two Phase III studies and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

The final OS analysis (12 January 2015) demonstrated a statistically significant improvement in OS for the combination compared with dabrafenib monotherapy (Figure 1). The 1-year (74%) and 2-year (51%) OS estimates for the combination arm were greater than those for dabrafenib monotherapy (68% and 42% respectively).

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



	Dabrafenib + trametinib (N=211)	Dabrafenib + placebo (N=212)
Overall Survival 12 January 2015		
Number of events (%)	99 (47%)	123 (58%)
Median OS (months)	25.1	18.7
Adjusted Hazard Ratio (95% CI)	0.71 (0.55, 0.92)	
Stratified Log-Rank P-Value	0.011	

Statistically significant improvements were observed for the primary endpoint of PFS and secondary endpoint of overall response rate (ORR). A longer duration of response (DoR) is also observed (Table 6).

Table 6 Efficacy results for Study MEK115306 (COMBI-d)

Endpoint	**Dabrafenib + Trametinib (N=211)**	**Dabrafenib + Placebo (N=212)**	**Dabrafenib + Trametinib (N=211)**	**Dabrafenib + Placebo (N=212)**
Data cut-off date	**26 August 2013**		**12 January 2015**	
PFS[a]				
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)
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)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)	
P value	0.035		<0.001	
ORR[b] (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8,74.8)	53 (46.3, 60.2)
ORR difference (95% CI)	15[e] (5.9, 24.5)		15[e] (6.0, 24.5)	
P value	0.0015		0.0014	
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)

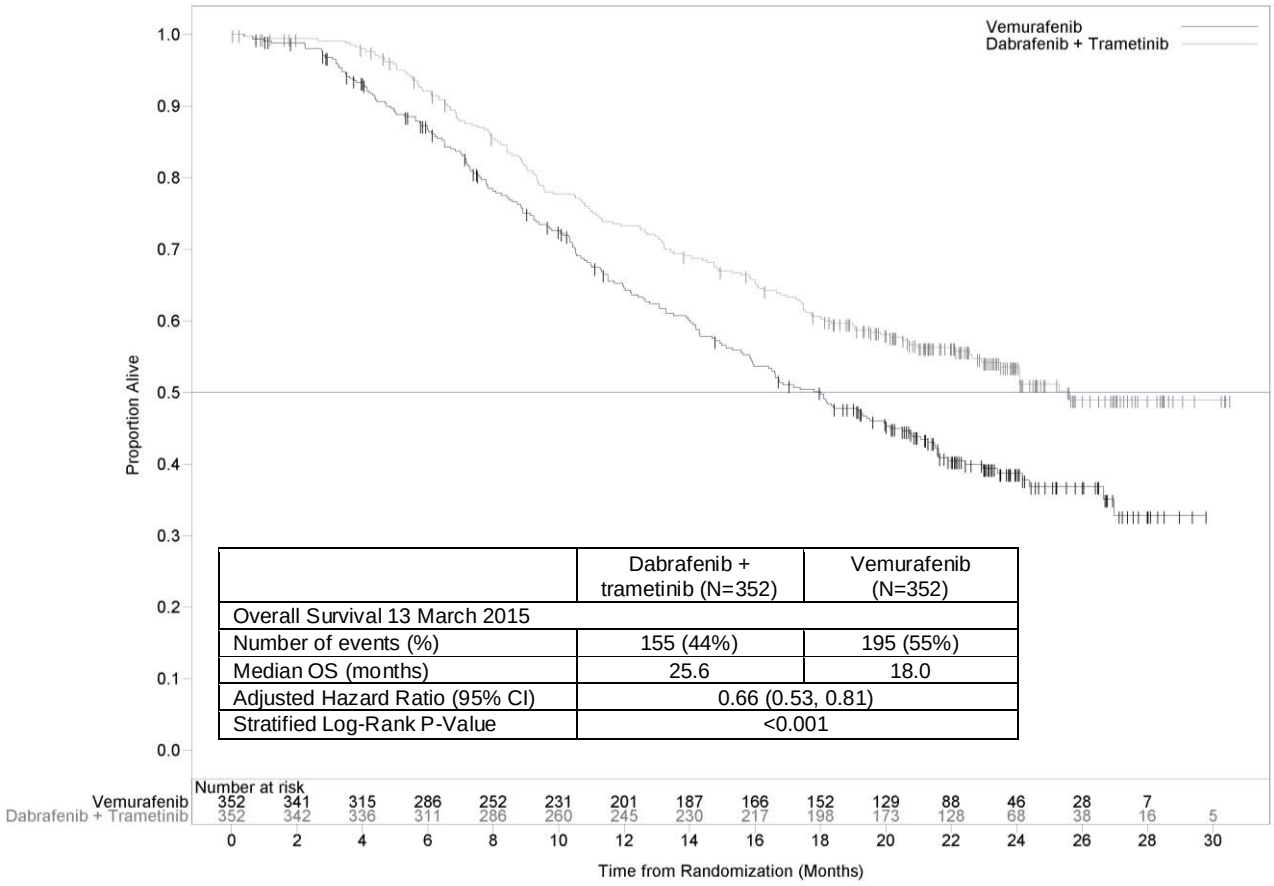
a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
e – ORR difference calculated based on the ORR result not rounded
NR = Not reached

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 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.

The updated OS analysis (13 March 2015) demonstrated a statistically significant improvement in OS for the combination compared with vemurafenib monotherapy (Figure 2). The 12-month OS estimate was 72% for combination therapy and 65% for vemurafenib.

Figure 2: Kaplan-Meier curves Updated OS analysis for Study MEK116513



Statistically significant improvements are observed for the secondary endpoints of PFS and ORR. A longer DoR is also observed (Table 7).

Table 7 Efficacy results for Study MEK116513 (COMBI-v)

Endpoint	**Dabrafenib + Trametinib (N=352)**	**Vemurafenib (N=352)**
PFS[a]		
Progressive disease or death, n (%)	166 (47)	217 (62)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)	
P value	<0.001	
ORR[b] (95% CI)	226 (64) (59.1, 69.4)	180 (51) (46.1, 56.8)
ORR difference (95% CI)	13 (5.7, 20.2)	
P value	0.0005	
DoR (months) Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

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).

- *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 studies (BRF113683 [BREAK-3], BRF113929 [BREAK-MB], and BRF113710 [BREAK-2]) including patients with BRAF V600E and/or V600K mutations.

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

No data is available in patients with melanoma harbouring BRAF V600 mutations 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 8. OS data from a further post-hoc analysis based on a 18 December 2012 data cut are shown in Figure 3.

Table 8 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.

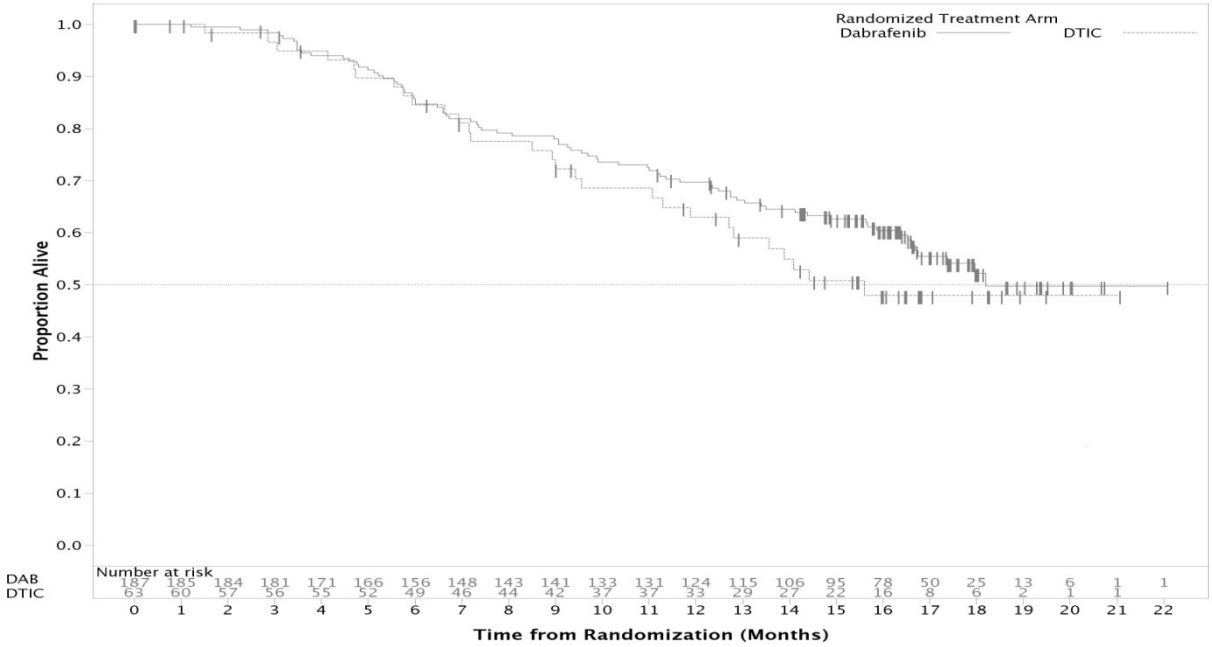
Table 9 Survival data from the primary analysis and post-hoc analyses

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 10.

Table 10 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 positive tumours.

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 'Response Evaluation Criteria In Solid Tumors' (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 medication 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.

For the primary endpoint of investigator-assessed ORR, the 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 response was durable with median DoR in the previously treated population reaching 9.8 months (95% CI, 6.9, 16.0) by investigator assessment. In the first line population, 68% of patients had not progressed after 9 months. The median DoR and PFS were not yet estimable (Table 11). The efficacy of the combination with trametinib was superior when indirectly compared to dabrafenib monotherapy in Cohort A.

Table 11 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 By IRC	22 (61.1%) (43.5, 76.9) 22 (61.1%) (43.5, 76.9)	38 (66.7%) (52.9, 78.6) 36 (63.2%) (49.3, 75.6)
Median DoR Months (95% CI)	By Investigator By IRC	NE[2] (8.3, NE) NE (6.9, NE)	9.8 (6.9, 16.0) 12.6 (5.8, NE)
Median PFS Months (95% CI)	By Investigator By IRC	-[3] -[3]	10.2 (6.9, 16.7) 8.6 (5.2, 16.8)
Median OS Months (95% CI)	-	24.6 (11.7, NE)[4]	18.2 (14.3, NE)

[1] Data cut-off: 8th August 2016
[2] NE: Not Evaluable
[3] Median PFS currently not estimable
[4] Event rate for OS calculation was 28% and hence the defined median value still needs to mature

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.

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 1478 ng/ml, 4341 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.

Dabrafenib is a substrate of human P-glycoprotein (Pgp) and murine BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low. Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of Pgp *in vitro*. Dabrafenib and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP); however, based on clinical exposure, the risk of a drug-drug interaction is minimal.

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro*, the risk of a drug-drug interaction is minimal based on clinical exposure.

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

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

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

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

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed (≥0.2 times adult human clinical exposure based on AUC).

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at doses ≥100 mg/kg (>44 times clinical exposure based on 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

2 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

26 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://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

GLAXO WELLCOME, S.A.
Avda. Extremadura, 3, Pol. Ind. Allendeduero
09400, Aranda de Duero (Burgos)
Spain

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 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**

The requirements for submission of periodic safety update reports 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 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.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to conduct post-authorisation measures**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE 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

Capsule, hard

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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 OUTER PACKAGING AND 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

Capsule, hard

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE 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

Capsule, hard

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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 OUTER PACKAGING AND 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

Capsule, hard

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules
dabrafenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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. Don't 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 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, nurse or pharmacist.

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 38.5ºC 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, lightheadedness, 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.

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
- medicines that **reduce stomach acid** such as omeprazole
- 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 4 weeks after you stop taking it and for 4 months 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 reliable method of birth control such as a barrier method (e.g. condom) 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 Tafinlar 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, or
- 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 missed 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, nurse or pharmacist tells you. Do not change your dose or stop Tafinlar or trametinib unless your doctor, nurse or pharmacist 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, nurse or pharmacist. 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, nurse or pharmacist tells you.

4. Possible side effects

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

Possible side effects in patients taking Tafinlar alone

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 38.5ºC or above) 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 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
If you notice any changes in your skin while taking this medicine, please talk to your doctor, pharmacist or nurse as soon as possible.

Up to 1 in 10 people taking Tafinlar may develop a different type of skin cancer called *cutaneous squamous cell carcinoma (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
Up to 1 in 100 people taking Tafinlar alone or in combination with trametinib can develop an eye problem called uveitis, which could damage your vision if it is not treated. 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.

The other 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
- Changes in how the heart pumps blood

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

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 read the trametinib Package Leaflet for details of the side effects you may get when taking this medicine.

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):
- Infection of the urinary system
- 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

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

Common side effects (may affect up to 1 in 10 people):

- 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
- Heart pumping less efficiently
- Low blood pressure (hypotension)
- Localised tissue swelling
- Shortness of breath
- Inflammation of the lung (pneumonitis)
- 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)
- Kidney failure
- Inflammation of the mucosa
- Flu-like illness
- Swelling of the face

Common side effects that may show up in your blood tests

- 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), inflammation of the eye (uveitis), 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 pancreas
- A hole (perforation) in the stomach or intestines
- Inflammation of the intestines (colitis)
- Inflammation of the kidneys

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.

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 take Tafinlar after the expiry date (EXP) which is stated on the bottle label and the carton. 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.

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Glaxo Wellcome, S.A., Avda. Extremadura, 3, 09400 Aranda De Duero, Burgos, Spain
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom
Novartis Pharma GmbH, Roonstraße 25, D-90429 Nuremberg, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last revised in

Other sources of information

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

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