SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

VITRAKVI 100 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains larotrectinib sulfate equivalent to 100 mg of larotrectinib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (capsule).

White opaque hard gelatine capsule, size 0 (22 mm long x 7 mm wide), with blue printing of BAYER-cross and “100 mg” on body of capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with VITRAKVI should be initiated by physicians experienced in the administration of anticancer therapies.

The presence of an *NTRK* gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI.

Posology

Adults
The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs.

Paediatric population
Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.
For paediatric patients from birth to less than 3 months the recommended starting dose is 50 mg/m^2 twice daily (see section 5.2).

Missed dose
If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

Dose modification
For all grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

For all grade 3 or 4 adverse reactions not referring to liver function test abnormalities:
- VITRAKVI should be withheld until the adverse reaction resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

The recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications for VITRAKVI for adverse reactions

Dose modification	Adult and paediatric patients with body surface area of at least 1.0 m^2	Paediatric patients aged 3 months or older with body surface area less than 1.0 m^2	Paediatric patients aged less than 3 months
First	75 mg twice daily	75 mg/m^2 twice daily	25 mg/m^2 twice daily
Second	50 mg twice daily	50 mg/m^2 twice daily	-
Third	100 mg once daily	25 mg/m^2 twice daily[a]	-

[a] Paediatric patients on third dose modification at 25 mg/m² twice daily should remain on this dose (25 mg/m^2 twice daily) even if body surface area increases during the treatment.

VITRAKVI should be permanently discontinued in patients who are unable to tolerate VITRAKVI after three dose modifications.

The recommended dose modifications in case of liver function tests abnormalities during treatment with VITRAKVI are provided in Table 2.

Table 2: Recommended dose modifications and management for VITRAKVI for liver function test abnormalities

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST (>3x ULN and ≤5x ULN)	- Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5x ULN and ≤20x ULN) or Grade 4 ALT and/or AST (>20x ULN), with bilirubin <2x ULN	- Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. - Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk. - Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3x ULN with bilirubin ≥2x ULN	- Withhold treatment and monitor liver function frequently until resolution or return to baseline. - Consider permanent treatment discontinuation. - Treatment should only be resumed in patients where the benefit outweighs the risk. - If resumed, start at the next lower dose. Monitor liver function frequently upon restart. - Permanently discontinue treatment if adverse reaction recurs after resuming treatment.

ALT Alanine aminotransferase
AST Aspartate aminotransferase
ULN upper limit of normal

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Hepatic impairment
The starting dose of VITRAKVI should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Co-administration with strong CYP3A4 inhibitors
If co-administration with a strong CYP3A4 inhibitor is necessary, the VITRAKVI dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, VITRAKVI should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor (see section 4.5).

Method of administration

VITRAKVI is for oral use.

VITRAKVI is available as a capsule or oral solution with equivalent oral bioavailability and may be used interchangeably.

The patient should be advised to swallow the capsule whole with a glass of water. Due to the bitter taste, the capsule should not be opened, chewed or crushed.

The capsules can be taken with or without food but should not be taken with grapefruit or grapefruit juice.

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

Efficacy across tumour types

The benefit of VITRAKVI has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of VITRAKVI have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genetic alterations (see section 5.1). For these reasons, VITRAKVI should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

Neurologic reactions

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib (see section 4.8). For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms (see section 4.2).

Hepatotoxicity

Abnormalities of liver function tests including increased ALT, AST, alkaline phosphatase (ALP) and bilirubin have been observed in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred within 3 months of starting treatment. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported.
In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue VITRAKVI based on the severity (see section 4.2).
Liver function including ALT, AST, ALP and bilirubin should be monitored before the first dose, then every 2 weeks during the first month of treatment, then monthly for the next 6 months of treatment, then periodically during treatment. In patients who develop transaminase elevations, more frequent testing is needed (see section 4.2).

Co-administration with CYP3A4/P-gp inducers

Avoid co-administration of strong or moderate CYP3A4/P-gp inducers with VITRAKVI due to a risk of decreased exposure (see section 4.5).

Contraception in female and male

Women of childbearing potential must use highly effective contraception while taking VITRAKVI and for at least one month after stopping treatment (see sections 4.5 and 4.6).
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on larotrectinib

Effect of CYP3A, P-gp and BCRP inhibitors on larotrectinib
Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of VITRAKVI with strong or moderate CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations (see section 4.2).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with itraconazole (a strong CYP3A inhibitor and P-gp and BCRP inhibitor) 200 mg once daily for 7 days increased larotrectinib C_{max} and AUC by 2.8-fold and 4.3-fold, respectively.
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with a single dose of 600 mg rifampicin (a P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 1.8-fold and 1.7-fold, respectively.

Effect of CYP3A and P-gp inducers on larotrectinib
Co-administration of VITRAKVI with strong or moderate CYP3A inducers and strong P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided (see section 4.4).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with rifampicin (a strong CYP3A and P-gp inducer) 600 mg once daily for 11 days decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively. No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected.

Effects of larotrectinib on other agents

Effect of larotrectinib on CYP3A substrates
Clinical data in healthy adult subjects indicate that co-administration of VITRAKVI (100 mg twice daily for 10 days) increased the C_{max} and AUC of oral midazolam 1.7-fold compared to midazolam alone, suggesting that larotrectinib is a weak inhibitor of CYP3A.
Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking VITRAKVI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Effect of larotrectinib on CYP2B6 substrates
In vitro studies indicate that larotrectinib induces CYP2B6. Co-administration of larotrectinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may decrease their exposure.

Effect of larotrectinib on other transporter substrates
In vitro studies indicate that larotrectinib is an inhibitor of OATP1B1. No clinical studies have been performed to investigate interactions with OATP1B1 substrates. Therefore, it cannot be excluded whether co-administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure.

Effect of larotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that larotrectinib is a weak inducer of PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Hormonal contraceptives
It is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on the mechanism of action, foetal harm cannot be excluded when administering larotrectinib to a pregnant woman. Women of childbearing potential should have a pregnancy test prior to starting treatment with VITRAKVI.
Women of reproductive potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose. As it is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives, women using systemically acting hormonal contraceptives should be advised to add a barrier method.
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Pregnancy

There are no data from the use of larotrectinib in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of VITRAKVI during pregnancy.

Breast-feeding

It is unknown whether larotrectinib/metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with VITRAKVI and for 3 days following the final dose.

Fertility

There are no clinical data on the effect of larotrectinib on fertility. No relevant effects on fertility were observed in repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

VITRAKVI has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (36%), increased AST (33%), vomiting (30%), anaemia (28%), constipation (28%), diarrhoea (27%), nausea (24%), fatigue (23%), and dizziness (20%).
The majority of adverse reactions were grade 2 or 3. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (2%), ALT increased (1%), AST increased, leukocyte count decreased, platelet count decreased, muscular weakness and blood alkaline phosphatase increased (each in < 1%). The highest reported grade was grade 3 for adverse reactions anaemia (7%), weight increased (6%), diarrhoea (4%), gait disturbance and vomiting (each 1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and constipation (each in < 1%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases each of neutrophil count decreased, ALT increased, and AST increased, 1 case each of gait disturbance, and muscular weakness). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in 361 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT") and post-marketing. The safety population characteristics were comprised of patients with a median age of 39.0 years (range: 0, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=361) was 16.2 months (range: 0.1, 89.1).
The adverse drug reactions reported in patients (n=361) treated with VITRAKVI are shown in Table 3 and Table 4.

The adverse drug reactions are classified according to the System Organ Class.
Frequency groups are defined by 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 available data).
Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=361) and post-marketing

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common	Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia)[a] Leukocyte count decreased (Leukopenia)[a]
	Uncommon		Platelet count decreased (Thrombocytopenia)[a, b]
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Gait disturbance
	Uncommon		Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	
	Common	Dysgeusia[c]	Diarrhoea Vomiting
	Uncommon		Nausea Constipation
Hepatobiliary disorders	Not known	Liver injury[d]	
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	
	Uncommon		Myalgia Muscular weakness[a, b]
General disorders and administration site conditions	Very common	Fatigue	
	Uncommon		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)
	Uncommon		Blood alkaline phosphatase increased[a, b]

[a] grade 4 reactions were reported

[b] each grade frequency was less than <1%

[c] ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

[d] includes cases with ALT/AST ≥3x ULN and bilirubin ≥2x ULN

Table 4: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=135); all grades

System organ class	Frequency	Infants and toddlers (n=43)[a]	Children (n=67)[b]	Adolescents (n=25)[c]	Paediatric patients (n=135)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)
	Common		Platelet count decreased (Thrombocytopenia)	Platelet count decreased (Thrombocytopenia)	
Nervous system disorders	Very common			Dizziness	
	Common	Dizziness	Dizziness Paraesthesia Gait disturbance	Paraesthesia Gait disturbance	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common		Myalgia	Myalgia	Myalgia
	Common	Muscular weakness	Muscular weakness	Muscular weakness	Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) reactions and 2 Blood alkaline phosphatase increased reported. Grade 3 reactions included 11 cases of Neutrophil count decreased (Neutropenia), 4 cases of ALT increased, 3 cases each of Anaemia, Diarrhoea, and Weight increased (Abnormal weight gain), and 2 cases each of Blood alkaline phosphatase increased, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leukocytes count decreased reported. 9 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 4 cases of Weight increased (Abnormal weight gain), 2 cases each of ALT increased, Anaemia, Diarrhoea, and Vomiting and 1 case each of AST increased, Gait disturbance, Paraesthesia and Myalgia.

[c] Adolescents (12 to <18 years): no grade 4 reactions were reported. Grade 3 reactions were reported in 1 case each of ALT increased, AST increased, Fatigue, Gait disturbance, and Muscular weakness.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n=361), the maximum grade neurologic adverse reaction observed was grade 3 or 4 which was observed in 10 (3%) patients and included gait disturbance (4 patients, 1%), dizziness (3 patients, <1%), and paraesthesia (3 patients, <1%). The overall incidence was 20% for dizziness, 7% for paraesthesia and 5% for gait disturbance. Neurologic reactions leading to dose modification or interruptions included dizziness (1%), gait disturbance (<1%), and paraesthesia (<1%). One patient permanently discontinued the treatment due to grade 3 gait disturbance. In all cases except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Hepatotoxicity

Abnormalities of liver function tests including ALT, AST, ALP and bilirubin have been observed in patients treated with VITRAKVI.

In the overall safety database (n=361), the maximum grade transaminase elevation observed was grade 4 ALT increase in 7 patients (2%) and AST increase in 4 patients (1%). Grade 3 ALT and AST increases in 26 (7%) and 22 (6%) of patients, respectively. Majority of grade 3 elevations were transient appearing in the first three months of treatment and resolving to grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 37 (10%) and 33 (9%) of patients, respectively, and grade 1 ALT and AST increases were observed in 173 (48%) and 177 (49%) of patients, respectively.

ALT and AST increases leading to dose modifications or interruptions occurred in 25 (7%) patients and 21 (6%) patients, respectively (see section 4.4). Two patients permanently discontinued the treatment with 1 patient due to grade 3 ALT and grade 3 AST increases. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported. In some cases, the dose of VITRAKVI was withheld and restarted at a reduced dose, while in other cases treatment was permanently discontinued (see section 4.4).

Additional information on special populations

Paediatric patients

Of the 361 patients treated with VITRAKVI, 135 (37%) patients were from birth to < 18 years of age (n=13 from birth to < 3 months, n=4 ≥ 3 months to < 6 months, n=17 ≥ 6 months to < 12 months, n=9 ≥ 12 months to < 2 years, n=30 ≥ 2 years to < 6 years, n=37 ≥ 6 years to < 12 years, n=25 ≥ 12 years to < 18 years). The majority of adverse reactions were grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. Adverse reactions of grade 3 or 4 in severity were generally observed more frequently in patients < 6 years of age. They were reported in 77% of patients from birth to < 3 months and in 47% of patients ≥ 3 months to < 6 years. Decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption.

Elderly
Of the 361 patients in the overall safety population who received VITRAKVI, 69 (19%) patients were 65 years or older and 22 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (30% versus 28% in all adults), anaemia (36% versus 28% in all adults), diarrhoea (25% versus 23% in all adults), muscular weakness (13% versus 11% in all adults), platelet count decreased (12% versus 6% in all adults), gait disturbance (9% versus 5% in all adults), and dysgeusia (9% versus 6% in all adults) were more frequent in patients of 65 years or older.

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 https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience of overdose with VITRAKVI. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX12.

Mechanism of action

Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor that was rationally designed to avoid activity with off-target kinases. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by *NTRK1*, *NTRK2* and *NTRK3* genes, respectively. In a broad panel of purified enzyme assays, larotrectinib inhibited TRKA, TRKB, and TRKC with IC_{50} values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations. In *in vitro* and *in vivo* tumour models, larotrectinib demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.

In-frame gene fusion events resulting from chromosomal rearrangements of the human genes *NTRK1*, *NTRK2*, and *NTRK3* lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed, driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell

proliferation and survival leading to TRK fusion-positive cancer.

Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

The molecular causes for primary resistance to larotrectinib are not known. It is therefore not known if the presence of a concomitant oncogenic driver in addition to an *NTRK* gene fusion affects the efficacy of TRK inhibition. The measured impact of any concomitant genomic alterations on larotrectinib efficacy is provided below (see clinical efficacy).

Pharmacodynamic effects

Cardiac electrophysiology
In 36 healthy adult subjects receiving single doses ranging from 100 mg to 900 mg, VITRAKVI did not prolong the QT interval to any clinically relevant extent.
The 200 mg dose corresponds to a peak exposure (C_{max}) similar to that observed with larotrectinib 100 mg BID at steady state. A shortening of QTcF was observed with VITRAKVI dosing, with a maximum mean effect observed between 3 and 24 hours after C_{max}, with a geometric mean decrease in QTcF from baseline of -13.2 msec (range -10 to -15.6 msec). Clinical relevance of this finding has not been established.

Clinical efficacy

Overview of studies
The efficacy and safety of VITRAKVI were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients (Table 5). Two studies are still ongoing.
Patients with and without documented *NTRK* gene fusion were allowed to participate in Study 1 and Study 3 ("SCOUT"). Patients enrolled to Study 2 ("NAVIGATE") were required to have TRK fusion-positive cancer. The pooled primary analysis set of efficacy includes 364 patients with TRK fusion-positive cancer enrolled across the three studies that had measurable disease assessed by RECIST v1.1, a non-CNS primary tumour and received at least one dose of larotrectinib as of July 2024. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC).
In addition, 60 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Fifty-seven of the 60 primary CNS tumour patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria.

Identification of *NTRK* gene fusions relied on tissue samples for the molecular test methods: next generation sequencing (NGS) used in 327 patients, polymerase chain reaction (PCR) used in 14 patients, fluorescence *in situ* hybridization (FISH) used in 18 patients, and other testing methods (Sequencing, Nanostring, Sanger sequencing, or Chromosome Microarray) used in 5 patients.

Table 5: Clinical studies contributing to the efficacy analyses in solid and primary CNS tumours

Study name, design and patient population	Dose and formulation	Tumour types included in efficacy analysis	n
Study 1 NCT02122913 • Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours with an *NTRK* gene fusion	Doses up to 200 mg once or twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=4) Salivary gland (n=3) GIST (n=2)[a] Soft tissue sarcoma (n=2) NSCLC (n=1)[b, c] Unknown primary cancer (n=1)	13
Study 2 "NAVIGATE" NCT02576431 • Phase 2 multinational, open label, tumour "basket" study • Adult and paediatric patients ≥ 12 years with advanced solid tumours with an *NTRK* gene fusion	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	NSCLC (n=29)[b, c] Soft tissue sarcoma (n=28) Thyroid (n=26)[b] Colon (n=25) Salivary gland (n=24) Primary CNS (n=19) Melanoma (n=10)[b] Breast, non-secretory (n=10)[b] Pancreas (n=7) Breast, secretory (n=5) Cholangiocarcinoma (n=4) GIST (n=3)[a] Gastric (n=3) Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma, Cervix, Hepatic[e], Duodenal, External auditory canal[b], Oesophageal, SCLC[b, d], Rectal, Testes[b], Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	210
Study 3 "SCOUT" NCT02637687 • Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an *NTRK* gene fusion, including locally advanced infantile fibrosarcoma • Paediatric patients from birth to 21 years with advanced cancer or with primary CNS tumours	Doses up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Infantile fibrosarcoma (n=49) Soft tissue sarcoma (n=42)[b] Primary CNS (n=41) Congenital mesoblastic nephroma (n=2) Bone sarcoma (n=2) Breast secretory, Cervix, Lipofibromatosis, Melanoma, Thyroid (n=1 each)	141
Total number of patients (n)[*]			364

* consist of 304 patients with IRC tumour response assessment and 60 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, oligodendroglioma, and primitive neuro-ectodermal tumour, not specified) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour

[b] brain metastases were observed in some patients in the following tumour types: lung (NSCLC, SCLC), thyroid, melanoma, breast (non-secretory), external auditory canal, soft tissue sarcoma and testes

[c] NSCLC: non-small cell lung cancer

[d] SCLC: small cell lung cancer

[e] hepatocellular carcinoma

Baseline characteristics for the pooled 304 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 44.5 years (range 0-90 years); 33% < 18 years of age, and 67% ≥ 18 years; 55% white and 47% male; and ECOG PS 0-1 (88%), 2 (10%), or 3 (2%). Ninety-one percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 72% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-eight percent of all patients had received no prior systemic therapy. Of those 304 patients the most common tumour types represented were soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung cancer (11%), thyroid cancer (10%), salivary gland tumour (9%) and colon cancer (8%).
Baseline characteristics for the 60 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 9.1 years (range 0-79 years); 43 patients < 18 years of age, and 17 patients ≥ 18 years, and 39 patients white and 28 patients male; and ECOG PS 0-1 (52 patients), or 2 (5 patients). Fifty-seven (95%) patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. There was a median of 1 prior systemic treatment regimen received.

Efficacy results
The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population (n=304) and with post-hoc addition of primary CNS tumours (n=60) resulting in the pooled population (n=364), are presented in Table 6 and Table 7.

Table 6: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	**Analysis in solid tumours excluding primary CNS tumours (n=304)[a]**	**Analysis in solid tumours including primary CNS tumours (n=364)[a, b]**
Overall response rate (ORR) % (n) [95% CI]	65% (198) [59, 70]	60% (219) [55, 65]
Complete response (CR)	22% (66)	20% (71)
Pathological complete response[c]	7% (20)	5% (20)
Partial response (PR)	37% (112)	35% (128)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 49.87]
Duration of response (median, months) [range] **% with duration ≥ 12 months** **% with duration ≥ 24 months** **% with duration ≥ 36 months** **% with duration ≥ 48 months**	43.3 [0.0+, 84.7+] 80% 66% 57% 48%	43.3 [0.0+, 84.7+] 79% 65% 54% 47%

+ denotes ongoing

[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (304 patients).

[b] Evaluated using either RANO or RECIST v1.1 criteria for primary CNS tumours (60 patients).

[c] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1.

Table 7: Overall response rate and duration of response by tumour type*

Tumour type	Patients (n=364)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	72	68%	56%, 79%	80%	72%	60%	0.03+, 84.7+
Primary CNS	60	35%	23%, 48%	66%	50%	50%	2.8, 70.9+
Infantile fibrosarcoma	49	94%	83%, 99%	83%	66%	60%	1.6+, 73.7+
Lung	32	69%	50%, 84%	75%	52%	45%	1.9+, 67.2+
Thyroid	31	65%	45%, 81%	85%	63%	47%	3.7, 83.9+
Salivary gland	27	85%	66%, 96%	91%	86%	76%	2.7, 81.1+
Colon	25	48%	28%, 69%	83%	62%	31%	3.9, 56.3+
Breast	16						
Non-secretory[c]	10	30%	7%, 65%	67%	0%	0%	7.4, 15.3+
Secretory[b]	6	83%	36%, 100%	80%	80%	80%	11.1, 69.2+
Melanoma	11	45%	17%, 77%	50%	NR	NR	1.9+, 23.2+
Pancreas	7	14%	0%, 58%	0%	0%	0%	5.8, 5.8
Gastrointestinal stromal tumour	5	80%	28%, 99%	75%	38%	38%	9.5, 50.4+
Bone sarcoma	3	33%	1%, 91%	0%	0%	0%	9.5, 9.5
Congenital mesoblastic nephroma	2	100%	16%, 100%	100%	100%	50%	32.9, 44.5
Cervix	2	50%	1%, 99%	100%	NR	NR	18.7+, 18.7+
Unknown primary cancer	2	100%	16%, 100%	0	0	0	5.6, 7.4
External auditory canal	1	100%	3%, 100%	100%	100%	100%	45.1+, 45.1+
Lipofibromatosis	1	100%	3%, 100%	100%	NR	NR	17.7+, 17.7+

DOR: duration of response
NE: not evaluable
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); gastric (n=3); prostate (n=2); appendix, hepatic, duodenal, oesophageal, rectal, testes, thymus, urothelial, uterus (n=1 each)
+ denotes ongoing response
[a] evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated using either RANO or RECIST v1.1 criteria
[b] with 2 complete, 2 partial response
[c] with 1 complete, 2 partial response

Due to the rarity of TRK fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

In the adult sub-population (n=222), the ORR was 51%. In the paediatric sub-population (n=142), the ORR was 74%.

In 257 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 120 patients who had other genomic alterations in addition to *NTRK* gene fusion was 53%, and in 137 patients without other genomic alterations ORR was 68%.

Pooled primary analysis set

The pooled primary analysis set consisted of 304 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 15.9 months (range: 0.1 to 99.4 months) based on July 2024 cut-off. Fifty-five percent of patients had received VITRAKVI for 12 months or more, 37% had received VITRAKVI 24 months or more, and 28% had received VITRAKVI 36 months or more. Follow-up was ongoing at the time of the analysis for 27% of patients.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 84.7+), an estimated 80% [95% CI: 74, 86] of responses lasted 12 months or longer, 66% [95% CI: 59, 74] of responses lasted 24 months or longer, and 57% [95% CI: 49, 64] of responses lasted 36 months or longer. Eighty-three percent (83%) [95% CI: 79, 88] of patients treated were alive one year after the start of therapy, 73% [95% CI: 68, 78] after two years after the start of therapy, and 68% [95% CI: 63, 74] after three years with the median for overall survival not yet being reached. Median progression free survival was 28.0 months at the time of the analysis, with a progression free survival rate of 63% [95% CI: 57, 69] after 1 year, 54% [95% CI: 48, 60] after 2 years, and 44% [95% CI: 38, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of 66%.

Patients with primary CNS tumours

At the time of data cut-off, of the 60 patients with primary CNS tumours confirmed response was observed in 21 patients (35%) with 5 of the 60 patients (8%) being complete responders and 16 patients (27%) being partial responders. Further 24 patients (40%) had stable disease. 13 patients (22%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 67.3 months and was ongoing in 20 out of 60 patients, with all of these patients receiving post-progression treatment.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.
The Medicines and Healthcare products Regulatory Agency (MHRA) will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

In cancer patients given VITRAKVI capsules, peak plasma levels (C_{max}) of larotrectinib were achieved at approximately 1 hour after dosing. Half-life ($t_{½}$) is approximately 3 hours and steady state is reached within 8 days with a systemic accumulation of 1.6 fold. At the recommended dose of 100 mg taken twice daily, steady-state arithmetic mean (± standard deviation) C_{max} and daily AUC in adults were 914 ± 445 ng/mL and 5410 ± 3813 ng*h/mL, respectively. *In vitro* studies indicate that larotrectinib is not a substrate for either OATP1B1 or OATP1B3.

In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.
In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations and is unlikely to affect clearance of substrates of these transporters.

Absorption

VITRAKVI is available as a capsule and oral solution formulation.
The mean absolute bioavailability of larotrectinib was 34% (range: 32% to 37%) following a single 100 mg oral dose. In healthy adult subjects, the AUC of larotrectinib in the oral solution formulation was similar to the capsule, with C_{max} 36% higher with the oral solution formulation.
Larotrectinib C_{max} was reduced by approximately 35% and there was no effect on AUC in healthy subjects administered VITRAKVI after a high-fat and high-calorie meal compared to the C_{max} and AUC after overnight fasting.

Effect of gastric pH-elevating agents on larotrectinib
Larotrectinib has pH-dependent solubility. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib is unlikely to be affected by pH-modifying agents.

Distribution

The mean volume of distribution of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose. Binding of larotrectinib to human plasma proteins *in vitro* was approximately 70% and was independent of drug concentration. The blood-to-plasma concentration ratio was approximately 0.9.

Biotransformation

Larotrectinib was metabolised predominantly by CYP3A4/5 *in vitro*. Following oral administration of a single 100 mg dose of radiolabelled larotrectinib to healthy adult subjects, unchanged larotrectinib (19%) and an O-glucuronide that is formed following loss of the hydroxypyrrolidine-urea moiety (26%) were the major circulating radioactive drug components.

Elimination

The half-life of larotrectinib in plasma of cancer patients given 100 mg twice daily of VITRAKVI was approximately 3 hours. Mean clearance (CL) of larotrectinib was approximately 34 L/h following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose of VITRAKVI.

Excretion

Following oral administration of 100 mg radiolabelled larotrectinib to healthy adult subjects, 58% of the administered radioactivity was recovered in faeces and 39% was recovered in urine and when an IV microtracer dose was given in conjunction with a 100 mg oral dose of larotrectinib, 35% of the administered radioactivity was recovered in faeces and 53% was recovered in urine. The fraction excreted as unchanged drug in urine was 29% following IV microtracer dose, indicating that direct renal excretion accounted for 29% of total clearance.

Linearity / non-linearity

The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of larotrectinib after a single dose in healthy adult subjects were dose proportional up to 400 mg and slightly greater than proportional at doses of 600 to 900 mg.

Special populations

Paediatric patients
Based on population pharmacokinetic analyses, exposure (C_{max} and AUC) in paediatric patients at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was higher than in adults (≥ 18 years of age) given the dose of 100 mg BID (see Table 8).
Data defining exposure in small children (1 month to < 2 years of age) at the recommended dose is limited (n=46).

Table 8: Exposure (C_{max} and AUC[a]) in patients grouped by age group at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID

Age group	n=438[b]	Fold difference compared to patients ≥ 18 years of age[c]	
		C_{max}	AUC[a]
1 to < 3 months	12	3.2	4.5
3 to < 6 months	4	3.0	3.2
6 to < 12 months	19	2.1	1.7
1 to < 2 years	11	1.6	1.1
2 to < 6 years	37	1.6	1.1
6 to < 12 years	38	1.3	1.2
12 to < 18 years	32	0.9	0.8
≥ 18 years	285	1.0	1.0

[a] area under the plasma concentration-time curve at steady-state
[b] number of patients from 23 September 2024 data cut-off
[c] fold difference is the ratio of stated age group to ≥18 years group. A fold-difference of 1 equates to no difference.

Simulations have shown that the dose of 50 mg/m^2 BID in patients aged less than 3 months results in exposures comparable to patients aged 3 months to less than 2 years at a dose of 100 mg/m^2 BID, without the exposure metrics (C_{max}, AUC, C_{trough}) falling below the simulated exposure in patients aged 3 months to less than 2 years. There is no clinical data with a dose of 50 mg/m^2 BID in patients aged less than 3 months.

Elderly
There is no clinically meaningful difference in larotrectinib exposure in patients > 65 years compared to those in younger patients (< 65 years).

Patients with hepatic impairment
A pharmacokinetic study was conducted in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib $AUC_{0\text{-}inf}$ was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively.

Patients with renal impairment
A pharmacokinetic study was conducted in subjects with end stage renal disease requiring dialysis, and in healthy adult control subjects with normal renal function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib C_{max} and $AUC_{0\text{-}inf}$, of 1.25 and 1.46-fold respectively was observed in renally impaired subjects versus those with normal renal function.

Other special populations
Gender and race have no effect on the systemic exposure of larotrectinib based on population pharmacokinetic analysis.

5.3 Preclinical safety data

Systemic toxicity

Systemic toxicity was assessed in studies with daily oral administration up to 3 months in rats and monkeys. Dose limiting skin lesions were only seen in rats and were primarily responsible for mortality and morbidity. Skin lesions were not seen in monkeys.

Clinical signs of gastrointestinal toxicity were dose limiting in monkeys. In rats, severe toxicity (STD10) was observed at doses corresponding to 1- to 2-times the human AUC at the recommended clinical dose. No relevant systemic toxicity was observed in monkeys at doses which correspond to > 10-times the human AUC at the recommended clinical dose.

Embryotoxicity / Teratogenicity

Larotrectinib was not teratogenic and embryotoxic when dosed daily during the period of organogenesis to pregnant rats and rabbits at maternotoxic doses, i.e. corresponding to 32-times (rats) and 16-times (rabbits) the human AUC at the recommended clinical dose. Larotrectinib crosses the placenta in both species.

Reproduction toxicity

Fertility studies with larotrectinib have not been conducted. In 3-months toxicity studies, larotrectinib had no histological effect on the male reproductive organs in rats and monkeys at the highest tested doses corresponding to approximately 7-times (male rats) and 10-times (male monkeys) the human AUC at the recommended clinical dose. In addition, larotrectinib had no effect on spermatogenesis in rats.

In a 1-month repeat-dose study in rats, fewer corpora lutea, increased incidence of anestrus and decreased uterine weight with uterine atrophy were observed and these effects were reversible. No effects on female reproductive organs were seen in the 3-months toxicity studies in rats and monkeys at doses corresponding to approximately 3-times (female rats) and 17-times (female monkeys) the human AUC at the recommended clinical dose.

Larotrectinib was administered to juvenile rats from postnatal day (PND) 7 to 70. Pre-weaning mortality (before PND 21) was observed at the high dose level corresponding to 2.5- to 4-times the AUC at the recommended dose. Growth and nervous system effects were seen at 0.5- to 4-times the AUC at the recommended dose. Body weight gain was decreased in pre-weaning male and female pups, with a post-weaning increase in females at the end of exposure whereas reduced body weight gain was seen in males also post-weaning without recovery. The male growth

reduction was associated with delayed puberty. Nervous system effects (i.e. altered hindlimb functionality and, likely, increases in eyelid closure) demonstrated partial recovery. A decrease in pregnancy rate was also reported despite normal mating at the high-dose level.

Genotoxicity and carcinogenicity

Carcinogenicity studies have not been performed with larotrectinib.

Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in *in vitro* mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test at the maximum tolerated dose of 500 mg/kg.

Safety pharmacology

The safety pharmacology of larotrectinib was evaluated in several *in vitro* and *in vivo* studies that assessed effects on the CV, CNS, respiratory, and GI systems in various species. Larotrectinib had no adverse effect on haemodynamic parameters and ECG intervals in telemetered monkeys at exposures (C_{max}) which are approximately 6-fold the human therapeutic exposures. Larotrectinib had no neurobehavioural findings in adult animals (rats, mice, cynomolgus monkeys) at exposure (C_{max}) at least 7-fold higher than the human exposure. Larotrectinib had no effect on respiratory function in rats; at exposures (C_{max}) at least 8-times the human therapeutic exposure. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac, bleached dewaxed
Indigo carmine aluminium lake (E 132)
Titanium dioxide (E 171)
Propylene glycol (E 1520)
Dimeticone 1000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE)-bottles with a child-resistant polypropylene (PP) screw cap with a polyethylene (PE) heat seal layer.

Each carton contains one bottle of 56 hard capsules.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00010/0743

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/09/2025

10 DATE OF REVISION OF THE TEXT

12/02/2026