ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Finlee 10 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains dabrafenib mesilate equivalent to 10 mg of dabrafenib.

Excipient with known effect

Each dispersible tablet contains <0.00078 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

White to slightly yellow, round, biconvex 6 mm tablet debossed with “D” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Low-grade glioma

Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

High-grade glioma

Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

4.2 Posology and method of administration

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

Before taking Finlee, patients must have confirmation of BRAF V600E mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, confirmation of BRAF V600E should be assessed by an alternative validated test.

Finlee is used in combination with trametinib powder for oral solution. See the summary of product characteristics (SmPC) for posology of trametinib powder for oral solution.

Finlee is not to be replaced with other dabrafenib formulations as bioequivalence was not shown (see section 5.2).

Posology

The recommended twice-daily dose of Finlee is determined by body weight (Table 1).

Table 1 Dosing regimen by body weight

Body weight*	**Recommended dose (mg dabrafenib) twice daily**	**Recommended dose (number of 10 mg tablets) twice daily**
8 to 9 kg	20 mg	2
10 to 13 kg	30 mg	3
14 to 17 kg	40 mg	4
18 to 21 kg	50 mg	5
22 to 25 kg	60 mg	6
26 to 29 kg	70 mg	7
30 to 33 kg	80 mg	8
34 to 37 kg	90 mg	9
38 to 41 kg	100 mg	10
42 to 45 kg	110 mg	11
46 to 50 kg	130 mg	13
≥51 kg	150 mg	15
*Round body weight to the nearest kg, if necessary. The recommended dose for patients with a body weight less than 8 kg has not been established. Please refer to the trametinib powder for oral solution SmPC, "Posology" and "Method of administration", for dosing instructions for treatment with trametinib when used in combination with Finlee.		

Duration of treatment

Treatment with Finlee should continue until disease progression or until the development of unacceptable toxicity. There are limited data in patients older than 18 years of age with glioma, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Missed or delayed doses

If a dose of Finlee is missed, it should only be taken if it is more than 6 hours until the next scheduled dose. If vomiting occurs after taking Finlee, an additional dose should not be administered and the next dose should be taken at the next scheduled time.

Dose modification

The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation (see Tables 2 and 3).

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

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous malignancies (see section 4.4).

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

Grade (CTCAE)*	**Recommended dabrafenib dose modifications**
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy. Refer to Table 3 for dose level guidance.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy. Refer to Table 3 for dose level guidance.
* The intensity of clinical adverse reactions graded by the Common Terminology Criteria for Adverse Events (CTCAE)	

Table 3 Recommended dose reduction levels for adverse reactions

Body weight	**Recommended dose (mg dabrafenib) twice daily**	**Reduced dose (number of 10 mg tablets) twice daily**		
		First reduction level	**Second reduction level**	**Third reduction level**
8 to 9 kg	20 mg	1	N/A	N/A
10 to 13 kg	30 mg	2	1	N/A
14 to 17 kg	40 mg	3	2	1
18 to 21 kg	50 mg	3	2	1
22 to 25 kg	60 mg	4	3	2
26 to 29 kg	70 mg	5	4	2
30 to 33 kg	80 mg	5	4	3
34 to 37 kg	90 mg	6	5	3
38 to 41 kg	100 mg	7	5	3
42 to 45 kg	110 mg	7	6	4
46 to 50 kg	130 mg	9	7	4
≥51 kg	150 mg	10	8	5
N/A=not applicable Permanently discontinue Finlee if unable to tolerate 10 mg twice daily or a maximum of 3 dose reductions.				

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 the recommended dose indicated in Table 1.

Dose modifications for selected adverse reactions

Pyrexia

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

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

Uveitis

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

RAS mutation-positive non-cutaneous malignancies

The benefits and risks must 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 (see section 4.4).

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

If an absolute decrease of >10% in LVEF compared to baseline occurs, and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib powder for oral solution SmPC (section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib (see section 4.4).

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 powder for oral solution SmPC (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 powder for oral solution SmPC (section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

Special populations

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. There are no clinical data in patients 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.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. There are no clinical data in patients 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.

Paediatric population

The safety and efficacy of combination therapy with dabrafenib and trametinib in children below 1 year of age have not been established. No data are available. Studies in juvenile animals have shown effects of dabrafenib which were not observed in adult animals (see section 5.3). Longer-term safety data in paediatric patients are currently limited.

Method of administration

Finlee is for oral use.

Finlee should be taken without food, at least one hour prior to or two hours after a meal (see section 5.2). Breast-feeding and/or baby formula may be given on demand if a patient is unable to tolerate the fasting conditions.

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

If the patient is unable to swallow and has a nasogastric tube in situ, the Finlee tablet suspension can be administered via the tube.

Instructions for preparation and administration are provided in section 6.6.

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

Finlee is intended for use in combination with trametinib powder for oral solution as there are limited efficacy data for dabrafenib monotherapy and for trametinib monotherapy in BRAF V600 mutation-positive glioma. The trametinib powder for oral solution SmPC must be consulted prior to intiation of treatment. For additional information on warnings and precautions associated with trametinib treatment, please refer to the trametinib powder for oral solution SmPC.

BRAF V600E testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF glioma. Dabrafenib should not be used in patients with wild-type BRAF glioma (see section 5.1).

New malignancies

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

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma and new primary melanoma have been observed in adult patients treated with dabrafenib in combination with trametinib (see section 4.8). 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. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Suspicious skin lesions should be managed with dermatological excision and do not require treatment modifications. Patients should be instructed to inform their physicians immediately if new skin lesions develop.

Non-cutaneous malignancies

In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAP kinase) signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to increased risk of non-cutaneous malignancies with dabrafenib exposure (see section 4.8) when RAS mutations are present. RAS-associated malignancies have been reported in adult clinical studies, 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 trametinib (colorectal cancer, pancreatic cancer).

The benefits and risks should be considered before administering dabrafenib in patients with a prior or concurrent cancer associated with RAS mutations. Patients should be screened for occult pre-existing malignancies.

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 have been reported in adult and paediatric patients taking dabrafenib in combination with trametinib (see section 4.8). Major haemorrhagic events and fatal haemorrhages have occurred in adult patients taking dabrafenib in combination with trametinib. The potential for these events in patients with low platelet counts (<75 000/mm^3) has not been established as such patients were excluded from clinical studies. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.

Visual impairment

Ophthalmological reactions, including uveitis and iridocyclitis, have been reported in paediatric patients taking dabrafenib in combination with trametinib (see section 4.8), in some cases with a time to onset of several months. In clinical studies in adult patients treated with dabrafenib, ophthalmological reactions, including uveitis, iridocyclitis and iritis, have been reported. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

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

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

RPED and RVO may occur with dabrafenib in combination with trametinib. Please refer to the trametinib powder for oral solution SmPC (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 adult and paediatric clinical studies with dabrafenib (see section 4.8). Serious non-infectious febrile events were identified (defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function). In paediatric patients who received dabrafenib in combination with trametinib, the median time to onset of the first occurrence of pyrexia was 1.5 months. In adult patients with unresectable or metastatic melanoma who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one third of the patients had 3 or more events. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

Therapy with dabrafenib and trametinib should be interrupted if the patient's temperature is ≥38ºC (see section 5.1). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).

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

Dabrafenib in combination with trametinib has been reported to decrease LVEF in both adult and paediatric patients (see section 4.8). In clinical studies in paediatric patients, the median time to onset of the first occurrence of LVEF decrease was around one month. In clinical studies in adult patients, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 and 5 months.

In patients receiving dabrafenib in combination with trametinib, there have been occasional reports of acute, severe left ventricular dysfunction due to myocarditis. Full recovery was observed when stopping treatment. Physicians should be alert to the possibility of myocarditis in patients who develop new or worsening cardiac signs or symptoms. Please refer to the trametinib powder for oral solution SmPC (section 4.4) for additional information. No dose modification of dabrafenib is required when taken in combination with trametinib.

Renal failure

Renal failure has been identified in ≤1% of adult patients treated with dabrafenib in combination with trametinib. Observed cases in adult patients were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has also been reported in adult patients. Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, treatment 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 reactions have been reported in adult and paediatric patients in clinical studies with dabrafenib in combination with trametinib (see section 4.8). It is recommended that patients have liver function monitored every four weeks for 6 months after treatment initiation. Liver monitoring may be continued thereafter as clinically indicated.

Blood pressure changes

Both hypertension and hypotension have been reported in patients in clinical studies with dabrafenib in combination with trametinib (see section 4.8). Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in adult patients in clinical studies with dabrafenib in combination with trametinib. Please refer to the trametinib powder for oral solution SmPC for additional information.

Rash

Rash has been observed in 49% of paediatric patients in clinical studies when dabrafenib is used in combination with trametinib (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Severe cutaneous adverse reactions

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

Rhabdomyolysis

Rhabdomyolysis has been reported in adult patients taking dabrafenib in combination with trametinib. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated. Please refer to the trametinib powder for oral solution SmPC for additional information.

Pancreatitis

Pancreatitis has been reported in adult and paediatric patients treated with dabrafenib in combination with trametinib in clinical studies (see section 4.8). Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when restarting treatment after an episode of pancreatitis.

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

Pulmonary embolism or deep vein thrombosis can occur. 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 treatment for life-threatening pulmonary embolism.

Gastrointestinal disorders

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

Sarcoidosis

Cases of sarcoidosis have been reported in adult patients treated with dabrafenib in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with dabrafenib and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered.

Women of childbearing potential/Fertility in males

Before initiating treatment in women of childbearing potential, appropriate advice on effective methods of contraception should be provided. Women of childbearing potential must use effective methods of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and for 16 weeks following discontinuation of trametinib. Male patients taking dabrafenib in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible (see section 4.6).

Haemophagocytic lymphohistiocytosis

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

Tumour lysis syndrome (TLS)

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

Effects of other medicinal products on dabrafenib

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

Effects of dabrafenib on other medicinal products

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

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

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

Excipients

Potassium
This medicinal product contains potassium, less than 1 mmol (39 mg) per maximum daily dose, i.e. essentially 'potassium-free'.

Benzyl alcohol
This medicinal product contains <0.00078 mg benzyl alcohol in each dispersible tablet.

Benzyl alcohol may cause allergic reactions.

Patients below 3 years of age should be monitored for respiratory symptoms.

Patients who are, or may become, pregnant should be advised of the potential risk to the foetus from the excipient benzyl alcohol, which may accumulate over time and cause metabolic acidosis.

Dabrafenib dispersible tablets should be used with caution in patients with hepatic or renal impairment, as benzyl alcohol may accumulate over time and cause metabolic acidosis.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Effect of other medicinal products on dabrafenib

Dabrafenib is a substrate for the metabolising enzymes CYP2C8 and CYP3A4, while the active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are therefore likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Dabrafenib should be used with caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4 should be avoided.

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71% increase in dabrafenib AUC and a 33% increase in dabrafenib C_{max} relative to administration of dabrafenib 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 alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤13%).

Administration of rifampin (a CYP3A4/CYP2C8 inducer) 600 mg once daily, with dabrafenib 150 mg twice daily, resulted in a decrease in repeat-dose dabrafenib C_{max} (27%) and AUC (34%). No relevant change in AUC was noted for hydroxy-dabrafenib. There was an increase in AUC of 73% for carboxy-dabrafenib and a decrease in AUC of 30% for desmethyl-dabrafenib.

Co-administration of repeat doses of dabrafenib 150 mg twice daily and the pH-elevating agent rabeprazole 40 mg once daily resulted in a 3% increase in AUC and a 12% decrease in dabrafenib C_{max}. These changes in dabrafenib AUC and C_{max} are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Effect of dabrafenib on other medicinal products

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 and may increase the synthesis of transporters. This results in reduced plasma levels of medicinal products metabolised by these enzymes and may affect some transported medicinal products. The reduction in plasma concentrations can lead to lost or reduced clinical effect of these medicinal products. There is also a risk of increased formation of active metabolites of these medicinal products. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGTs (glucuronide conjugating enzymes). The transport protein P-gp may also be induced as well as other transporters, e.g. MRP-2. Induction of OATP1B1/1B3 and BCRP is not likely based on the observations from a clinical study with rosuvastatin.

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

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

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

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

- Analgesics (e.g. fentanyl, methadone)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anti-cancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptics (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin, see section 4.4)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives (see section 4.6)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Upon discontinuation of dabrafenib offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter substrates (e.g. P-gp or MRP-2) may increase and patients should be monitored for toxicity and dose of these agents may need to be adjusted.

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

Effects of dabrafenib on substance transport systems

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

Also refer to the guidance for medicinal product interactions for trametinib found in sections 4.4 and 4.5 of the trametinib powder for oral solution SmPC.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective methods of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and for 16 weeks following discontinuation of trametinib.

Dabrafenib may decrease the efficacy of oral or any systemic hormonal contraceptives and an effective alternative 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 also the trametinib powder for oral solution SmPC (section 4.6) for additional information on trametinib.

Breast-feeding

It is not known whether dabrafenib is 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 in combination with trametinib. Dabrafenib may impair male and female fertility as effects on male and female reproductive organs have been seen in animals (see section 5.3). Male patients taking dabrafenib in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Please see the trametinib powder for oral solution SmPC for additional information.

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, dizziness or eye problems to affect these activities.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies of paediatric patients treated with dabrafenib in combination with trametinib, the most common adverse reactions (reported at a frequency ≥20%) were: pyrexia (70%), rash (49%), headache (47%), vomiting (40%), fatigue (36%), dry skin (35%), diarrhoea (34%), haemorrhage (34%), nausea (29%), dermatitis acneiform (29%), abdominal pain (28%), neutropenia (26%), cough (24%) and transaminases increased (22%). The most frequently reported severe (Grade 3/4) adverse reactions were: neutropenia (15%), pyrexia (11%), transaminases increased (6%) and weight increased (5%). Long-term data on growth and skeletal maturation in paediatric patients are currently limited (see section 5.3).

The safety profile in paediatric patients was largely consistent with the safety profile previously established in adult patients. The following additional adverse reactions have so far only been reported in adult patients treated with dabrafenib capsules and trametinib tablets: cutaneous squamous cell carcinoma, seborrhoeic keratosis, peripheral neuropathy (including sensory and motor neuropathy), lymphoedema, dry mouth, actinic keratosis, renal failure (common), melanoma, acrochordon, sarcoidosis, chorioretinopathy, pneumonitis, acute renal failure, nephritis, cardiac failure, left ventricular dysfunction, interstitial lung disease, rhabdomyolysis (uncommon), gastrointestinal perforation, haemophagocytic lymphohistiocytosis (rare), tumour lysis syndrome, myocarditis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (frequency not known). In addition, cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada syndrome have been reported in adult patients.

Tabulated list of adverse reactions

The safety of dabrafenib in combination with trametinib has been evaluated in a pooled safety set of 171 paediatric patients across two studies in patients with BRAF V600 mutation-positive advanced solid tumours. Four (2.3%) patients were 1 to <2 years of age, 39 (22.8%) patients were 2 to <6 years of age, 54 (31.6%) patients were 6 to <12 years of age and 74 (43.3%) patients were 12 to <18 years of age at enrolment. The mean treatment duration was 2.3 years.

Adverse reactions (Table 4) are listed below by MedDRA system organ class ranked by frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 Adverse reactions with dabrafenib in combination with trametinib

Infections and infestations	
Very common	Paronychia, nasopharyngitis*[1]
Common	Urinary tract infection, cellulitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Very common	Skin papilloma
Blood and lymphatic system disorders	
Very common	Neutropenia*[2], anaemia, leukopenia*
Common	Thrombocytopenia*
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Common	Dehydration, decreased appetite
Nervous system disorders	
Very common	Headache, dizziness*[3]
Eye disorders	
Common	Vision blurred, visual impairment, uveitis*[4]
Uncommon	Retinal detachment, periorbital oedema
Cardiac disorders	
Common	Ejection fraction decreased, bradycardia*
Uncommon	Atrioventricular block[5]
Vascular disorders	
Very common	Haemorrhage*[6]
Common	Hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough*
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Abdominal pain*, constipation, diarrhoea, nausea, vomiting
Common	Pancreatitis, stomatitis
Uncommon	Colitis*
Skin and subcutaneous tissue disorders	
Very common	Dermatitis acneiform*[7], dry skin*[8], pruritus, rash*[9], erythema
Common	Dermatitis exfoliative generalised*[10], alopecia, palmar-plantar erythrodysaesthesia syndrome, folliculitis, skin lesion, panniculitis, hyperkeratosis, photosensitivity*[11]
Uncommon	Acute febrile neutrophilic dermatosis[12], skin fissures, night sweats, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, pain in extremity
Common	Myalgia*, muscle spasms*[13]
General disorders and administration site conditions	
Very common	Pyrexia*, fatigue*[14], weight increased
Common	Mucosal inflammation, face oedema*, chills, oedema peripheral, influenza-like illness

Investigations	
Very common	Transaminases increased*[15]
Common	Hyponatraemia, hypophosphataemia, hyperglycaemia, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased

*Denotes grouped term of two or more MedDRA preferred terms that were considered clinically similar.

[1] nasopharyngitis includes pharyngitis
[2] neutropenia includes neutrophil count decreased and febrile neutropenia
[3] dizziness includes vertigo
[4] uveitis includes iridocyclitis
[5] atrioventricular block includes atrioventricular block first degree
[6] haemorrhage includes epistaxis, haematuria, contusion, haematoma, international normalised ratio increased, anal haemorrhage, catheter site haemorrhage, cerebral haemorrhage, ecchymosis, extradural haematoma, gastrointestinal haemorrhage, haematochezia, petechiae, post-procedural haemorrhage, rectal haemorrhage, red blood cell count decreased, upper gastrointestinal haemorrhage, uterine haemorrhage, heavy menstrual bleeding and purpura
[7] dermatitis acneiform includes acne and acne pustular
[8] dry skin includes xerosis and xeroderma
[9] rash includes rash maculo-papular, rash pustular, rash erythematous, rash papular, rash macular
[10] dermatitis exfoliative generalised includes skin exfoliation and dermatitis exfoliative
[11] photosensitivity includes photosensitivity reaction and sunburn
[12] acute febrile neutrophilic dermatosis is an adverse drug reaction seen also with dabrafenib monotherapy (Tafinlar)
[13] muscle spasms include musculoskeletal stiffness
[14] fatigue includes malaise and asthenia
[15] transaminases increased includes aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased and hypertransaminasaemia

Description of selected adverse reactions

Weight increased

Weight increase has only been reported in the paediatric population. It was reported as an adverse reaction in 16% of paediatric patients including Grade 3 cases in 5% of patients, with a discontinuation rate of 0.6% of patients. The median time to onset of the first occurrence of the reported weight increase in paediatric patients receiving dabrafenib in combination with trametinib was 3.5 months. Weight increase from baseline of ≥2 BMI (body mass index)-for-age percentile categories was observed in 36% of patients.

Haemorrhage

Haemorrhagic events were observed in 34% of paediatric patients, with Grade 3 events occurring in 1.2% of patients. The most frequent haemorrhagic event (epistaxis) was reported in 18% of paediatric patients. The median time to onset of the first occurrence of haemorrhagic events in paediatric patients was 2.6 months. Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in adult patients taking dabrafenib in combination with trametinib.

The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated (see section 4.4).

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

Decreased LVEF has been reported in 5.3% of paediatric patients, with Grade 3 events occurring in <1% of patients. The median time to onset of the first occurrence of LVEF decrease was around one month.

Patients with LVEF lower than the institutional lower limit of normal were not included in clinical studies with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4). Please refer to the trametinib powder for oral solution SmPC (section 4.4).

Pyrexia
Fever has been reported in clinical studies with dabrafenib in combination with trametinib (see section 4.4). Pyrexia was reported in 70% of paediatric patients, with Grade 3 events occurring in 11% of patients. Approximately half of the first occurrences of pyrexia in adult patients 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 adult safety population, serious non-infectious febrile events were identified (defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function). 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 reactions have been reported in adult and paediatric clinical studies with dabrafenib in combination with trametinib. In the paediatric safety population, increased ALT and AST were very common, reported in 13% and 16% of patients, respectively (see section 4.4). Please refer to the trametinib powder for oral solution SmPC for additional information.

Blood pressure changes
Hypertension was reported in 2.3% of paediatric patients, with Grade 3 events occurring in 1.2% of patients. The median time to onset of the first occurrence of hypertension in paediatric patients was 5.4 months.

Hypotension was reported in 4.1% of paediatric patients, with Grade ≥3 events occurring in 2.3% of patients. The median time to onset of the first occurrence of hypotension in paediatric patients was 2.2 months.

Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate (see section 4.4).

Arthralgia
Arthralgia was reported very commonly in the integrated adult and paediatric safety populations of dabrafenib in combination with trametinib. In the paediatric safety population, arthralgia was reported in 13% of patients, with <1% of patients with Grade 3 severity. Arthralgia was reported in 25% of adult patients, although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%).

Hypophosphataemia
Hypophosphataemia has been reported commonly in the integrated adult and paediatric safety populations of dabrafenib in combination with trametinib in 4% and 5.8% of patients, respectively. It should be noted that Grade 3 events occurred in 1% of adult patients. In paediatric patients, hypophosphataemia occurred only with Grade 1 and 2 severity.

Pancreatitis
Pancreatitis was reported in 1.2% of paediatric patients, with <1% of patients with Grade 3 severity. In clinical studies in adult patients, one pancreatitis event occurred on the first day of dabrafenib dosing of a metastatic melanoma patient and recurred following rechallenge 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 restarting treatment after an episode of pancreatitis (see section 4.4).

Cutaneous malignancies
In the integrated adult safety population for dabrafenib in combination with trametinib, 2% of patients developed cuSCC with a median time to onset of 18 to 31 weeks. The median time to diagnosis of the first occurrence of cuSCC was 223 days (range 56 to 510 days). All adult patients who developed cuSCC or new primary melanoma continued on treatment without dose modification (see section 4.4).

Non-cutaneous malignancies
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% of patients in the integrated adult safety population of dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib in combination with trametinib. Patients should be monitored as clinically appropriate.

Renal failure
Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon in adult patients; 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).

Reporting of suspected adverse reactions

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

4.9 Overdose

No acute overdose symptoms have been reported in paediatric patients who received dabrafenib in combination with trametinib in clinical studies. There is no specific treatment for overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. The most commonly observed BRAF mutation is V600E, which has been identified in 19% of paediatric LGG and approximately 5% of paediatric HGG.

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. In human cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.

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 cancer cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation-positive xenografts.

Pharmacodynamic effects

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 WT	3.2
CRAF WT	5.0

Clinical efficacy and safety

Paediatric population
The clinical efficacy and safety of dabrafenib plus trametinib combination therapy in paediatric patients aged 1 to <18 years with BRAF V600 mutation-positive glioma was evaluated in a multi-centre, open-label, Phase II clinical study (EudraCT 2015-004015-20). Patients with low-grade glioma (WHO 2016 Grades 1 and 2) who required first systemic therapy were randomised in a 2:1 ratio to dabrafenib plus trametinib or carboplatin plus vincristine, and patients with relapsed or refractory high-grade glioma (WHO 2016 Grades 3 and 4) were enrolled into a single-arm dabrafenib plus trametinib cohort.

BRAF mutation status was identified prospectively via a local test, or a central laboratory real-time polymerase chain reaction (PCR) test when a local test was not available. In addition, retrospective testing of available tumour samples by the central laboratory was performed to confirm the BRAF V600E mutation.

Dabrafenib and trametinib dosing in the clinical study was age- and weight-dependent, with dabrafenib dosed orally at 2.625 mg/kg twice daily for ages <12 years and at 2.25 mg/kg twice daily for ages 12 years and older; trametinib was dosed orally at 0.032 mg/kg once daily for ages <6 years and at 0.025 mg/kg once daily for ages 6 years and older. Dabrafenib doses were capped at 150 mg twice daily and trametinib doses at 2 mg once daily. Carboplatin and vincristine were dosed based on age and body surface area at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively, as weekly infusions. Carboplatin and vincristine were administered in one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The primary efficacy endpoint in both cohorts was overall response rate (ORR, sum of confirmed complete/CR and partial responses/PR) by independent review based on RANO (2017) criteria for the LGG cohort and RANO (2010) criteria for the HGG cohort. The primary analysis was performed when all patients in both cohorts had completed at least 32 weeks of therapy. The final analysis was performed 2 years after completion of enrolment in both cohorts.

BRAF mutation-positive paediatric low-grade glioma (WHO Grades 1 and 2)
In the low-grade glioma cohort, 110 patients were randomised to dabrafenib plus trametinib (n=73) or carboplatin plus vincristine (n=37). Median age was 9.5 years, with 34 patients (30.9%) aged 12 months to <6 years, 36 patients (32.7%) aged 6 to <12 years and 40 patients (36.4%) aged 12 to <18 years; 60% were female. The majority of patients (80%) had Grade 1 glioma at initial diagnosis. The most common pathologies were pilocytic astrocytoma (30.9%), ganglioglioma (27.3%) and LGG not otherwise specified (NOS) (18.2%). Metastatic sites were present in 9 patients (8.2%). Prior surgery was reported in 91 patients (82.7%), among those patients the procedure at last surgery was resection in 28 patients (25.5%). Systemic corticosteroid use was reported in 44 patients (41.5%).

At the time of the primary analysis, the ORR in the dabrafenib plus trametinib arm showed a statistically significant improvement over carboplatin plus vincristine. The subsequent hierarchical testing also demonstrated a statistically significant improvement in progression-free survival (PFS) over chemotherapy (Table 6).

At the time of the primary analysis, conducted after all patients had completed at least 32 weeks of treatment or had discontinued earlier, the overall survival (OS) data were still immature (one death was reported in the carboplatin plus vincristine (C+V) arm).

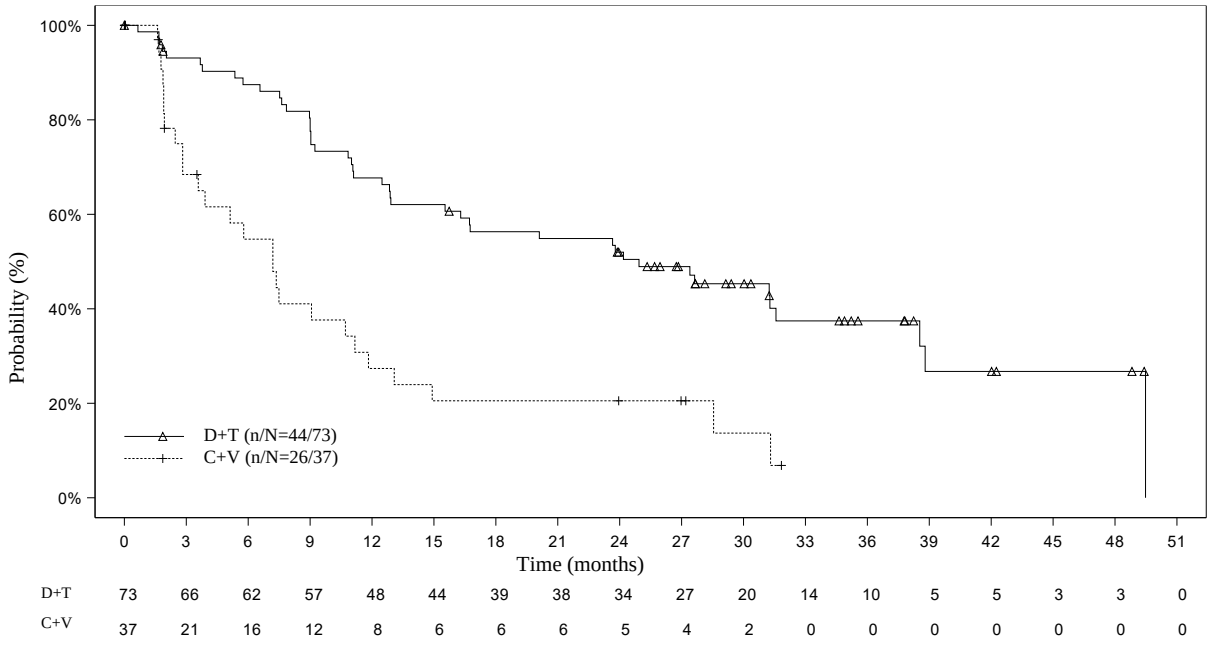
Table 6 Response and progression-free survival based on independent review in the pivotal study G2201 (LGG cohort, primary analysis)

	Dabrafenib + Trametinib (D+T) N=73	**Carboplatin + Vincristine (C+V) N=37**
Best overall response		
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (43.8)	3 (8.1)
Stable disease (SD), n (%)	30 (41.1)	15 (40.5)
Progressive disease (PD), n (%)	8 (11.0)	12 (32.4)
Unknown, n (%)	1 (1.4)	6 (16.2)[1]
Overall response rate		
ORR (CR+PR), (95% CI)	46.6% (34.8 - 58.6%)	10.8% (3.0 - 25.4%)
Odds ratio[2], p-value	7.19 (2.3 - 22.4), p<0.001	
Risk difference	35.8% (20.6 - 51.0)	
Progression-free survival (PFS)		
Median (months), (95% CI)	20.1 (12.8 - NE)	7.4 (3.6 - 11.8)
Hazard ratio (95% CI), p-value	0.31 (0.17 - 0.55), p<0.001	

NE=not estimable
[1] 4 patients randomised to C+V discontinued prior to receiving treatment.
[2] Odds ratio (D+T vs C+V) and 95% CI are from a logistic regression with treatment as the only covariate, i.e. it is the odds of observing a response in the D+T arm compared to the odds of observing a response in the C+V arm. Odds ratio >1 favours D+T.

At the time of the final analysis (median duration of follow-up: 39.0 months), the ORR based on independent review was 54.8% in the D+T arm and 16.2% in the C+V arm with an odds ratio of 6.26. The analysis also confirmed improved PFS over chemotherapy based on independent review with an estimated 64% risk reduction in progression/death (hazard ratio 0.36). The median PFS was 24.9 months in the D+T arm and 7.2 months in the C+V arm. No additional deaths were reported in either arm at the time of the final analysis.

Figure 1 Kaplan-Meier curves for progression-free survival based on independent review in the pivotal study G2201 (LGG cohort, final analysis)



BRAF mutation-positive paediatric high-grade glioma (WHO Grades 3 and 4)
In the single-arm high-grade glioma cohort, 41 patients with relapsed or refractory HGG were enrolled and treated with dabrafenib plus trametinib. Median age was 13.0 years, with 5 patients (12.2%) aged 12 months to <6 years, 10 patients (24.4%) aged 6 to <12 years and 26 patients (63.4%) aged 12 to <18 years; 56% were female. The histological grade at initial diagnosis was Grade 4 in 20 patients (48.8%), Grade 3 in 13 patients (31.7%), Grade 2 in 4 patients (9.8%), Grade 1 in 3 patients (7.3%) and missing in 1 patient (2.4%). The most common pathologies were glioblastoma multiforme (31.7%), anaplastic pleomorphic xanthoastrocytoma (14.6%), HGG NOS (9.8%) and pleomorphic xanthoastrocytoma (9.8%). Prior surgery was reported in 40 patients (97.6%), among those patients the procedure at last surgery was resection in 24 patients (58.5%). Prior antineoplastic chemotherapy was reported for 33 patients (80.5%). Prior radiotherapy was reported for 37 patients (90.2%). Systemic corticosteroid use while on study treatment was reported in 24 patients (58.5%).

At the time of the final analysis (median duration of follow-up: 45.2 months), the ORR based on independent review was 56.1% (23/41), (95% CI: 39.7, 71.5): CR in 14 patients (34.1%) and PR in 9 patients (22.0%). The median duration of response (DoR) was 27.4 months (95% CI: 9.2, NE).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of dabrafenib have mostly been determined in adult patients using the solid (capsule) formulation. The pharmacokinetics of dabrafenib following single or repeat weight-adjusted dosing were also evaluated in 243 paediatric patients. The population pharmacokinetic analysis included 61 patients aged 1 to <6 years, 77 patients aged 6 to <12 years and 105 patients aged 12 to <18 years. Clearance was comparable with clearance in adult patients. Weight was identified as a significant covariate of dabrafenib clearance. Age was not a significant additional covariate. The pharmacokinetic exposures of dabrafenib at the recommended weight-adjusted dose in paediatric patients were within range of those observed in adults.

Absorption

The dabrafenib dispersible tablet suspension was absorbed rapidly with a median time to achieve peak plasma concentration of 1.5 hours post-dose. The mean absolute oral bioavailability of dabrafenib capsules was 94.5%. The suspension is expected to have 20% lower bioavailability. Based on data from adult patients with the capsule formulation, a decrease in exposure was observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratio was 0.73.

Dabrafenib exposure (C_{max} and AUC) increased in a dose-proportional manner between 12 mg and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice-daily dosing.

In the pivotal paediatric study, steady-state geometric mean (%CV) C_{max} and AUC_{tau} were 1330 ng/ml (93.5%) and 4910 ng*hr/ml (54.0%) in the LGG cohort and 1520 ng/ml (65.9%) and 4300 ng*hr/ml (44.7%) in the HGG cohort.

Food effect
Administration of a single 150 mg dose of the dispersible tablet suspension with a low-fat, low-calorie meal reduced the bioavailability (C_{max} and AUC decreased by 35% and 29%, respectively) and delayed the absorption of dabrafenib when compared to the fasted state in an adult healthy volunteer study.

Distribution

Dabrafenib binds to human plasma proteins and is 99.7% bound. The steady-state volume of distribution following intravenous microdose administration in adults was 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 to 22 hours). In paediatric patients, the mean metabolite-to-parent AUC ratios (%CV) following repeat-dose administration of the capsules or of the dispersible tablet suspension were 0.64 (28%), 15.6 (49%) and 0.69 (62%) for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib while the activity of carboxy-dabrafenib is not likely to be significant.

Elimination

Terminal half-life of dabrafenib following an intravenous single microdose in adult patients was 2.6 hours. Dabrafenib terminal half-life after a single oral dose of the dispersible tablet formulation was 11.5 hours (CV of 67.7%) in an adult healthy volunteer study. The apparent clearance of dabrafenib in paediatric patients (median body weight: 38.7 kg) was 11.8 L/h (CV of 49%).

After an oral dose, the major route of elimination of dabrafenib is metabolism, mediated via CYP3A4 and CYP2C8. Dabrafenib-related material was 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.

Medicinal product interactions

Effects of other medicinal products on dabrafenib
Dabrafenib is a substrate of human P-glycoprotein (P-gp) and human BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of P-gp or BCRP is low. Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of P-gp *in vitro*.

Effects of dabrafenib on other medicinal products
Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter 1 (OAT1) and OAT3 *in vitro*, and dabrafenib and its desmethyl- metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro*, the risk of a drug-drug interaction with these transporters is minimal based on clinical exposure of dabrafenib and its metabolites.

Special patient populations

Hepatic impairment
A population pharmacokinetic analysis in adult patients 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 in adult patients 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 patients with severe renal impairment (see section 4.2).

Race
A population pharmacokinetic analysis in adult patients 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.

Gender
Based on population pharmacokinetic analyses in adult and paediatric patients, estimated clearance of dabrafenib was slightly lower in female patients, but the difference was not considered clinically relevant.

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 human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see section 4.6).

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

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

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

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

Combination with trametinib

In a study in dogs in which dabrafenib and trametinib 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

Mannitol (E 421)
Microcrystalline cellulose (E 460)
Crospovidone (E 1202)
Hypromellose (E 464)
Acesulfame potassium (E 950)
Magnesium stearate (E 470b)
Artificial berry flavour (maltodextrin, propylene glycol [E 1520], artificial flavours, triethyl citrate [E 1505], benzyl alcohol [E 1519])
Silica, colloidal anhydrous (E 551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Dispersible tablet

2 years.

Dispersible tablet suspension

Use within 30 minutes of preparation.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

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

Each bottle contains 210 dispersible tablets and two 2 g desiccant canisters. Patients should be instructed to keep the desiccant canisters in the bottle and not to swallow them.

Packs containing:
- 1 bottle (210 dispersible tablets) and 2 dosing cups.
- 2 bottles (420 dispersible tablets) and 2 dosing cups.

Each dosing cup is 30 ml in volume with 5 ml graduated increments.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the dispersible tablet suspension

- The prescribed dose of Finlee dispersible tablets should be placed in the dosing cup containing approximately 5 ml or 10 ml of still drinking water.
- The amount of still drinking water depends on the prescribed number of dispersible tablets. For a dose of 1 to 4 dispersible tablets, use approximately 5 ml of water; for a dose of 5 to 15 dispersible tablets, use approximately 10 ml of water.
- It may take 3 minutes (or more) to fully disperse the tablets.
- The contents should be gently stirred with the handle of a stainless steel teaspoon and then administered immediately.
- Administer the suspension no later than 30 minutes after preparation (after the tablets have fully dispersed). If more than 30 minutes have passed, do not use the suspension.
- After administration of the prepared suspension, there will be tablet residue inside the dosing cup. The residue may be difficult to see. Add approximately 5 ml of still drinking water to the empty dosing cup and stir with the handle of the stainless steel teaspoon to re-suspend any remaining particles. The entire contents of the dosing cup should be administered.

Administration using a feeding tube or an oral syringe

- Once the suspension is prepared, withdraw all of the suspension from the dosing cup into a syringe compatible with a feeding tube or oral administration.
- If administering via a feeding tube, flush the feeding tube with still drinking water before administering, and dispense the suspension into the feeding tube as per the manufacturer's instructions, and flush the feeding tube with still drinking water after administering.
- If administering via an oral syringe, place the end of the oral syringe inside the mouth with the tip touching the inside of either cheek. Slowly push the plunger all the way down to deliver the full dose.

A complete and illustrated set of instructions for use is provided at the end of the package leaflet "Instructions for use".

Disposal

The dosing cup can be used for up to 4 months after first use. After 4 months, the dosing cup can be thrown away in the household waste.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1767/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2023

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000, Ljubljana
Slovenia

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

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

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Finlee 10 mg dispersible tablets
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains dabrafenib mesilate equivalent to 10 mg of dabrafenib.

3. LIST OF EXCIPIENTS

Contains benzyl alcohol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible tablet

1 bottle of 210 dispersible tablets + 2 cups
420 (2 bottles of 210) dispersible tablets + 2 cups

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Disperse tablets in water before swallowing.

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
Use within 30 minutes of preparation.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1767/001	1 bottle of 210 dispersible tablets + 2 cups
EU/1/23/1767/002	420 (2 bottles of 210) dispersible tablets + 2 cups

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Finlee 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Finlee 10 mg dispersible tablets
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains dabrafenib mesilate equivalent to 10 mg of dabrafenib.

3. LIST OF EXCIPIENTS

Contains benzyl alcohol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible tablets

210 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Disperse tablets in water before swallowing.

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
Use within 30 minutes of preparation.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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/1/23/1767/001	1 bottle of 210 dispersible tablets + 2 cups
EU/1/23/1767/002	420 (2 bottles of 210) dispersible tablets + 2 cups

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Finlee 10 mg dispersible tablets
dabrafenib

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

What is in this leaflet

1. What Finlee is and what it is used for

Finlee is a medicine that contains the active substance dabrafenib.

It is used in combination with another medicine (trametinib oral solution) in children aged 1 year and older to treat a type of brain tumour called glioma.

Finlee can be used in patients with:
- low-grade glioma
- high-grade glioma when the patient has received at least one radiation and/or chemotherapy treatment.

Finlee is used to treat patients whose brain tumour has a specific mutation (change) in the so-called BRAF gene. This mutation causes the body to make faulty proteins which in turn may cause the tumour to develop. The doctor will test for this mutation before starting treatment.

In combination with trametinib, Finlee targets these faulty proteins and slows down or stops the development of the tumour. **Also read the leaflet for trametinib oral solution.**

2. What you need to know before you give Finlee

Do not give Finlee
- **if your child is allergic** to dabrafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to the doctor before giving Finlee. The doctor needs to know if your child:
- has **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).
- has **heart problems** such as heart failure or problems with the way their heart beats.
- has or has had any **kidney problems**.
- has or has had any **liver problems**.
- has or has had any **lung or breathing problems**, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue.
- has or has had any **gastrointestinal problems** such as diverticulitis (inflamed pouches in the colon) or metastases to the gastrointestinal tract.

Before your child starts taking Finlee, during and after their treatment, the doctor will make checks to avoid complications.

Skin examination
Finlee may cause skin cancer. Usually, these skin changes remain local and can be removed with surgery and treatment with Finlee can be continued without interruption. The doctor may check your child's skin before and regularly during treatment.

Check your child's skin monthly during the treatment and for 6 months after they stop taking this medicine. **Tell the doctor** as soon as possible if you notice any changes to your child's skin such as a new wart, skin sore or reddish bump that bleeds or does not heal, or a change in the size or colour of a mole.

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

Children younger than 1 year old
The effects of Finlee in children younger than 1 year old are not known. Therefore, Finlee is not recommended in this age group.

Patients older than 18 years of age
Information on treating patients older than 18 years of age with glioma is limited, therefore continued treatment into adulthood should be assessed by the doctor.

Other medicines and Finlee
Before starting treatment, tell the doctor, pharmacist or nurse if your child is taking, has recently taken or might take any other medicines. This includes medicines obtained without a prescription.

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

Tell the doctor, pharmacist or nurse if your child is taking any of these (or if you are not sure). The doctor may decide to adjust the dose.

Pregnancy, breast-feeding and fertility

Pregnancy
- If your child is pregnant, or if you think your child may be pregnant, ask the doctor or nurse for advice before taking this medicine. Finlee may potentially harm an unborn baby.
- If your child becomes pregnant while taking this medicine, tell the doctor immediately.

Breast-feeding
It is not known whether Finlee can pass into breast milk. If your child is breast-feeding, or planning to breast-feed, you must tell the doctor. You, your child and the doctor will decide if they will take Finlee or breast-feed.

Fertility
Finlee may reduce sperm count and this may not return to normal levels after stopping treatment with Finlee.

Taking Finlee with trametinib oral solution: Trametinib may impair fertility in both males and females.

Prior to starting treatment with Finlee, talk to the doctor about options to improve your child's chances to have children in the future.

Contraception

- If your child could become pregnant, they must use a reliable method of birth control (contraception) while they are taking Finlee in combination with trametinib oral solution and for at least 16 weeks following the last dose of Finlee in combination with trametinib.
- Birth control containing hormones (such as pills, injections or patches) may not work as well while taking Finlee in combination with trametinib oral solution. An alternative effective method of birth control should be used to avoid the risk of pregnancy while taking this combination of medicines. Ask the doctor or nurse for advice.

Driving and using machines
Finlee can have side effects that may affect your child's ability to drive, ride a bike/scooter, use machines, or take part in other activities that need alertness. If your child has problems with vision or feels tired or weak, or their energy levels are low, they should avoid such activities.

Descriptions of these effects can be found in section 4. Read all the information in this leaflet for guidance.

Discuss with the doctor, pharmacist or nurse if you are unsure about anything. Your child's disease, symptoms and treatment situation may also affect their ability to take part in such activities.

Finlee contains potassium
This medicine contains potassium, less than 1 mmol (39 mg) per maximum daily dose, i.e. essentially 'potassium-free'.

Finlee contains benzyl alcohol
This medicine contains <0.00078 mg benzyl alcohol in each dispersible tablet.

Benzyl alcohol may cause allergic reactions.

Ask the doctor or pharmacist for advice if your child is pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build up in your child's body and may cause side effects (called "metabolic acidosis").

Ask the doctor or pharmacist for advice if your child has a liver or kidney disease. This is because large amounts of benzyl alcohol can build up in your child's body and may cause side effects (called "metabolic acidosis").

3. How to give Finlee

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

How much to give
The doctor will decide on the correct dose of Finlee based on your child's body weight.

The doctor may decide that your child should be given a lower dose if they get side effects.

How to give it
Please read the Instructions for Use at the end of this leaflet for details on how to prepare and give the dispersible tablet solution.

- Give **Finlee twice a day**. Giving Finlee at the same time each day will help you to remember when to give the medicine. Give each dose of Finlee about 12 hours apart. Trametinib oral solution is only taken once a day. Give trametinib oral solution with **either** the morning dose **or** the evening dose of Finlee.
- Give Finlee on an empty stomach, at least one hour before or two hours after a meal, this means that:
    - after taking Finlee, your child must wait **at least 1 hour** before eating.
    - after eating, your child must wait **at least 2 hours** before taking Finlee.
    - if necessary, breast-feeding and/or baby formula may be given on demand.

If you give more Finlee than you should
If you give too much Finlee, **contact the doctor, pharmacist or nurse for advice.** If possible, show them the Finlee pack and this leaflet.

If you forget to give Finlee
If the missed dose is less than 6 hours late, give it as soon as you remember.
If the missed dose is 6 hours or more than 6 hours late, skip that dose. Give the next dose at the usual time and carry on giving Finlee at regular times as usual.
Do not give a double dose to make up for a forgotten dose.

If your child vomits after taking Finlee
If your child vomits after taking Finlee, do not give another dose until the next scheduled dose.

If you stop giving Finlee
Give Finlee for as long as the doctor recommends. Do not stop unless the doctor advises you to.

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

4. Possible side effects

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

Stop giving this medicine and seek urgent medical attention if your child has any of the following symptoms:
- coughing up of blood, passing blood in urine, vomit containing blood or that looks like “coffee grounds”, red or black stools that look like tar. These may be signs of bleeding.
- fever (temperature 38°C or above).
- chest pain or shortness of breath, sometimes with fever or cough. These may be signs of pneumonitis or inflamed lungs (interstitial lung disease).
- blurred vision, loss of vision or other vision changes. These may be signs of retinal detachment.
- eye redness, eye pain, increased sensitivity to light. These may be signs of uveitis.
- unexplained muscle pain, muscle cramps or muscle weakness, dark urine. These may be signs of rhabdomyolysis.

- strong abdominal pain. This may be a sign of pancreatitis.
- fever, swollen lymph glands, bruising or skin rash at the same time. These may be signs of a condition where the immune system makes too many infection-fighting cells that may cause various symptoms (haemophagocytic lymphohistiocytosis).
- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be signs of a condition resulting from a rapid breakdown of cancer cells which in some people may be fatal (tumour lysis syndrome or TLS).
- reddish patches on the trunk that are circular or target-shaped, with or without central blisters, skin peeling, ulcers of the mouth, throat, nose, genitals and eyes. These may be signs of serious skin rashes, which can be life-threatening, and can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome), widespread rash, fever and enlarged lymph nodes (DRESS).

Other possible side effects

Very common *(may affect more than 1 in 10 people)*
- Headache
- Dizziness
- Cough
- Diarrhoea, feeling sick (nausea), being sick (vomiting), constipation, stomach ache
- Skin problems such as rash, acne-like rash, dry or itching skin, redness of skin
- Wart-like growths (skin papilloma)
- Nail bed infection
- Pain in arms or legs or joints
- Lack of energy or feeling weak or tired
- Increase in weight
- Upper respiratory tract infections with symptoms such as sore throat and stuffy nose (nasopharyngitis)
- Increase of liver enzymes seen in blood tests
- Decreased level of white blood cells (neutropenia, leukopenia)
- Decreased level of red blood cells (anaemia)

Common *(may affect up to 1 in 10 people)*
- Frequent urination with pain or burning sensation (urinary tract infection)
- Skin effects including infection of the skin (cellulitis), inflammation of hair follicles in the skin, inflamed flaky skin (dermatitis exfoliative generalised), thickening of the outer layer of the skin (hyperkeratosis)
- Decreased appetite
- Low blood pressure (hypotension)
- High blood pressure (hypertension)
- Shortness of breath
- Sore mouth or mouth ulcers, inflammation of mucosa
- Inflammation of the fatty layer under the skin (panniculitis)
- Unusual loss of hair or thinning
- Red, painful hands and feet (hand-foot syndrome)
- Muscle spasms
- Chills
- Allergic reaction (hypersensitivity)
- Dehydration
- Eyesight problems including blurred vision
- Decreased heart rate (bradycardia)
- Tiredness, chest discomfort, light headedness, palpitations (ejection fraction decreased)
- Tissue swelling (oedema)
- Muscle pain (myalgia)
- Tiredness, chills, sore throat, joint or muscles aching (influenza-like illness)

- Abnormal test results related to creatine phosphokinase, an enzyme found mainly in heart, brain and skeletal muscle
- Increase in blood sugar level
- Low levels of sodium or phosphate in the blood
- Decreased level of blood platelets (cells that help blood to clot)
- Increased sensitivity of the skin to sun

Uncommon *(may affect up to 1 in 100 people)*
- Irregular heartbeat (atrioventricular block)
- Inflammation of the intestines (colitis)
- Cracking of skin
- Night sweats
- Excessive sweating
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

In addition to the side effects described above, the following side effects have so far only been reported in adult patients, but may also occur in children:
- problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)
- dry mouth
- kidney failure
- benign skin tumour (acrochordon)
- inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)
- inflammation of the kidneys
- a hole (perforation) in the stomach or intestines
- inflammation of the heart muscle which can result in breathlessness, fever, palpitations and chest pain

Reporting of side effects
If your child gets any side effects, talk to the 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 Finlee

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

Do not use this medicine after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.
Administer the solution no later than 30 minutes after the tablets have dissolved.

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask the 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 Finlee contains
- The active substance is dabrafenib. Each dispersible tablet contains dabrafenib mesilate equivalent to 10 mg of dabrafenib.
- The other ingredients are: mannitol (E 421), microcrystalline cellulose (E 460), crospovidone (E 1202), hypromellose (E 464), acesulfame potassium (E 950) (see section 2), magnesium stearate (E 470b), artificial berry flavour (maltodextrin, propylene glycol [E 1520], artificial flavours, triethyl citrate [E 1505], benzyl alcohol [E 1519] [see section 2]), and colloidal anhydrous silica (E 551).

What Finlee looks like and contents of the pack
Finlee 10 mg dispersible tablets are white to slightly yellow, round tablets of 6 mm marked “D” on one side and “NVR” on the other.

The bottles are white plastic with threaded plastic closures.

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

Finlee 10 mg dispersible tablets are available in packs containing 1 or 2 bottles (210 or 420 dispersible tablets) and 2 dosing cups.

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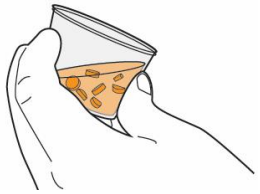
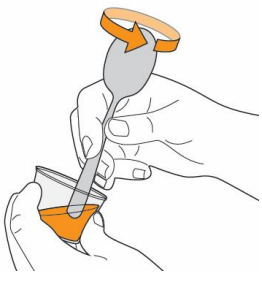
Other sources of information

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

INSTRUCTIONS FOR USE

SECTION A ADMINISTRATION VIA DOSING CUP	
You must dissolve the tablets in water before giving Finlee. Follow the instructions below to dissolve the tablets in water. If Finlee solution gets on your skin, wash the area well with soap and water. If Finlee solution gets in your eyes, rinse your eyes well with cool water. In case of spillage, follow the information in the "SPILLAGE CLEANING" section.	
1 Wash and dry your hands before administering Finlee.	
2 Add still drinking water to the dosing cup: o About 5 ml for 1 to 4 tablets o About 10 ml for 5 to 15 tablets	
3 Remove the child-resistant cap by pushing down on the cap and turning it anti-clockwise.	
4 Count the prescribed number of tablets into your hand and put them in the dosing cup. The bottle contains 2 plastic canisters with silica gel desiccant to keep the tablets dry. Put the canisters back into the bottle if they fall out. **Do not** throw the canisters away. Close the bottle with the cap. Store the closed bottle in the carton out of sight and reach of children.	
5 Slightly tilt the dosing cup and gently stir with the handle of a stainless steel teaspoon until the tablets are fully dissolved (it may take 3 minutes or more). The solution will be cloudy white when it is ready. Administer the solution no later than 30 minutes after the tablets have dissolved.	

6 Ensure that your child drinks all of the solution from the dosing cup.	
7 Add about 5 ml of still drinking water to the empty dosing cup and stir with the handle of the stainless steel teaspoon (there will be tablet residue inside the dosing cup which may be difficult to see).	
8 Ensure that your child also drinks all of this solution from the dosing cup.	
9 If 5 to 15 prescribed tablets: repeat Steps 7 to 8.	
10 For cleaning instructions, see “SECTION C”.	

SECTION B ADMINISTRATION VIA ORAL SYRINGE OR FEEDING TUBE

Feeding tube minimum size:

Your dose	**Minimum size**
1 to 3 tablets	10 French gauge
4 to 15 tablets	12 French gauge

1 Follow Steps 1 to 5 in "SECTION A" to dissolve the tablets, then move to Step 2 in this section.	
2 Withdraw all of the solution from the dosing cup into a syringe compatible with a feeding tube or oral administration.	
3a **Administering via oral syringe:** Place the end of the oral syringe inside the mouth with the tip touching the inside of either cheek. Slowly push the plunger all the way down to give the full dose. **WARNING:** Administering Finlee to the throat or pushing the plunger too fast may cause choking.	
3b **Administering via feeding tube:** Dispense the solution into the feeding tube as per the feeding tube manufacturer's instructions.	
4 Add about 5 ml of still drinking water to the empty dosing cup and stir with the handle of the stainless steel teaspoon to loosen the residue (there will be tablet residue inside the cup which may be difficult to see).	
5 Withdraw all of the solution from the dosing cup into a syringe compatible with a feeding tube or oral administration.	

6 Dispense the solution into the feeding tube or into the inside of the cheek.	
7 Repeat Steps 4 to 6 a total of 3 times to give a full dose.	
8 For cleaning instructions, see “SECTION C”.	

SECTION C CLEANING

Dosing cup

- Rinse the dosing cup with water immediately after dosing. Do not use hot water as the dosing cup may deform.
- Shake off excess water then wipe dry using clean paper towels.
- Always keep the dosing cup away from other kitchen items to avoid contamination.
- If both of your dosing cups become dirty and cannot be cleaned with water only, contact your pharmacist for a new dosing cup.

Teaspoon

- Hand wash the teaspoon with warm, soapy water or wash it in a dishwasher.

Oral Syringe

If used, clean the oral syringe as follows:

1. Fill a glass with warm, soapy water.
2. Place the oral syringe into the glass with the warm, soapy water.
3. Pull water into the oral syringe and empty again 4 to 5 times.
4. Separate the plunger from the barrel.
5. Rinse the glass, plunger and barrel under warm tap water.
6. Leave the plunger and barrel on a dry surface to air dry before next use.

You can use the dosing cup for up to 4 months after first use. After 4 months, throw away the dosing cup in the household waste.

SPILLAGE CLEANING

Follow these steps if you spill any Finlee solution:

1. Put on plastic gloves.
2. Soak up the solution completely using an absorbent material, such as paper towels soaked with a mixture of water and household disinfectant.
3. Repeat the cleaning with fresh soaked absorbent material at least 3 times until the area is clean.
4. Dry the area with paper towels.
5. Throw away all the disposable materials used to clean the spillage into a sealable plastic bag.
6. Ask the pharmacist how to throw away the plastic bag.
7. Wash your hands well with soap and water.