ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spexotras 0.05 mg/ml powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One bottle contains trametinib dimethyl sulfoxide equivalent to 4.7 mg of trametinib.

Each ml of the reconstituted solution contains 0.05 mg of trametinib.

Excipients with known effect

Each ml of the reconstituted solution contains 100 mg of sulfobutylbetadex sodium, 0.8 mg of methyl parahydroxybenzoate and 1.98 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.

White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Low-grade glioma

Spexotras in combination with dabrafenib 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

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

Before taking Spexotras, 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.

Spexotras is used in combination with dabrafenib dispersible tablets. See the summary of product characteristics (SmPC) for posology of dabrafenib dispersible tablets.

Posology

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

Table 1 Dosing regimen by body weight

Body weight*	**Recommended dose**	
	Volume of oral solution (ml) once daily	**corresponding to mg trametinib**
8 kg	6 ml	0.30 mg
9 to 10 kg	7 ml	0.35 mg
11 kg	8 ml	0.40 mg
12 to 13 kg	9 ml	0.45 mg
14 to 17 kg	11 ml	0.55 mg
18 to 21 kg	14 ml	0.70 mg
22 to 25 kg	17 ml	0.85 mg
26 to 29 kg	18 ml	0.90 mg
30 to 33 kg	20 ml	1 mg
34 to 37 kg	23 ml	1.15 mg
38 to 41 kg	25 ml	1.25 mg
42 to 45 kg	28 ml	1.40 mg
46 to 50 kg	32 ml	1.60 mg
≥51 kg	40 ml	2 mg

*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 dabrafenib dispersible tablets SmPC, "Posology" and "Method of administration", for dosing instructions for treatment with dabrafenib when used in combination with Spexotras.

Duration of treatment
Treatment with Spexotras 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 Spexotras is missed, it should only be taken if it is more than 12 hours until the next scheduled dose. If vomiting occurs after taking Spexotras, 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 trametinib and dabrafenib 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 dabrafenib dispersible tablets SmPC for further details).

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

Grade (CTCAE)*	Recommended trametinib 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)	

The recommended dose reductions to approximately 75% of the recommended dose (first dose reduction level) and to approximately 50% of the recommended dose (second dose reduction level) are shown in Table 3.

Table 3 Recommended dose reduction levels for adverse reactions

Body weight	Recommended dose	Reduced dose	
	ml solution (mg trametinib) (once daily)	Dose after the first reduction (once daily)	Dose after the second reduction (once daily)
8 kg	6 ml (0.30 mg)	5 ml	3 ml
9 to 10 kg	7 ml (0.35 mg)	5 ml	4 ml
11 kg	8 ml (0.40 mg)	6 ml	4 ml
12 to 13 kg	9 ml (0.45 mg)	7 ml	5 ml
14 to 17 kg	11 ml (0.55 mg)	8 ml	6 ml
18 to 21 kg	14 ml (0.70 mg)	11 ml	7 ml
22 to 25 kg	17 ml (0.85 mg)	13 ml	9 ml
26 to 29 kg	18 ml (0.90 mg)	14 ml	9 ml
30 to 33 kg	20 ml (1 mg)	15 ml	10 ml
34 to 37 kg	23 ml (1.15 mg)	17 ml	12 ml
38 to 41 kg	25 ml (1.25 mg)	19 ml	13 ml
42 to 45 kg	28 ml (1.40 mg)	21 ml	14 ml
46 to 50 kg	32 ml (1.60 mg)	24 ml	16 ml
≥51 kg	40 ml (2 mg)	30 ml	20 ml
Dose adjustment for Spexotras below 50% of the recommended dose is not recommended.			

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 trametinib 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 trametinib and dabrafenib 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 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

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

Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring (see section 4.4).

Trametinib should be permanently discontinued in patients with Grade 3 or 4 left ventricular dysfunction or clinically significant LVEF reduction which does not recover within 4 weeks (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 trametinib and dabrafenib, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. If RPED is diagnosed, follow the dose modification schedule in Table 4 below for trametinib (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib for confirmed cases of RVO or RPED.

Table 4 Recommended dose modifications for trametinib for RPED

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2 or 3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2 or 3 RPED that improves to Grade 0 or 1 within 3 weeks	Resume trametinib at a lower dose level (see Table 3) or discontinue trametinib in patients on the lowest dose level.
Grade 2 or 3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

Interstitial lung disease (ILD)/Pneumonitis

Trametinib must be withheld in patients 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. Trametinib must be permanently discontinued in patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

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).

Special populations
Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment. Available data from a clinical pharmacology study indicate a limited impact of moderate to severe hepatic impairment on trametinib exposure (see section 5.2). Trametinib 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 data with trametinib in patients with severe renal impairment; therefore, the potential need for dose adjustment cannot be determined (see section 5.2). Trametinib should be used with caution in patients with severe renal impairment.

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

Method of administration

Spexotras is for oral use.

Spexotras powder must be reconstituted to the oral solution by the pharmacist prior to being dispensed. It is recommended that a healthcare professional discusses how to administer the prescribed daily dose of the oral solution with the patient or caregiver prior to administration of the first dose.

Spexotras exposure is not affected by food (see section 5.2). Spexotras should be taken at the same time as dabrafenib dispersible tablet, which has reduced exposure with food. Spexotras should therefore 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 dose of Spexotras is taken at a similar time every day, using the re-usable oral syringe provided. The once-daily dose of Spexotras should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

If the patient is unable to swallow and has a nasogastric tube in situ, the Spexotras oral solution can be administered via the tube.

Instructions for preparation 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

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

BRAF V600E testing

The efficacy and safety of trametinib in combination with dabrafenib have not been evaluated in patients whose glioma tested negative for the BRAF V600E mutation.

New malignancies

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

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 trametinib in combination with dabrafenib (see section 4.8). It is recommended that skin examination be performed prior to initiation of therapy with trametinib and monthly throughout treatment and for up to six months after treatment. Monitoring should continue for 6 months following discontinuation of trametinib 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
Based on its mechanism of action, dabrafenib may increase the risk of non-cutaneous malignancies when RAS mutations are present. Please refer to the dabrafenib dispersible tablets SmPC (section 4.4). No dose modification of trametinib is required for RAS mutation-positive malignancies when taken in combination with dabrafenib.

Haemorrhage

Haemorrhagic events have been reported in adult and paediatric patients taking trametinib in combination with dabrafenib (see section 4.8). Major haemorrhagic events and fatal haemorrhages have occurred in adult patients taking trametinib in combination with dabrafenib. 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.

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

Trametinib in combination with dabrafenib 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.

Trametinib should be used with caution in patients with impaired left ventricular function. Patients with left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant uncontrolled arrhythmias, and uncontrolled hypertension were excluded from clinical studies; safety of use in this population is therefore unknown. LVEF should be evaluated in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3-monthly intervals while on treatment (see section 4.2 regarding dose modification).

In patients receiving trametinib in combination with dabrafenib, 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.

Pyrexia

Fever has been reported in adult and paediatric clinical studies with trametinib (see section 4.8). The incidence and severity of pyrexia are increased with the combination therapy (see dabrafenib dispersible tablets SmPC section 4.4). In patients receiving trametinib in combination with dabrafenib, pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency. In paediatric patients who received trametinib in combination with dabrafenib, the median time to onset of the first occurrence of pyrexia was 1.5 months.

Therapy with trametinib and dabrafenib 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).

Blood pressure changes

Both hypertension and hypotension have been reported in patients in clinical studies with trametinib in combination with dabrafenib (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

In a Phase III study in adult patients, 2.4% (5/211) of patients treated with trametinib monotherapy developed ILD or pneumonitis; all five patients required hospitalisation. The median time to onset of the first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days). In two studies in adult patients treated with trametinib in combination with dabrafenib, 1% of patients developed pneumonitis or ILD (see section 4.8).

Trametinib must be withheld in patients 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. Trametinib should be permanently discontinued in patients diagnosed with treatment-related ILD or pneumonitis (see section 4.2). Therapy with dabrafenib may be continued at the same dose.

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, may occur with trametinib, in some cases with a time to onset of several months. Symptoms such as blurred vision, decreased acuity and other visual phenomena have been reported in adult clinical studies with trametinib. In clinical studies, uveitis and iridocyclitis have also been reported in adult and paediatric patients treated with trametinib in combination with dabrafenib.

Trametinib is not recommended in patients with a history of RVO. The safety of trametinib in patients with predisposing factors for RVO, including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes, has not been established.

If patients report new visual disturbances, such as diminished central vision, blurred vision or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. If RPED is diagnosed, the dose modification schedule in Table 4 should be followed (see section 4.2); if uveitis is diagnosed, please refer to the dabrafenib dispersible tablets SmPC (section 4.4). In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued.

No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Rash

Rash has been observed in 49% of paediatric patients in clinical studies when trametinib is used in combination with dabrafenib (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 trametinib/dabrafenib 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 trametinib. In some cases, patients were able to continue trametinib. In more severe cases, hospitalisation, interruption or permanent discontinuation of therapy was required. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated.

Pancreatitis

Pancreatitis has been reported in adult and paediatric patients treated with trametinib in combination with dabrafenib 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.

Renal failure

Renal failure has been identified in ≤1% of adult patients treated with trametinib in combination with dabrafenib. 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. Trametinib 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 trametinib in combination with dabrafenib (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.

Hepatic impairment

As metabolism and biliary excretion are the primary routes of elimination of trametinib, administration of trametinib should be undertaken with caution in patients with moderate to severe hepatic impairment (see sections 4.2 and 5.2).

Deep vein thrombosis/Pulmonary embolism

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 trametinib in combination with dabrafenib (see section 4.8). Colitis and gastrointestinal perforation, including fatal outcome, have been reported in adult patients. Trametinib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medicinal products with a recognised risk of gastrointestinal perforation.

Sarcoidosis

Cases of sarcoidosis have been reported in adult patients treated with trametinib in combination with dabrafenib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with trametinib and dabrafenib 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 16 weeks after the last dose of Spexotras. Male patients taking trametinib in combination with dabrafenib 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 trametinib in combination with dabrafenib. Caution should be taken when trametinib is administered in combination with dabrafenib. If HLH is confirmed, administration of trametinib and dabrafenib 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 trametinib in combination with dabrafenib (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.

Excipients

Sulfobutylbetadex sodium
Spexotras oral solution contains the cyclodextrin sulfobutylbetadex sodium (100 mg/ml). Cyclodextrins (CDs) are excipients which can influence the properties of the active substance and other medicines. In preclinical studies in animals that were administered CDs intravenously, there were observations of renal toxicity and ototoxicity. Safety aspects of CDs have been considered during the development and safety assessment of the medicinal product. There are limited safety data on the effects of CDs in children <2 years of age.

Methyl parahydroxybenzoate
This medicinal product contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Sodium
This medicinal product contains 1.98 mg sodium per ml of Spexotras oral solution, equivalent to 4% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult at the maximum daily trametinib dose of 2 mg (40 ml).

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

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 trametinib

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (e.g. carboxyl-esterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions (see section 5.2). Drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.

Trametinib is an *in vitro* substrate of the efflux transporter P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

Effect of trametinib on other medicinal products

Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interaction with CYP enzymes or transporters (see section 5.2). Trametinib may result in transient inhibition of BCRP substrates (e.g. pitavastatin) in the gut, which may be minimised with staggered dosing (2 hours apart) of these agents and trametinib.

Based on clinical data, no loss of efficacy of hormonal contraceptives is expected when co-administered with trametinib (see section 5.2). However, use with dabrafenib may render hormonal contraceptives less effective.

Effect of the excipient sulfobutylbetadex sodium on other oral medicinal products with low bioavailability and narrow therapeutic index

The trametinib oral solution contains 100 mg/ml of sulfobutylbetadex sodium which may have the potential to affect the solubility and bioavailability of other oral medicinal products. Caution should be taken when the trametinib oral solution is administered with oral medicinal products that have low bioavailability and a narrow therapeutic index (e.g. imipramine, desipramine).

Also refer to the guidance for medicinal product interactions for dabrafenib found in sections 4.4 and 4.5 of the dabrafenib dispersible tablets 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 treatment with trametinib and for 16 weeks after stopping treatment.

Use with 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 during trametinib/dabrafenib combination therapy. Please refer to the dabrafenib dispersible tablets SmPC for further information.

Pregnancy

There are no data from the use of trametinib in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Trametinib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is not known whether trametinib is excreted in human milk. A risk to the breast-feeding child cannot be excluded. Trametinib should not be administered to breast-feeding mothers. A decision should be made whether to discontinue breast-feeding or discontinue trametinib, 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 trametinib. In animals, no fertility studies have been performed, but effects were seen on female reproductive organs (see section 5.3). Trametinib may impair fertility in humans.

Men taking trametinib in combination with dabrafenib
Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients taking trametinib in combination with dabrafenib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Please refer to the dabrafenib dispersible tablets SmPC for further information.

4.7 Effects on ability to drive and use machines

Trametinib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of trametinib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and 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 trametinib in combination with dabrafenib, 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 trametinib tablets and dabrafenib capsules: 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, tattoo-associated skin reactions (frequency not known).

Tabulated list of adverse reactions

The safety of trametinib in combination with dabrafenib 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 5) 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 5 Adverse reactions with trametinib in combination with dabrafenib

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, skin fissures, night sweats, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, pain in extremity
Common	Myalgia*, muscle spasms*[12]
General disorders and administration site conditions	
Very common	Pyrexia*, fatigue*[13], weight increased
Common	Mucosal inflammation, face oedema*, chills, oedema peripheral, influenza-like illness

Investigations	
Very common	Transaminases increased*[14]
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] muscle spasms include musculoskeletal stiffness
[13] fatigue includes malaise and asthenia
[14] 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 trametinib in combination with dabrafenib 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, occurred in adult patients taking trametinib in combination with dabrafenib.

The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patents 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. 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 to 5 months.

Patients with LVEF lower than the institutional lower limit of normal were not included in clinical studies with trametinib. Trametinib in combination with dabrafenib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Pyrexia
Pyrexia has been reported in clinical studies with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy (see section 4.4). Pyrexia was reported in 70% of paediatric patients, with Grade 3 events occurring in 11% of patients. Please refer to the dabrafenib dispersible tablets SmPC.

Hepatic events
Hepatic adverse reactions have been reported in adult and paediatric clinical studies with trametinib in combination with dabrafenib. In the paediatric safety population, increased ALT and AST were very common, reported in 13% and 16% of patients, respectively (see section 4.4). The hepatic adverse reactions of increased ALT and AST were the most common events in adult patients, the majority of these events were either Grade 1 or 2. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Liver events were detected in clinical studies with monitoring every four weeks. It is recommended that patients receiving treatment with trametinib have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

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).

Interstitial lung disease (ILD)/Pneumonitis
Patients treated with trametinib may develop ILD or pneumonitis. Trametinib should be withheld in patients 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. For patients diagnosed with treatment-related ILD or pneumonitis, trametinib should be permanently discontinued (see sections 4.2 and 4.4).

Visual impairment
In paediatric patients treated with trametinib in combination with dabrafenib, ophthalmological reactions, including uveitis 3.5% and iridocyclitis 1.8%, have been reported. Grade 3 uveitis occured in 1.8% of paediatric patients. Retinal pigment epithelial detachment (RPED) occurred in <1% of paediatric patients. Disorders associated with visual disturbances, including RPED and RVO, have also been observed with trametinib in adult patients. Symptoms such as blurred vision, decreased acuity and other visual disturbances have been reported in adult clinical studies with trametinib (see sections 4.2 and 4.4).

Rash
Rash has been observed in 49% of paediatric patients in trametinib and dabrafenib combination studies in the integrated safety population. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions (see sections 4.2 and 4.4).

Rhabdomyolysis
Rhabdomyolysis has been reported in adult patients taking trametinib. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated (see section 4.4).

Pancreatitis
Pancreatitis was reported in 1.2% of paediatric patients, with <1% of patients with Grade 3 severity. 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).

Renal failure
Renal failure has been reported with trametinib in combination with dabrafenib. Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon in adult patients; however, trametinib 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 trametinib in combination with dabrafenib in clinical studies. Persistent overdosing of trametinib could result in increased rash, decreased LVEF, or retinal abnormalities. 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, mitogen-activated protein kinase (MEK) inhibitors, ATC code: L01EE01

Mechanism of action

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.

Combination with dabrafenib
Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway.

Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of trametinib with dabrafenib 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.

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 in tumour tissue via a local test, or by a central laboratory using the bioMérieux THxID-BRAF kit 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	

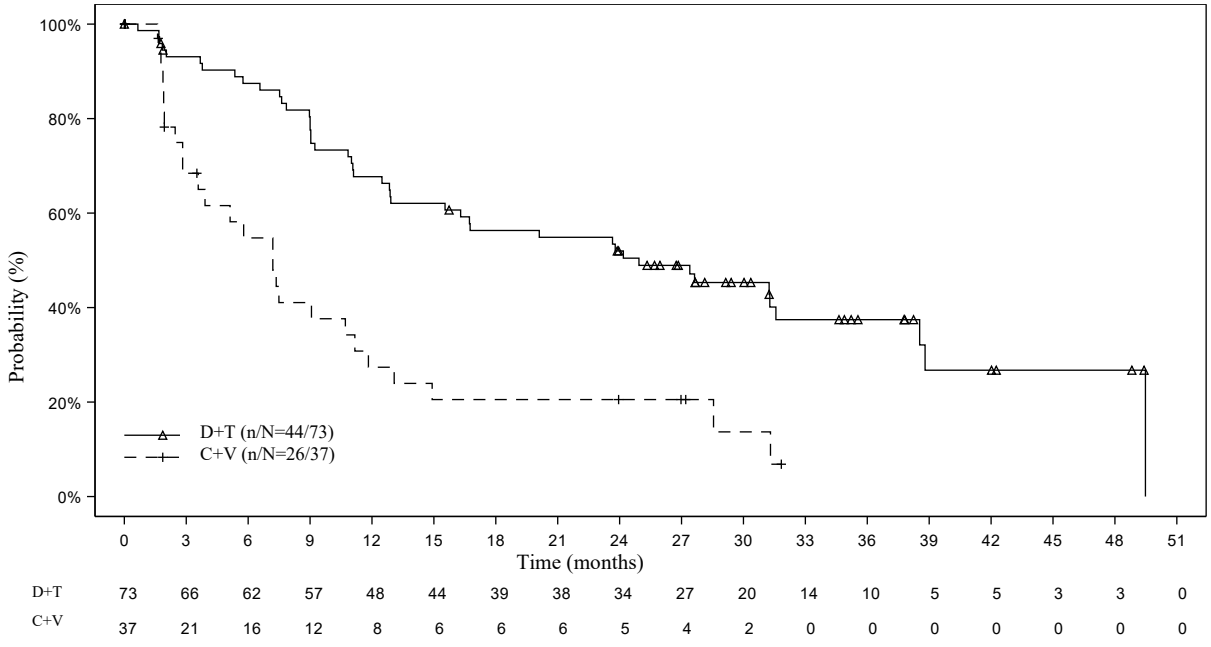
NE=not estimable

[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 trametinib have mostly been determined in adult patients using the solid (tablet) formulation. The pharmacokinetics of trametinib following single or repeat weight-adjusted dosing were also evaluated in 244 paediatric patients. Pharmacokinetic characteristics (drug absorption rate and drug clearance) of trametinib in paediatric patients were comparable to those of adults. Weight was found to influence trametinib oral clearance, while age did not. The pharmacokinetic exposures of trametinib at the recommended weight-adjusted dose in paediatric patients were within range of those observed in adults.

Absorption

The trametinib oral solution was rapidly absorbed with a median time to achieve peak plasma concentration (T_{max}) of 1 hour post-dose. The mean absolute oral bioavailability of the trametinib tablets was 72%. In a relative bioavailability study comparing the oral solution formulation and the tablet formulation after single-dose administration in the fasted state in adults, administration of the oral solution formulation resulted in a 12%, 10% and 71% higher $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$ and C_{max} respectively as compared to the tablet formulation.

Trametinib exposure increased in a dose-proportional manner between 0.125 mg and 4 mg following repeat once-daily dosing.

In the pivotal paediatric study, steady-state geometric mean (%CV) C_{max} and AUC_{tau} were 22.7 ng/ml (41.1%) and 339 ng*hr/ml (22.2%) in the LGG cohort and 21.3 ng/ml (36.3%) and 307 ng*hr/ml (22.8%) in the HGG cohort.

Trametinib accumulates with repeat daily dosing. A mean accumulation ratio of 6.0 was observed for the tablet formulation at 2 mg once-daily dose. Steady state was achieved by Day 15.

Food effect
Administration of a single 2 mg dose of the trametinib oral solution with a low-fat, low-calorie meal resulted in a 12% decrease in C_{max} compared to fasted conditions, which is not considered to be clinically significant. The AUC_{last} remained unchanged.

Distribution

Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of approximately 1200 L determined following administration of a 5 μg intravenous microdose.

Biotransformation

In vitro and *in vivo* studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolised by glucuronidation. CYP3A4 oxidation is considered a minor pathway of metabolism. The deacetylation is mediated by the carboxyl-esterases 1b, 1c and 2, with possible contributions by other hydrolytic enzymes.

Following single and repeated doses of trametinib, trametinib as parent is the main circulating component in plasma.

Elimination

Mean terminal half-life of trametinib is 127 hours (5.3 days) after single-dose administration. The apparent clearance of trametinib in paediatric patients (median body weight: 32.85 kg) was 3.44 L/h (CV of 20%).

Total dose recovery was low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long elimination half-life. Trametinib-related material was excreted predominantly in the faeces (>80% of recovered radioactivity) and to a minor extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered as parent in urine.

Medicinal product interactions

Effects of trametinib on drug-metabolising enzymes and transporters
In vitro and *in vivo* data suggest that trametinib is unlikely to affect the pharmacokinetics of other medicinal products. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Based on *in vitro* studies, trametinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, P-gp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the *in vitro* potency of inhibition or induction values, trametinib is not considered to be an *in vivo* inhibitor or inducer of these enzymes or transporters, although transient inhibition of BCRP substrates in the gut may occur (see section 4.5).

Effects of other medicinal products on trametinib
In vivo and *in vitro* data suggest that the pharmacokinetics of trametinib are unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the transporters BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2 and MATE1. Trametinib is an *in vitro* substrate of BSEP and the efflux transporter P-gp. Although trametinib exposure is unlikely to be affected by inhibition of BSEP, increased levels of trametinib upon strong inhibition of hepatic P-gp cannot be excluded (see section 4.5).

Effects of trametinib on other medicinal products
The effect of repeat-dose trametinib on the steady-state pharmacokinetics of combination oral contraceptives, norethindrone and ethinyl estradiol, was assessed in a clinical study that consisted of 19 female patients with solid tumours. Norethindrone exposure increased by 20% and ethinyl estradiol exposure was similar when co-administered with trametinib. Based on these results, no loss of efficacy of hormonal contraceptives is expected when co-administered with trametinib.

Special patient populations

Hepatic impairment
Population pharmacokinetic analyses and data from a clinical pharmacology study in adult patients with normal hepatic function or with mild, moderate or severe bilirubin and/or AST elevations (based on National Cancer Institute [NCI] classification) indicate that hepatic function does not significantly affect trametinib oral clearance.

Renal impairment
Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib were characterised in 223 adult patients enrolled in clinical studies with trametinib who had mild renal impairment and 35 adult patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (<6% for either group). No data are available in patients with severe renal impairment (see section 4.2).

Race
There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics as clinical experience is limited to Caucasians.

Gender
Based on population pharmacokinetic analyses in adult and paedatric patients, gender was found to influence trametinib oral clearance. Although female patients are predicted to have higher exposure than male patients, these differences are unlikely to be clinically relevant and no dose adjustment is warranted.

5.3 Preclinical safety data

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC.

Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues.

In embryo-foetal developmental toxicity studies in rats and rabbits, trametinib induced maternal and developmental toxicity. In rats, decreased foetal weights and increased post-implantation loss were seen at exposures below or slightly above the human clinical exposure based on AUC. In an embryo-foetal developmental toxicity study with rabbits, decreased foetal body weight, increased abortions, increased incidence of incomplete ossification and skeletal malformations were seen at sub-clinical exposures based on AUC.

In repeat-dose studies the effects seen after trametinib exposure are found mainly in the skin, gastrointestinal tract, haematological system, bone and liver. Most of the findings are reversible after drug-free recovery. In rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks. In adult rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver and kidney and haemorrhage in the lung at exposures comparable to the human clinical exposure. In rats, hypertrophy of the physis and increased bone turnover were observed. In rats and dogs given trametinib at or below human clinical exposures, bone marrow necrosis, lymphoid atrophy in thymus and GALT and lymphoid necrosis in lymph nodes, spleen and thymus were observed, which have the potential to impair immune function. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately 2 times the human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC_{50} at 2.92 µg/ml, ≥130 times the human clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

Combination with dabrafenib

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulfobutylbetadex sodium
Sucralose (E 955)
Citric acid monohydrate (E 330)
Disodium phosphate (E 339)
Potassium sorbate (E 202)
Methyl parahydroxybenzoate (E 218)
Strawberry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder for oral solution

3 years.

Reconstituted oral solution

Store below 25ºC.
Do not freeze.
Discard any unused solution 35 days after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light and moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottle of 180 ml with a child-resistant screw cap closure, containing 12 g of powder.

Each carton contains one bottle, one press-in bottle adapter and one 20 ml re-usable oral dosing syringe with 0.5 ml graduation marks.

6.6 Special precautions for disposal and other handling

Spexotras powder must be reconstituted to the oral solution by the pharmacist prior to being dispensed.

Reconstitution instructions (for the pharmacist only):

1. Wash and dry your hands.
2. Check the powder expiry date on the bottle.
3. Tap the bottle to loosen the powder.
4. Remove the cap and add 90 ml distilled or purified water to the powder in the bottle.
5. Attach the cap and invert the bottle repeatedly for up to 5 minutes, until fully dissolved. You may also gently shake.
   Note: White floating particles inherent to the product may be visible in the final reconstituted solution.
6. Separate the bottle adapter from the oral syringe. Remove the bottle cap and insert the bottle adapter into the bottle neck. Push hard until the bottle adapter is fully inserted. The bottle adapter should be fully flush with the bottle neck.
7. Write the date of preparation on the carton. The solution expires 35 days after preparation.
8. Inform the recipient of the dose and the date the solution was prepared on.

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/1/23/1781/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 January 2024

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

Novartis Pharmaceuticals S.R.L.
Str. Livezeni nr.7A
540472 Targu Mures
Romania

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

Spexotras 0.05 mg/ml powder for oral solution
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 4.7 mg trametinib (as trametinib dimethyl sulfoxide). After reconstitution with 90 ml water, the solution contains 0.05 mg/ml trametinib.

3. LIST OF EXCIPIENTS

Contains cyclodextrin, sodium, E 218. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

1 bottle + 1 bottle adapter + 1 oral syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Fully insert the bottle adapter after reconstitution.

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 35 days of reconstitution.
Solution prepared on:
Discard any unused solution 35 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.
Before reconstitution: Store in a refrigerator.
After reconstitution: Store below 25°C. Do not freeze.

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/1/23/1781/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spexotras 0.05 mg/ml

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

Spexotras 0.05 mg/ml powder for oral solution
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 4.7 mg trametinib (as trametinib dimethyl sulfoxide). After reconstitution with 90 ml water, the solution contains 0.05 mg/ml trametinib.

3. LIST OF EXCIPIENTS

Contains cyclodextrin, sodium, E 218. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

4.7 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard any unused solution 35 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.
Before reconstitution: Store in a refrigerator.
After reconstitution: Store below 25°C. Do not freeze.

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

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12. MARKETING AUTHORISATION NUMBER(S)

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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

Spexotras 0.05 mg/ml powder for oral solution
trametinib

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 Spexotras is and what it is used for
2. What you need to know before you give Spexotras
3. How to give Spexotras
4. Possible side effects
5. How to store Spexotras
6. Contents of the pack and other information

1. What Spexotras is and what it is used for

Spexotras is a medicine that contains the active substance trametinib.

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

Spexotras 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.

Spexotras in combination with dabrafenib dispersible tablets 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 dabrafenib, Spexotras targets these faulty proteins and slows down or stops the development of the tumour. **Also read the leaflet for dabrafenib dispersible tablets.**

2. What you need to know before you give Spexotras

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

Warnings and precautions
Talk to the doctor before giving Spexotras. The doctor needs to know if your child:
- has **heart problems** such as heart failure or problems with the way their heart beats.
- 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 **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 or has had any **liver problems**.
- has or has had any **kidney problems**.
- 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 Spexotras, during and after their treatment, the doctor will make checks to avoid complications.

Skin examination
The treatment may cause skin cancer. Usually, these skin changes remain local and can be removed with surgery and the treatment 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
Spexotras in combination with dabrafenib dispersible tablets has not been tested in children younger than 1 year old. Therefore, Spexotras 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 Spexotras
Before starting treatment, tell the doctor, pharmacist or nurse if your child is taking, has recently taken or might take any other medicines, including medicines used to thin the blood or any other medicines obtained without a prescription.

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. Spexotras can harm the unborn baby.
- If your child becomes pregnant while taking this medicine, tell the doctor immediately.

Breast-feeding
It is not known whether Spexotras 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 Spexotras or breast-feed.

Fertility
Spexotras may impair fertility in both males and females.

Taking Spexotras with dabrafenib dispersible tablets: Dabrafenib may reduce sperm count and this may not return to normal levels after stopping treatment with dabrafenib.

Prior to starting treatment with dabrafenib dispersible tablets, 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 Spexotras and for at least 16 weeks after they stop taking it.
- Birth control containing hormones (such as pills, injections or patches) may not work as well while taking Spexotras in combination with dabrafenib dispersible tablets. 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
Spexotras 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.

Spexotras contains a cyclodextrin
This medicine contains 100 mg of a cyclodextrin in each ml of Spexotras oral solution.

Spexotras contains methyl parahydroxybenzoate
May cause allergic reactions (possibly delayed).

Spexotras contains sodium
This medicine contains 1.98 mg sodium (main component of cooking/table salt) in each ml of Spexotras oral solution. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult at the highest recommended trametinib dose.

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

3. How to give Spexotras

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 Spexotras 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 give the oral solution. The oral solution will be prepared for you by your pharmacist.

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

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

If you forget to give Spexotras
If the missed dose is less than 12 hours late, give it as soon as you remember.
If the missed dose is 12 hours or more than 12 hours late, skip that dose. Give the next dose at the usual time and carry on giving Spexotras at regular times as usual.
Do not give a double dose to make up for a forgotten dose.

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

If you stop giving Spexotras
Give Spexotras 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
- skin reactions localised in tattoos

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 Spexotras

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.

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

Before reconstitution: Store in a refrigerator (2°C – 8°C).

After reconstitution: Store below 25ºC. Do not freeze. Discard any unused solution 35 days after reconstitution.

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 Spexotras contains
- The active substance is trametinib. One bottle contains trametinib dimethyl sulfoxide equivalent to 4.7 mg of trametinib. Each ml of the reconstituted solution contains 0.05 mg of trametinib.
- The other ingredients are: sulfobutylbetadex sodium (see section 2), sucralose (E 955), citric acid monohydrate (E 330), disodium phosphate (E 339) (see section 2), potassium sorbate (E 202) (see section 2), methyl parahydroxybenzoate (E 218) (see section 2), and strawberry flavour.

What Spexotras looks like and contents of the pack
Spexotras 0.05 mg/ml powder for oral solution is a white or almost white powder.

Spexotras is supplied in an amber glass bottle of 180 ml with a child-resistant screw cap closure, containing 12 g of powder. Each carton contains one bottle, one press-in bottle adapter and one 20 ml re-usable oral dosing syringe with 0.5 ml graduation marks.

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This leaflet was last revised in

Other sources of information

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

The following information is intended for pharmacists only:

Reconstitution instructions (for the pharmacist only):

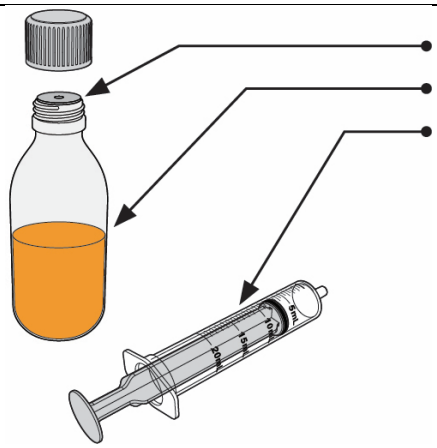
1. Wash and dry your hands.
2. Check the powder expiry date on the bottle.
3. Tap the bottle to loosen the powder.
4. Remove the cap and add 90 ml distilled or purified water to the powder in the bottle.
5. Attach the cap and invert the bottle repeatedly for up to 5 minutes, until fully dissolved. You may also gently shake.
   Note: White floating particles inherent to the product may be visible in the final reconstituted solution.
6. Separate the bottle adapter from the oral syringe. Remove the bottle cap and insert the bottle adapter into the bottle neck. Push hard until the bottle adapter is fully inserted. The bottle adapter should be fully flush with the bottle neck.
7. Write the date of preparation on the carton. The solution expires 35 days after preparation.
8. Inform the recipient of the dose and the date the solution was prepared on.

INSTRUCTIONS FOR USE

Ask your healthcare professional or pharmacist to show you how to use Spexotras correctly. Always use Spexotras exactly as your healthcare professional or pharmacist tells you to.

If you have any questions about how to use Spexotras, contact your healthcare professional or pharmacist.

SECTION A ADMINISTRATION VIA ORAL SYRINGE

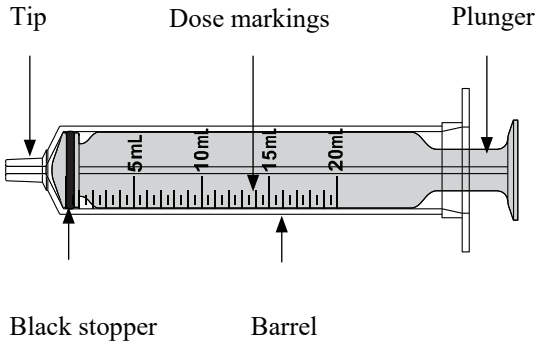


To administer Spexotras, you will need:
Bottle adapter (already inserted into the bottle neck)
Solution in bottle
Oral syringe

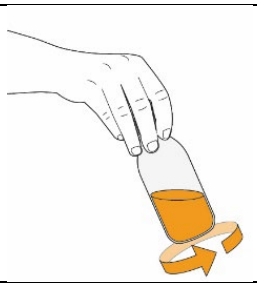
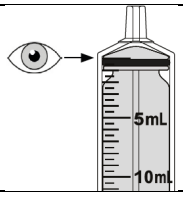
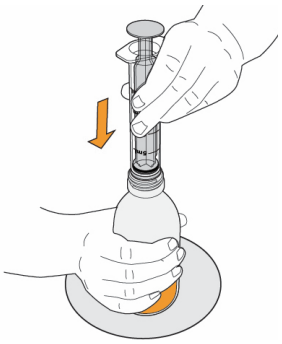
In case of spillage or contact of the Spexotras solution with the skin or eyes, follow the information in the "SPILLAGE CLEANING" section.

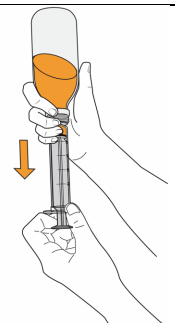
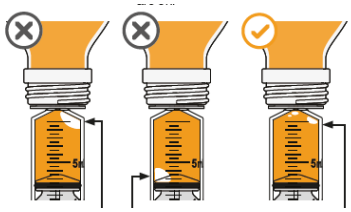
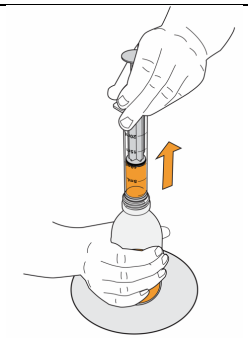
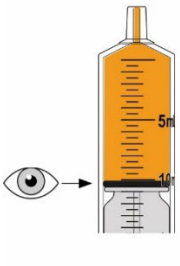
Wash and dry your hands before administering Spexotras.

Resuable oral syringe parts:



1 Check the solution preparation date on the carton. **Do not** administer Spexotras if more than 35 days have passed after solution preparation. **Note:** The printed expiry date on the right side of the bottle label does **NOT** apply to the solution. This printed expiry date applies only to the powder before it is reconstituted into a solution by your pharmacist.	

2 Gently swirl the bottle for 30 seconds to mix the solution. If foam appears, allow the bottle to stand until the foam disappears.	
3 Remove the child-resistant cap by pushing down on the cap and turning it anti-clockwise.	
4 Check if there is a bottle adapter already inserted in the bottle neck. If not inserted, contact your pharmacist.	
5 Push the plunger down into the oral syringe as far as it will go to remove all the air inside.	
6 Place the bottle on a flat surface and hold it upright. Insert the tip of the oral syringe into the opening of the bottle adapter. Make sure the oral syringe is securely attached. **IMPORTANT:** Due to air pressure, the plunger may move by itself when you measure your dose during Step 7. Hold the plunger to prevent it moving.	

7 Carefully turn the bottle upside down and pull the plunger to measure out your dose. With the tip facing up, the **top** of the black stopper must line up with your prescribed dose. If large air bubbles appear in the syringe, as shown in the pictures, push the medicine back into the bottle and withdraw your dose again. Keep doing this until there are no large air bubbles present. Small air bubbles are acceptable.	  **Large air bubble** **Small air bubbles**
8 Continue to hold the plunger in place, turn the bottle back around and place it onto a flat surface. Remove the oral syringe from the bottle by gently pulling straight up.	
9 Double check the **top** of the black stopper is at your prescribed dose. If not, repeat Steps 6 to 8. If you are administering via oral syringe, continue to Step 10. If you are administering via a feeding tube, go to “SECTION B”.	
10 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 Spexotras to the throat or pushing the plunger too fast may cause choking.	

11 Check there is no Spexotras left in the oral syringe. If there is any solution left in the oral syringe, administer it. **Note:** If your dose is larger than the oral syringe's capacity, repeat administration until the total volume is delivered.	
12 Place the cap back on the bottle and turn it clockwise to close it. Make sure the cap is securely attached onto the bottle. **Do not** remove the bottle adapter.	
13 Clean the oral syringe in accordance with the instructions in "SECTION C", then store the solution and oral syringe in accordance with the instructions in the "STORAGE" section.	

SECTION B ADMINISTRATION VIA A FEEDING TUBE
Please follow this section **only** if you are going to administer Spexotras via a feeding tube. To administer via a feeding tube, read the following information then move to Step 1. • The solution is suitable for administration via a feeding tube. • Use a Nasogastric (NG) or Gastric (G) feeding tube with a **minimum** size of 4 French gauge. • Always use the 20 ml oral syringe provided in this pack to administer Spexotras. • You may need an ENFIT adapter (not included in pack) to connect the 20 ml oral syringe to the feeding tube.
1 Flush the feeding tube according to the manufacturer's instructions immediately before administering Spexotras.
2 Follow Steps 1 to 9 in "SECTION A", then move to Step 3 in this section.
3 Connect the 20 ml oral syringe containing Spexotras to the feeding tube. You may need an ENFIT adapter to connect the oral syringe to the feeding tube.

4

Apply steady pressure to dispense the solution into the feeding tube.

5

Check there is no Spexotras left in the oral syringe. If there is any solution left in the oral syringe, administer it.

6

Flush the feeding tube again according to the manufacturer's instructions.

7

Go to "SECTION C" for cleaning.

SECTION C CLEANING

To prevent Spexotras coming into contact with other kitchen items, always clean the oral syringe separately from other kitchen items.

To clean the oral syringe:

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.

SPILLAGE CLEANING

If Spexotras gets on your skin, wash the area well with soap and water. If Spexotras gets in your eyes, rinse your eyes with water.

Follow these steps if you spill any Spexotras solution:

1. Put on plastic gloves.
2. Soak up the solution completely using an absorbent material, such as paper towels.
3. Place the absorbent material into a sealable plastic bag.
4. Wipe all surfaces exposed to the solution with an alcohol wipe.
5. Place the gloves and wipes into the same plastic bag and seal.
6. Ask the pharmacist how to throw away the plastic bag.
7. Wash your hands well with soap and water.

STORAGE
Keep your Spexotras solution and oral syringe out of the sight and reach of children. Store the solution upright, in the carton provided with the cap tightly closed. Store below 25°C. **Do not** freeze. Store your oral syringe in the carton provided alongside your Spexotras solution.