

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules
VITRAKVI 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VITRAKVI 25 mg hard capsules

Each hard capsule contains larotrectinib sulfate equivalent to 25 mg of larotrectinib.

VITRAKVI 100 mg hard capsules

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).

VITRAKVI 25 mg hard capsules

White opaque hard gelatine capsule, size 2 (18 mm long x 6 mm wide), with blue printing of BAYER-cross and “LARO 25 mg” on body of capsule.

VITRAKVI 100 mg hard capsules

White opaque hard gelatine capsule, size 0 (22 mm long x 7 mm wide), with blue printing of BAYER-cross and “LARO 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/m² larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

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. Patients with Grade 2 ALT and/or AST increases, should be followed with serial laboratory evaluations every one to two weeks after the observation of Grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.

For Grade 3 or 4 adverse reactions:

- 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 m² | Paediatric patients with body surface area less than 1.0 m² |
|--------------------------|---|---|
| First | 75 mg twice daily | 75 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 25 mg/m² twice daily should remain on this dose even if body surface area becomes greater 1.0 m² during the treatment. Maximum dose should be 25 mg twice daily at the third dose modification.

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

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).

Transaminase elevations

ALT and AST increase were reported in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred in the first 3 months of treatment.

Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, the VITRAKVI dose should be modified when resumed (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 child bearing 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 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 rifampin (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 and P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, 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 rifampin (a strong CYP3A and P-gp inducer) 600 mg twice 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, pimozone, 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 child-bearing 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 the 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 or 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 ($\geq 20\%$) of VITRAKVI in order of decreasing frequency were increased ALT (32%), fatigue (30%), constipation (29%), increased AST (27%), dizziness (26%), vomiting (23%), anaemia (23%), and nausea (22%).

The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1%), ALT increased (1%), and AST increased ($< 1\%$). The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, dizziness, paraesthesia, muscular weakness, nausea, myalgia, gait disturbance, vomiting, and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (8%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in 5% of patients (one case each of ALT increased, AST increased, bile duct adenocarcinoma, gait disturbance, intestinal perforation, jaundice, malignant neoplasm progression, neutrophil count decreased, small intestinal obstruction, spinal cord compression, and viral infection). 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 196 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 (“NAVIGATE”), and 3 (“SCOUT”). The safety population characteristics were comprised of patients with a median age of 37.5 years (range: 0.1, 84) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=196) was 9.3 months (range: 0.10, 51.6).

The adverse drug reactions reported in patients (n=196) treated with VITRAKVI are shown in Table 2 and Table 3.

The adverse drug reactions are classified according to the System Organ Class.

Frequency groups are defined by the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=196)

| 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 | | Anaemia Neutrophil count decreased (Neutropenia) ^a |
| | Uncommon | | Leukocyte count decreased (Leukopenia) |
| Nervous system disorders | Very common | Dizziness | |
| | Common | Gait disturbance Paraesthesia | Dizziness Paraesthesia |
| | Uncommon | | Gait disturbance |
| Gastrointestinal disorders | Very common | Nausea Constipation Vomiting | |
| | Common | Dysgeusia ^b | |
| | Uncommon | | Nausea Vomiting |
| Musculoskeletal and connective tissue disorders | Very common | Myalgia | |
| | Common | Muscular weakness | Myalgia Muscular weakness |
| General disorders and administration site conditions | Very common | Fatigue | |
| | Common | | 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) |

^a Grade 4 reactions were reported

^b ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=73); all Grades

| System organ class | Frequency | Infants and toddlers (n=29) ^a | Children (n=30) ^b | Adolescents (n=14) ^c | Paediatric patients (n=73) |
|---|-------------|---|--|--|---|
| Blood and lymphatic system disorders | Very common | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) |
| Nervous system disorders | Very common | | | Dizziness | |
| | Common | | Dizziness Paraesthesia Gait disturbance | Paraesthesia | Dizziness Paraesthesia Gait disturbance |
| Gastrointestinal disorders | Very common | Nausea Constipation Vomiting | Nausea Constipation Vomiting | Nausea Vomiting | Nausea Constipation Vomiting |
| | Common | | Dysgeusia | Constipation | Dysgeusia |
| Musculoskeletal and connective tissue disorders | Common | | Myalgia Muscular weakness | Myalgia Muscular weakness | Myalgia 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 Blood alkaline phosphatase increased | Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Blood alkaline phosphatase increased | Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased |
| | Common | | Weight increased (Abnormal weight gain) | Weight increased (Abnormal weight gain) | |

^a Infant/toddlers (28 days to 23 months): two Grade 4 Neutrophil count decreased (Neutropenia) reactions reported. Grade 3 reactions included seven cases of Neutrophil count decreased (Neutropenia), three cases of Anaemia, three cases of Weight increased (Abnormal weight gain), and one case each of ALT increased and Vomiting.

^b Children (2 to 11 years): no Grade 4 reactions were reported. Three reported Grade 3 cases of Neutrophil count decreased (Neutropenia), and one case each of Paraesthesia and Myalgia.

^c Adolescents (12 to <18 years): no Grades 3 and 4 reactions were reported.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n=196), the maximum grade neurologic reaction observed was Grade 3 which was observed in five (3%) patients and included dizziness (two patients, 1%), paraesthesia (two patients, 1%), and gait disturbance (one patient, <1%). The overall incidence was 26% for dizziness, 8% for paraesthesia and 4% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%), paraesthesia (1%), and gait disturbance (<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).

Transaminase elevations

In the overall safety database (n=196), the maximum grade transaminase elevation observed was Grade 4 ALT increase in 2 patients (1%) and AST increase in 1 patient (<1%). Grade 3 ALT and AST increases in 4 (2%) and 2 (1%) of patients, respectively. Majority of Grade 3 elevations were transient appearing in the first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 10 (5%) and 8 (4%) of patients, respectively, and Grade 1 ALT and AST increases were observed in 47 (24%) and 41 (21%) of patients, respectively. ALT and AST increases leading to dose modifications occurred in 10 (5%) patients and 8 (4%) patients, respectively (see section 4.4). No patient permanently discontinued the treatment due to Grade 3-4 ALT and AST increases.

Additional information on special populations

Paediatric patients

Of the 196 patients treated with VITRAKVI, 73 (37%) patients were from 28 days to 18 years of age. Of these 73 patients, 40% were 28 days to < 2 years (n=29), 41% were 2 years to < 12 years (n=30), and 19% were 12 years to < 18 years (n=14). The safety profile in the paediatric population (< 18 years) was consistent in types of reported adverse reactions to those observed in the adult population. The majority of adverse reactions were Grade 1 or 2 in severity (see Table 3) and were resolved without VITRAKVI dose modification or discontinuation. The adverse reactions of vomiting (38% versus 15% in adults), leucocyte count decrease (16% versus 11% in adults), neutrophil count decrease (27% versus 7% in adults), and blood alkaline phosphatase increased (12% versus 4% in adults) were more frequent in paediatric patients compared to adults.

Elderly

Of the 196 patients in the overall safety population who received VITRAKVI, 35 (18%) patients were 65 years or older and 10 (5%) 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 gait disturbance (11% versus 5% in all adults) was 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 **the national reporting system** listed in [Appendix V](#).

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: L01XE53.

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 IC₅₀ 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 effect

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 4). The 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 164 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 2019. 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, 24 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 (“NAVIGATE”) and in Study 3 (“SCOUT”). All 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 upon the molecular test methods: next generation sequencing (NGS) used in 166 patients, reverse transcription-polymerase chain reaction (RT-PCR) used in 9 patients, fluorescence *in situ* hybridization (FISH) used in 12 patients, and Nanostring in 1 patient as routinely performed at certified laboratories.

Table 4: 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 <ul style="list-style-type: none"> Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an <i>NTRK</i> gene fusion Adult patients (≥ 18 years) with advanced solid tumours with an <i>NTRK</i> 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 <ul style="list-style-type: none"> Phase 2 multinational, open label, tumour “basket” study Adult and paediatric patients ≥ 12 years with advanced solid tumours with an <i>NTRK</i> gene fusion | 100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution) | Thyroid (n=23) ^b Salivary gland (n=18) Soft tissue sarcoma (n=16) NSCLC (n=11) ^{b, c} Colorectal (n=8) Primary CNS (n=7) Melanoma (n=6) Breast, non-secretory (n=3) Breast, secretory (n=2) GIST (n=2) ^a Biliary (n=2) Pancreas (n=2) SCLC (n=1) ^{b, d} Appendix (n=1) Bone sarcoma (n=1) Hepatic ^e (n=1) Prostate (n=1) | 105 |
| Study 3 “SCOUT” NCT02637687 <ul style="list-style-type: none"> Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an <i>NTRK</i> gene fusion, including locally advanced infantile fibrosarcoma Paediatric patients ≥ 1 month 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=32) Soft tissue sarcoma (n=18) Primary CNS (n=17) Bone sarcoma (n=1) Congenital mesoblastic nephroma (n=1) Melanoma (n=1) | 70 |
| Total number of patients (n)[*] | | | 188 |

^{*} consist of 164 patients with IRC tumour response assessment and 24 patients with primary CNS tumours (including astrocytoma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, and primitive neuro-ectodermal tumour) with investigator tumour response assessment

^a GIST: gastrointestinal stromal tumour

^b brain metastases observed in 6 NSCLC, 4 thyroid, 2 melanoma, 1 SCLC, and 1 breast (non-secretory) patient

^c NSCLC: non-small cell lung cancer

^d SCLC: small cell lung cancer

^e hepatocellular carcinoma

Baseline characteristics for the pooled 164 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 42 years (range 0.1-84 years); 34% < 18 years of age, and 66% ≥ 18 years; 77% white and 49% male; and ECOG PS 0-1 (86%), 2 (12%), or 3 (2%). Ninety-four percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 77% had received prior systemic therapy with a median of 1 prior systemic

treatment regimen. Twenty-two percent of all patients had received no prior systemic therapy. Of those 164 patients the most common tumour types represented were soft tissue sarcoma (22%), infantile fibrosarcoma (20%), thyroid cancer (16%), salivary gland tumour (13%), and lung cancer (8%).

Baseline characteristics for the 24 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 8 years (range 1.3-79 years); 20 patients < 18 years of age, and 4 patients ≥ 18 years, and 19 patients white and 11 patients male; and ECOG PS 0-1 (22 patients), or 2 (1 patient). All 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=164) and with post-hoc addition of primary CNS tumours (n=24) resulting in the pooled population (n=188), are presented in Table 5 and Table 6.

Table 5: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

| Efficacy parameter | Analysis in solid tumours excluding primary CNS tumours (n=164)^a | Analysis in solid tumours including primary CNS tumours (n=188)^{a, b} |
|---|--|---|
| Overall response rate (ORR) % (n) [95% CI] | 73% (119) [65, 79] | 66% (124) [59, 73] |
| Complete response (CR) | 19% (31) | 18% (33) |
| Pathological complete response ^c | 5% (8) | 4% (8) |
| Partial response (PR) | 49% (80) | 44% (83) ^d |
| Time to first response (median, months) [range] | 1.84 [0.92, 14.55] | 1.84 [0.92, 14.55] |
| Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months | NR [0.0+, 50.6+] 76% 67% | NR [0.0+, 50.6+] 74% 65% |

NR: not reached

+ denotes ongoing

^a Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (164 patients).

^b Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (24 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.

^d An additional 1% (2 patients with primary CNS tumours) had partial responses, pending confirmation.

Table 6: Overall response rate and duration of response by tumour type

| Tumour type | Patients (n=188) | ORR | | DOR | | |
|--|---------------------|--------|-----------|--------|------|-------------------|
| | | % | 95% CI | months | | Range (months) |
| | | | | ≥ 12 | ≥ 24 | |
| Soft tissue sarcoma ^a | 36 | 81% | 64%, 92% | 69% | 69% | 0.0+, 50.6+ |
| Infantile fibrosarcoma ^a | 32 | 97% | 84%, 100% | 72% | 63% | 1.6+, 28.6+ |
| Thyroid ^a | 27 | 56% | 35%, 75% | 93% | 58% | 3.7+, 32.9 |
| Primary CNS ^b | 24 | 21% | 7%, 42% | NR | NR | 1.7+, 10.1+ |
| Salivary gland ^a | 21 | 86% | 64%, 97% | 94% | 87% | 1.9+, 44.7+ |
| Lung ^a | 13 | 77% | 46%, 95% | 62% | 62% | 3.7, 36.8+ |
| Colon ^a | 8 | 38% | 9%, 76% | 50% | NR | 5.4+, 20.7+ |
| Melanoma ^a | 7 | 43% | 10%, 82% | 50% | NR | 1.9+, 23.2+ |
| Breast ^{a, c} | 5 | 60% | 15%, 95% | NR | NR | 5.6+, 9.2+ |
| Gastrointestinal stromal tumour ^a | 4 | 100% | 40%, 100% | 75% | 38% | 9.5, 31.1+ |
| Bone sarcoma ^a | 2 | 50% | 1%, 99% | 0% | 0% | 9.5 |
| Cholangiocarcinoma ^a | 2 | SD, NE | NA | NA | NA | NA |
| Pancreas ^a | 2 | SD, SD | NA | NA | NA | NA |
| Congenital mesoblastic nephroma ^a | 1 | 100% | 3%, 100% | 100% | NR | 20.8+ |
| Unknown primary cancer | 1 | 100% | 3%, 100% | 0% | 0% | 7.4 |
| Appendix ^a | 1 | SD | NA | NA | NA | NA |
| Hepatic | 1 | NE | NA | NA | NA | NA |
| Prostate | 1 | PD | NA | NA | NA | NA |

DOR: duration of response

NA: not applicable due to small numbers or lack of response

NE: not evaluable

NR: not reached

PD: progressive disease

SD: stable disease

+ denotes ongoing response

^a independent review committee analysis by RECIST v1.1

^b patients with a primary CNS tumour were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria

^c with 3 patients having non-secretory (1 complete, 1 partial responder and 1 progressive disease) and 2 patients having secretory breast cancer (1 partial and 1 stable disease)

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=109), the ORR was 63%. In the paediatric sub-population (n=55), the ORR was 91%.

In 165 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 79 patients who had other genomic alterations in addition to *NTRK* gene fusion was 58%, and in 86 patients without other genomic alterations ORR was 74%.

Pooled primary analysis set

The pooled primary analysis set consisted of 164 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 14.7 months (range: 0.10 to 51.6 months) based on July 2019 cut-off. Forty-four percent of patients had received VITRAKVI for 12 months or more and 21% had received VITRAKVI 24 months or more, with follow-up ongoing at the time of the analysis.

At the time of analysis, the median duration of response had not been reached, an estimated 76% [95% CI: 67, 85] of responses lasted 12 months or longer, and 67% [95% CI: 55, 78] of responses lasted 24 months or longer. Ninety percent (90%) [95% CI: 85, 95] of patients treated were alive one year after the start of therapy and 82% [95% CI: 75, 90] after two years with the median for overall survival not yet being reached. Median progression free survival was 33.4 months at the time of the analysis, with a progression free survival rate of 66% [95% CI: 58, 74] after 1 year and 58% [95% CI: 48, 67] after 2 years.

The median change in tumour size in the pooled primary analysis set was a decrease of 68%.

Patients with primary CNS tumours

At the time of data cut-off, of the 24 patients with primary CNS tumours confirmed response was observed in 5 patients (21%) with 2 of the 24 patients (8%) being complete responders and 3 patients (12.5%) being partial responders. In 2 additional patients (8%) a not yet confirmed partial response was observed. Further 15 patients (63%) had stable disease. Two patients (8%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 21.4 months and was ongoing in 15 out of 24 patients, with one 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 European Medicines Agency 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 ($t_{1/2}$) 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 (\pm 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 radiolabeled 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 radiolabeled 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 (1 month to <3 months of age) at the recommended dose of 100 mg/m² with a maximum of 100 mg BID was 3-fold higher than in adults (≥ 18 years of age) given the dose of 100 mg BID. At the recommended dose, the C_{max} in paediatric patients (≥ 3 months to <12 years of age) was higher than in adults, but the AUC was similar to that in adults. For paediatric patients older than 12 years of age, the recommended dose is likely to give similar C_{max} and AUC as observed in adults.

Data defining exposure in small children (1 month to <6 years of age) at the recommended dose is limited (n=33).

Elderly

There are limited data in elderly. PK data is available only in 2 patients over 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-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-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 did not appear to influence larotrectinib pharmacokinetics to a clinically significant extent. There was not enough data to investigate the potential influence of race on the systemic exposure of larotrectinib.

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

Indigo carmine aluminium lake (E 132)

Titanium dioxide (E 171)

Propylene glycol (E 1520)

Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE)-bottles with a child-resistant polypropylene (PP) 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 AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1385/001 – VITRAKVI 25 mg
EU/1/19/1385/002 – VITRAKVI 100 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

▼ 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 20 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains larotrectinib sulfate equivalent to 20 mg of larotrectinib.

Excipients with known effect:

Each mL of oral solution contains 295 mg sucrose, 22 mg sorbitol, 1.2 mg propylene glycol and 0.2 mg methyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear yellow to orange solution.

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/m² larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

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. Patients with Grade 2 ALT and/or AST increases, should be followed with serial laboratory evaluations every one to two weeks after the observation of Grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.

For Grade 3 or 4 adverse reactions:

- 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 m² | Paediatric patients with body surface area less than 1.0 m² |
|--------------------------|---|---|
| First | 75 mg twice daily | 75 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 25 mg/m² twice daily should remain on this dose even if body surface area becomes greater 1.0 m² during the treatment. Maximum dose should be 25 mg twice daily at the third dose modification.

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

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 oral solution should be administered by mouth using an oral syringe of 1 mL or 5 mL volume or enterally by using a nasogastric feeding tube.

- For doses below 1 mL a 1 mL oral syringe should be used. The calculated dose volume should be rounded to the nearest 0.1 mL.
- For doses of 1 mL and higher a 5 mL oral syringe should be used. The dose volume should be calculated to the nearest 0.2 mL.
- VITRAKVI should not be mixed with feeding formulas, if administered via nasogastric feeding tube. Mixing with the feeding formulas could lead to tube blockages.
- For instructions for use of oral syringes and feeding tubes see section 6.6.

The oral solution 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).

Transaminase elevations

ALT and AST increase were reported in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred in the first 3 months of treatment.

Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, the VITRAKVI dose should be modified when resumed (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 child bearing 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).

Important information about some of the ingredients

Sucrose: may be harmful to the teeth. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.

Sorbitol: patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Sodium: this medicinal product contains less than 1 mmol sodium (23 mg) per 5 mL, that is to say essentially 'sodium-free'.

Propylene glycol: co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

Parahydroxybenzoate: may cause allergic reactions (possibly delayed).

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 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 rifampin (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 and P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, 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 rifampin (a strong CYP3A and P-gp inducer) 600 mg twice 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, pimozone, 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 child-bearing 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 the 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 or 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 ($\geq 20\%$) of VITRAKVI in order of decreasing frequency were increased ALT (32%), fatigue (30%), constipation (29%), increased AST (27%), dizziness (26%), vomiting (23%), anaemia (23%), and nausea (22%).

The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1%), ALT increased (1%), and AST increased ($< 1\%$).

The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, dizziness, paraesthesia, muscular weakness, nausea, myalgia, gait disturbance, vomiting, and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (8%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in 5% of patients (one case each of ALT increased, AST increased, bile duct adenocarcinoma, gait disturbance, intestinal perforation, jaundice, malignant neoplasm progression, neutrophil count decreased, small intestinal obstruction, spinal cord compression, and viral infection). 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 196 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 (“NAVIGATE”), and 3 (“SCOUT”). The safety population characteristics were comprised of patients with a median age of 37.5 years (range: 0.1, 84) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=196) was 9.3 months (range: 0.10, 51.6).

The adverse drug reactions reported in patients (n=196) treated with VITRAKVI are shown in Table 2 and Table 3.

The adverse drug reactions are classified according to the System Organ Class.

Frequency groups are defined by the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=196)

| 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 | | Anaemia Neutrophil count decreased (Neutropenia) ^a |
| | Uncommon | | Leukocyte count decreased (Leukopenia) |
| Nervous system disorders | Very common | Dizziness | |
| | Common | Gait disturbance Paraesthesia | Dizziness Paraesthesia |
| | Uncommon | | Gait disturbance |
| Gastrointestinal disorders | Very common | Nausea Constipation Vomiting | |
| | Common | Dysgeusia ^b | |
| | Uncommon | | Nausea Vomiting |
| Musculoskeletal and connective tissue disorders | Very common | Myalgia | |
| | Common | Muscular weakness | Myalgia Muscular weakness |
| General disorders and administration site conditions | Very common | Fatigue | |
| | Common | | 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) |

^a Grade 4 reactions were reported

^b ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=73); all Grades

| System organ class | Frequency | Infants and toddlers (n=29) ^a | Children (n=30) ^b | Adolescents (n=14) ^c | Paediatric patients (n=73) |
|---|-------------|---|--|--|---|
| Blood and lymphatic system disorders | Very common | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) | Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) |
| Nervous system disorders | Very common | | | Dizziness | |
| | Common | | Dizziness Paraesthesia Gait disturbance | Paraesthesia | Dizziness Paraesthesia Gait disturbance |
| Gastrointestinal disorders | Very common | Nausea Constipation Vomiting | Nausea Constipation Vomiting | Nausea Vomiting | Nausea Constipation Vomiting |
| | Common | | Dysgeusia | Constipation | Dysgeusia |
| Musculoskeletal and connective tissue disorders | Common | | Myalgia Muscular weakness | Myalgia Muscular weakness | Myalgia 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 Blood alkaline phosphatase increased | Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Blood alkaline phosphatase increased | Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased |
| | Common | | Weight increased (Abnormal weight gain) | Weight increased (Abnormal weight gain) | |

^a Infant/toddlers (28 days to 23 months): two Grade 4 Neutrophil count decreased (Neutropenia) reactions reported. Grade 3 reactions included seven cases of Neutrophil count decreased (Neutropenia), three cases of Anaemia, three cases of Weight increased (Abnormal weight gain), and one case each of ALT increased and Vomiting.

^b Children (2 to 11 years): no Grade 4 reactions were reported. Three reported Grade 3 cases of Neutrophil count decreased (Neutropenia), and one case each of Paraesthesia and Myalgia.

^c Adolescents (12 to <18 years): no Grades 3 and 4 reactions were reported.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n=196), the maximum grade neurologic reaction observed was Grade 3 which was observed in five (3%) patients and included dizziness (two patients, 1%), paraesthesia (two patients, 1%), and gait disturbance (one patient, <1%). The overall incidence was 26% for dizziness, 8% for paraesthesia and 4% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%), paraesthesia (1%), and gait disturbance (<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).

Transaminase elevations

In the overall safety database (n=196), the maximum grade transaminase elevation observed was Grade 4 ALT increase in 2 patients (1%) and AST increase in 1 patient (<1%). Grade 3 ALT and AST increases in 4 (2%) and 2 (1%) of patients, respectively. Majority of Grade 3 elevations were transient appearing in the first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 10 (5%) and 8 (4%) of patients, respectively, and Grade 1 ALT and AST increases were observed in 47 (24%) and 41 (21%) of patients, respectively. ALT and AST increases leading to dose modifications occurred in 10 (5%) patients and 8 (4%) patients, respectively (see section 4.4). No patient permanently discontinued the treatment due to Grade 3-4 ALT and AST increases.

Additional information on special populations

Paediatric patients

Of the 196 patients treated with VITRAKVI, 73 (37%) patients were from 28 days to 18 years of age. Of these 73 patients, 40% were 28 days to < 2 years (n=29), 41% were 2 years to < 12 years (n=30), and 19% were 12 years to < 18 years (n=14). The safety profile in the paediatric population (< 18 years) was consistent in types of reported adverse reactions to those observed in the adult population. The majority of adverse reactions were Grade 1 or 2 in severity (see Table 3) and were resolved without VITRAKVI dose modification or discontinuation. The adverse reactions of vomiting (38% versus 15% in adults), leucocyte count decrease (16% versus 11% in adults), neutrophil count decrease (27% versus 7% in adults), and blood alkaline phosphatase increased (12% versus 4% in adults) were more frequent in paediatric patients compared to adults.

Elderly

Of the 196 patients in the overall safety population who received VITRAKVI, 35 (18%) patients were 65 years or older and 10 (5%) 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 gait disturbance (11% versus 5% in all adults) was 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 **the national reporting system** listed in [Appendix V](#).

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: L01XE53.

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 IC₅₀ 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 effect

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 4). The 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 164 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 2019. 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, 24 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 (“NAVIGATE”) and in Study 3 (“SCOUT”). All 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 upon the molecular test methods: next generation sequencing (NGS) used in 166 patients, reverse transcription-polymerase chain reaction (RT-PCR) used in 9 patients, fluorescence *in situ* hybridization (FISH) used in 12 patients, and Nanostring in 1 patient as routinely performed at certified laboratories.

Table 4: 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 <ul style="list-style-type: none"> Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an <i>NTRK</i> gene fusion Adult patients (≥ 18 years) with advanced solid tumours with an <i>NTRK</i> 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 <ul style="list-style-type: none"> Phase 2 multinational, open label, tumour “basket” study Adult and paediatric patients ≥ 12 years with advanced solid tumours with an <i>NTRK</i> gene fusion | 100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution) | Thyroid (n=23) ^b Salivary gland (n=18) Soft tissue sarcoma (n=16) NSCLC (n=11) ^{b, c} Colorectal (n=8) Primary CNS (n=7) Melanoma (n=6) Breast, non-secretory (n=3) Breast, secretory (n=2) GIST (n=2) ^a Biliary (n=2) Pancreas (n=2) SCLC (n=1) ^{b, d} Appendix (n=1) Bone sarcoma (n=1) Hepatic ^e (n=1) Prostate (n=1) | 105 |
| Study 3 “SCOUT” NCT02637687 <ul style="list-style-type: none"> Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an <i>NTRK</i> gene fusion, including locally advanced infantile fibrosarcoma Paediatric patients ≥ 1 month 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=32) Soft tissue sarcoma (n=18) Primary CNS (n=17) Bone sarcoma (n=1) Congenital mesoblastic nephroma (n=1) Melanoma (n=1) | 70 |
| Total number of patients (n)[*] | | | 188 |

* consist of 164 patients with IRC tumour response assessment and 24 patients with primary CNS tumours (including astrocytoma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, and primitive neuro-ectodermal tumour) with investigator tumour response assessment

^a GIST: gastrointestinal stromal tumour

^b brain metastases observed in 6 NSCLC, 4 thyroid, 2 melanoma, 1 SCLC patient, and 1 breast (non-secretory) patient

^c NSCLC: non-small cell lung cancer

^d SCLC: small cell lung cancer

^e hepatocellular carcinoma

Baseline characteristics for the pooled 164 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 42 years (range 0.1-84 years); 34% < 18 years of age, and 66% ≥ 18 years; 77% white and 49% male; and ECOG PS 0-1 (86%), 2 (12%), or 3 (2%). Ninety-four percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 77% had received prior systemic therapy with a median of 1 prior systemic

treatment regimen. Twenty-two percent of all patients had received no prior systemic therapy. Of those 164 patients the most common tumour types represented were soft tissue sarcoma (22%), infantile fibrosarcoma (20%), thyroid cancer (16%), salivary gland tumour (13%), and lung cancer (8%).

Baseline characteristics for the 24 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 8 years (range 1.3-79 years); 20 patients < 18 years of age, and 4 patients ≥ 18 years, and 19 patients white and 11 patients male; and ECOG PS 0-1 (22 patients), or 2 (1 patient). All 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=164) and with post-hoc addition of primary CNS tumours (n=24) resulting in the pooled population (n=188), are presented in Table 5 and Table 6.

Table 5: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

| Efficacy parameter | Analysis in solid tumours excluding primary CNS tumours (n=164)^a | Analysis in solid tumours including primary CNS tumours (n=188)^{a, b} |
|---|--|---|
| Overall response rate (ORR) % (n) [95% CI] | 73% (119) [65, 79] | 66% (124) [59, 73] |
| Complete response (CR) | 19% (31) | 18% (33) |
| Pathological complete response ^c | 5% (8) | 4% (8) |
| Partial response (PR) | 49% (80) | 44% (83) ^d |
| Time to first response (median, months) [range] | 1.84 [0.92, 14.55] | 1.84 [0.92, 14.55] |
| Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months | NR [0.0+, 50.6+] 76% 67% | NR [0.0+, 50.6+] 74% 65% |

NR: not reached

+ denotes ongoing

^a Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (164 patients).

^b Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (24 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.

^d An additional 1% (2 patients with primary CNS tumours) had partial responses, pending confirmation.

Table 6: Overall response rate and duration of response by tumour type

| Tumour type | Patients (n=188) | ORR | | DOR | | |
|--|---------------------|--------|-----------|--------|------|-------------------|
| | | % | 95% CI | months | | Range (months) |
| | | | | ≥ 12 | ≥ 24 | |
| Soft tissue sarcoma ^a | 36 | 81% | 64%, 92% | 69% | 69% | 0.0+, 50.6+ |
| Infantile fibrosarcoma ^a | 32 | 97% | 84%, 100% | 72% | 63% | 1.6+, 28.6+ |
| Thyroid ^a | 27 | 56% | 35%, 75% | 93% | 58% | 3.7+, 32.9 |
| Primary CNS ^b | 24 | 21% | 7%, 42% | NR | NR | 1.7+, 10.1+ |
| Salivary gland ^a | 21 | 86% | 64%, 97% | 94% | 87% | 1.9+, 44.7+ |
| Lung ^a | 13 | 77% | 46%, 95% | 62% | 62% | 3.7, 36.8+ |
| Colon ^a | 8 | 38% | 9%, 76% | 50% | NR | 5.4+, 20.7+ |
| Melanoma ^a | 7 | 43% | 10%, 82% | 50% | NR | 1.9+, 23.2+ |
| Breast ^{a, c} | 5 | 60% | 15%, 95% | NR | NR | 5.6+, 9.2+ |
| Gastrointestinal stromal tumour ^a | 4 | 100% | 40%, 100% | 75% | 38% | 9.5, 31.1+ |
| Bone sarcoma ^a | 2 | 50% | 1%, 99% | 0% | 0% | 9.5 |
| Cholangiocarcinoma ^a | 2 | SD, NE | NA | NA | NA | NA |
| Pancreas ^a | 2 | SD, SD | NA | NA | NA | NA |
| Congenital mesoblastic nephroma ^a | 1 | 100% | 3%, 100% | 100% | NR | 20.8+ |
| Unknown primary cancer | 1 | 100% | 3%, 100% | 0% | 0% | 7.4 |
| Appendix ^a | 1 | SD | NA | NA | NA | NA |
| Hepatic | 1 | NE | NA | NA | NA | NA |
| Prostate | 1 | PD | NA | NA | NA | NA |

DOR: duration of response

NA: not applicable due to small numbers or lack of response

NE: not evaluable

NR: not reached

PD: progressive disease

SD: stable disease

+ denotes ongoing response

^a independent review committee analysis by RECIST v1.1

^b patients with a primary CNS tumour were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria

^c with 3 patients having non-secretory (1 complete, 1 partial responder and 1 progressive disease) and 2 patients having secretory breast cancer (1 partial and 1 stable disease)

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=109), the ORR was 63%. In the paediatric sub-population (n=55), the ORR was 91%.

In 165 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 79 patients who had other genomic alterations in addition to *NTRK* gene fusion was 58%, and in 86 patients without other genomic alterations ORR was 74%.

Pooled primary analysis set

The pooled primary analysis set consisted of 164 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 14.7 months (range: 0.10 to 51.6 months) based on July 2019 cut-off. Forty-four percent of patients had received VITRAKVI for 12 months or more and 21% had received VITRAKVI 24 months or more, with follow-up ongoing at the time of the analysis.

At the time of analysis, the median duration of response had not been reached, an estimated 76% [95% CI: 67, 85] of responses lasted 12 months or longer, and 67% [95% CI: 55, 78] of responses lasted 24 months or longer. Ninety percent (90%) [95% CI: 85, 95] of patients treated were alive one year after the start of therapy and 82% [95% CI: 75, 90] after two years with the median for overall survival not yet being reached. Median progression free survival was 33.4 months at the time of the analysis, with a progression free survival rate of 66% [95% CI: 58, 74] after 1 year and 58% [95% CI: 48, 67] after 2 years.

The median change in tumour size in the pooled primary analysis set was a decrease of 68%.

Patients with primary CNS tumours

At the time of data cut-off, of the 24 patients with primary CNS tumours confirmed response was observed in 5 patients (21%) with 2 of the 24 patients (8%) being complete responders and 3 patients (12.5%) being partial responders. In 2 additional patients (8%) a not yet confirmed partial response was observed. Further 15 patients (63%) had stable disease. Two patients (8%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 21.4 months and was ongoing in 15 out of 24 patients, with one 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 European Medicines Agency 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 ($t_{1/2}$) 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 (\pm 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 radiolabeled 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 radiolabeled 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 (1 month to <3 months of age) at the recommended dose of 100 mg/m² with a maximum of 100 mg BID was 3-fold higher than in adults (≥ 18 years of age) given the dose of 100 mg BID. At the recommended dose, the C_{max} in paediatric patients (≥ 3 months to <12 years of age) was higher than in adults, but the AUC was similar to that in adults. For paediatric patients older than 12 years of age, the recommended dose is likely to give similar C_{max} and AUC as observed in adults. Data defining exposure in small children (1 month to <6 years of age) at the recommended dose is limited (n=33).

Elderly

There are limited data in elderly. PK data is available only in 2 patients over 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-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-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 did not appear to influence larotrectinib pharmacokinetics to a clinically significant extent. There was not enough data to investigate the potential influence of race on the systemic exposure of larotrectinib.

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

Purified water
Sucrose
Hydroxypropylbetadex
Glycerol (E 422)
Sorbitol (E 420)
Sodium citrate (E 331)
Sodium dihydrogen phosphate dihydrate (E 339)
Citric acid (E 330)
Propylene glycol (E 1520)
Potassium sorbate (E 202)
Methyl parahydroxybenzoate (E 218)
Citrus fruit flavour
Natural flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 30 days.
Store in a refrigerator (2 °C - 8 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass (type III) bottle with a child-resistant polypropylene (PP) cap with a polyethylene (PE) seal liner.

Each carton contains one bottle of 100 mL oral solution.

6.6 Special precautions for disposal and other handling

Instructions for use:

Oral syringe

- Use a suitable oral syringe with CE marking and bottle adapter (28 mm diameter) if applicable.
 - For volumes less than 1 mL use a 1 mL oral syringe with 0.1 mL graduation.
 - For volumes of 1 mL and higher use a 5 mL oral syringe with 0.2 mL graduation.
- Open the bottle: press the bottle cap and turn it counter clockwise.
- Insert the bottle adapter into the bottle neck and ensure it is well fixed.
- Take the oral syringe and ensure that the plunger is fully depressed. Put the oral syringe in the adapter opening. Turn the bottle upside down.
- Fill the oral syringe with small amount of solution by pulling the plunger down, then push the plunger upwards to remove any bubbles.
- Pull the plunger down to the graduation mark equal to the quantity in mL as prescribed.
- Turn the bottle the right way up and remove the oral syringe from the bottle adapter.
- Slowly depress the plunger, directing the liquid towards the inside cheek to allow for natural swallowing.
- Close the bottle with the original bottle cap (leaving the adapter in place).

Nasogastric feeding tube

- Use a suitable nasogastric feeding tube. The outer diameter of the nasogastric feeding tube should be selected based on the patient characteristics. Typical tube diameter, tube lengths and derived prime volumes are presented in Table 7.
- The feeding should be stopped and the tube flushed with at least 10 mL water. NOTE: See exceptions regarding neonates and patients with fluid restrictions in the sub-point directly below.
- A suitable syringe should be used to administer VITRAKVI to the nasogastric feeding tube. The tube should be flushed again with at least 10 mL water to ensure VITRAKVI is delivered and to clear the tube.
Neonates and children with fluid restrictions may require minimal flushing volume of 0.5 to 1 mL or flushing with air to deliver VITRAKVI.
- Restart the feeding.

Table 7: Recommended tube dimensions per age group

| Patient | Tube diameter for standard feeds | Tube diameter for high density feeds | Tube length (cm) | Tube prime volume (mL) |
|----------------|---|---|-------------------------|-------------------------------|
| Neonate | 4-5 FR | 6 FR | 40-50 | 0.25-0.5 |
| Children | 6 FR | 8 FR | 50-80 | 0.7-1.4 |
| Adult | 8 FR | 10 FR | 80-120 | 1.4-4.2 |

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1385/003 – VITRAKVI 20 mg/mL oral solution

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER 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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
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 medical prescription.

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|-------------------|
| In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE). | 30 June 2024 |
| In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data. | 31 March 2027 |
| In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT). | 30 September 2021 |

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 25 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg **hard** capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 25 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 100 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 100 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: sucrose, E 420, E 1520, E 218. **Read the package leaflet before use.**

4. PHARMACEUTICAL FORM AND CONTENTS

100 mL **oral solution**

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use **within 30 days of opening.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
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

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 20 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

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: sucrose, E 420, E 1520, E 218. **Read the package leaflet before use.**

4. PHARMACEUTICAL FORM AND CONTENTS

100 mL **oral solution**

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use **within 30 days of opening.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
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

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/003

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

VITRAKVI 25 mg hard capsules VITRAKVI 100 mg hard capsules larotrectinib

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace “you” with “your child” throughout.

What is in this leaflet:

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

1. What VITRAKVI is and what it is used for

What VITRAKVI is used for

VITRAKVI contains the active substance larotrectinib.

It is used in adults, adolescents and children to treat solid tumours (cancer) in various parts of the body that are caused by a change in the NTRK gene (neurotrophic tyrosine receptor kinase).

VITRAKVI is only used when

- these cancers are advanced or have spread to other parts of the body or if a surgery to remove the cancer is likely to cause severe complications **and**
- there are no satisfactory treatment options.

Before you are given VITRAKVI, your doctor will do a test to check if you have the change in the NTRK gene.

How VITRAKVI works

In patients whose cancer is due to an altered NTRK gene, the change in the gene causes the body to make an abnormal protein called TRK fusion protein, which can lead to uncontrolled cell growth and cancer. VITRAKVI blocks the action of TRK fusion proteins and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions on how VITRAKVI works or why it has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take VITRAKVI

Do not take VITRAKVI if

- you are allergic to larotrectinib or any of the other ingredients of this medicine (listed in section 6).

Tests and checks

VITRAKVI can increase the amount of the liver enzymes ALT and AST in your blood. Your doctor will do blood tests before and during treatment to check the level of ALT and AST and check how well your liver is working.

Other medicines and VITRAKVI

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way VITRAKVI works or VITRAKVI may affect how other medicines work.

In particular, tell your doctor, pharmacist or nurse if you are taking any of the following medicines:

- medicines used to treat fungal or bacterial infections called itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin
- a medicine used to treat Cushing's syndrome called ketoconazole
- medicines used to treat HIV infection called atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, rifabutin, efavirenz
- a medicine used to treat depression called nefazodone
- medicines used to treat epilepsy called phenytoin, carbamazepine, phenobarbital
- a herbal medicine used to treat depression called St. John's wort
- a medicine used to treat tuberculosis called rifampicin
- a medicine used for strong pain relief called alfentanil
- medicines used to prevent organ rejection after an organ transplant called ciclosporin, sirolimus, tacrolimus
- a medicine used to treat an abnormal heart rhythm called quinidine
- medicines used to treat migraines called dihydroergotamine, ergotamine
- a medicine used to treat long-term pain called fentanyl
- a medicine used to control involuntary movements or sounds called pimozide
- a medicine to help you stop smoking called bupropion
- medicines to reduce blood sugar levels called repaglinide, tolbutamide
- a medicine that prevents blood clots called warfarin
- a medicine used to reduce the amount of acid produced in the stomach called omeprazole
- a medicine used to help control high blood pressure called valsartan
- a group of medicines used to help lower cholesterol called statins
- hormonal medicines used for contraception, see section "contraception – for men and women" below.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Taking VITRAKVI with food and drink

Do not eat grapefruit or drink grapefruit juice while taking VITRAKVI. This is because it may increase the amount of VITRAKVI in your body.

Pregnancy and breast-feeding

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use VITRAKVI during pregnancy since the effect of VITRAKVI on the unborn is not known.

Breast-feeding

Do not breast-feed while taking this medicine and for 3 days after the last dose. This is because it is not known if VITRAKVI passes into breast milk.

Contraception – for men and women

You should avoid getting pregnant while taking this medicine.

If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.

You must use effective methods of contraception while taking VITRAKVI and for at least 1 month after the last dose, if

- you are able to become pregnant. If you use hormonal contraceptives, you should also use a barrier method, such as a condom.
- you have sex with a woman able to become pregnant.

Ask your doctor about the best method of contraception for you.

Driving, cycling and using machines

VITRAKVI may make you feel dizzy or tired. If this happens, do not drive, cycle or use any tools or machines.

3. How to take VITRAKVI

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

How much to take

Adults (from 18 years)

- The recommended dose of VITRAKVI is 100 mg (1 capsule of 100 mg or 4 capsules of 25 mg), two times a day.
- Your doctor will review your dose and change it as needed.

Children and adolescents

- Your child's doctor will work out the right dose for your child based on their height and weight.
- The maximum recommended dose is 100 mg (1 capsule of 100 mg or 4 capsules of 25 mg), two times a day.
- Your child's doctor will review the dose and change it as needed.

An oral solution of VITRAKVI is available for patients who cannot swallow the capsules.

How to take this medicine

- VITRAKVI can be taken with or without food.
- Do not eat grapefruit or drink grapefruit juice while taking this medicine.
- Swallow the VITRAKVI capsules whole with a glass of water. Do not open, chew or crush the capsule as it has a very bitter taste.

If you take more VITRAKVI than you should

Talk to your doctor, pharmacist or nurse or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you miss a dose of VITRAKVI

Do not take a double dose to make up for a forgotten dose or if you vomit after taking this medicine. Take your next dose at the usual time.

If you stop taking VITRAKVI

Do not stop taking this medicine without talking to your doctor first. It is important to take VITRAKVI for as long as your doctor tells you.

If you are not able to take the medicine as your doctor prescribed talk to your doctor straight away.

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

4. Possible side effects

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

You should **immediately contact your doctor** if you experience any of the following **serious side effects**:

- feeling dizzy (very common side effect, may affect more than 1 in 10 people), tingling, feeling numb, or a burning feeling in your hands and feet, difficulty walking normally (common side effect, may affect up to 1 in 10 people). This could be symptoms of **nervous system problems**. Your doctor may decide to lower the dose, or pause or stop the treatment.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):

- you may look pale and feel your heart pumping, which could be symptoms of low red blood cells (anaemia)
- flu like symptoms including fever, which could be symptoms of low white blood cells (neutropenia, leukopenia)
- feeling or being sick (nausea or vomiting)
- constipation
- muscle pain (myalgia)
- feeling tired (fatigue)
- increased amount of liver enzymes in blood tests
- weight increase.

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

- change in how things taste (dysgeusia)
- muscle weakness
- increased amount of “alkaline phosphatase” in blood tests (very common in children).

Reporting of side effects

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

5. How to store VITRAKVI

- 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 carton and the bottle label after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that capsules look damaged.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VITRAKVI contains

The active substance is larotrectinib.

Each VITRAKVI 25 mg capsule contains 25 mg of larotrectinib (as sulfate).

Each VITRAKVI 100 mg capsule contains 100 mg of larotrectinib (as sulfate).

The other ingredients are:

Capsule shell:

- Gelatin
- Titanium dioxide (E 171)

Printing ink:

- Shellac
- Indigo carmine aluminium lake (E 132)
- Titanium dioxide (E 171)
- Propylene glycol (E 1520)
- Dimeticone

What VITRAKVI looks like and the contents of the bottle

- VITRAKVI 25 mg is supplied as white opaque hard gelatine capsule, (18 mm long x 6 mm wide), with blue printing of BAYER-cross and “LARO 25 mg” on the body of the capsule
- VITRAKVI 100 mg is supplied as white opaque hard gelatine capsule, (22 mm long x 7 mm wide), with blue printing of BAYER-cross and “LARO 100 mg” on the body of the capsule

Each carton contains 1 child-resistant plastic bottle containing 56 hard gelatine capsules.

Marketing Authorisation Holder

Bayer AG
51368 Leverkusen
Germany

Manufacturer

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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

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Slovenská republika

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Bayer Oy

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Sverige

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United Kingdom

Bayer plc

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the patient

VITRAKVI 20 mg/mL oral solution larotrectinib

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace “you” with “your child” throughout.

What is in this leaflet:

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

1. What VITRAKVI is and what it is used for

What VITRAKVI is used for

VITRAKVI contains the active substance larotrectinib.

It is used in adults, adolescents and children to treat solid tumours (cancer) in various parts of the body that are caused by a change in the NTRK gene (neurotrophic tyrosine receptor kinase).

VITRAKVI is only used when

- these cancers are advanced or have spread to other parts of the body or if a surgery to remove the cancer is likely to cause severe complications **and**
- there are no satisfactory treatment options.

Before you are given VITRAKVI, your doctor will do a test to check if you have the change in the NTRK gene.

How VITRAKVI works

In patients whose cancer is due to an altered NTRK gene, the change in the gene causes the body to make an abnormal protein called TRK fusion protein, which can lead to uncontrolled cell growth and cancer. VITRAKVI blocks the action of TRK fusion proteins and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions on how VITRAKVI works or why it has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take VITRAKVI

Do not take VITRAKVI if

- you are allergic to larotrectinib or any of the other ingredients of this medicine (listed in section 6).

Tests and checks

VITRAKVI can increase the amount of the liver enzymes ALT and AST in your blood. Your doctor will do blood tests before and during treatment to check the level of ALT and AST and check how well your liver is working.

Other medicines and VITRAKVI

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way VITRAKVI works or VITRAKVI may affect how other medicines work.

In particular, tell your doctor, pharmacist or nurse if you are taking any of the following medicines:

- medicines used to treat fungal or bacterial infections called itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin
- a medicine used to treat Cushing's syndrome called ketoconazole
- medicines used to treat HIV infection called atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, rifabutin, efavirenz
- a medicine used to treat depression called nefazodone
- medicines used to treat epilepsy called phenytoin, carbamazepine, phenobarbital
- a herbal medicine used to treat depression called St. John's wort
- a medicine used to treat tuberculosis called rifampicin
- a medicine used for strong pain relief called alfentanil
- medicines used to prevent organ rejection after an organ transplant called ciclosporin, sirolimus, tacrolimus
- a medicine used to treat an abnormal heart rhythm called quinidine
- medicines used to treat migraines called dihydroergotamine, ergotamine
- a medicine used to treat long-term pain called fentanyl
- a medicine used to control involuntary movements or sounds called pimozide
- a medicine to help you stop smoking called bupropion
- medicines to reduce blood sugar levels called repaglinide, tolbutamide
- a medicine that prevents blood clots called warfarin
- a medicine used to reduce the amount of acid produced in the stomach called omeprazole
- a medicine used to help control high blood pressure called valsartan
- a group of medicines used to help lower cholesterol called statins
- hormonal medicines used for contraception, see section "contraception – for men and women" below.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Taking VITRAKVI with food and drink

Do not eat grapefruit or drink grapefruit juice while taking VITRAKVI. This is because it may increase the amount of VITRAKVI in your body.

Pregnancy and breast-feeding

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use VITRAKVI during pregnancy since the effect of VITRAKVI on the unborn is not known.

Breast-feeding

Do not breast-feed while taking this medicine and for 3 days after the last dose. This is because it is not known if VITRAKVI passes into breast milk.

Contraception – for men and women

You should avoid getting pregnant while taking this medicine.

If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.

You must use effective methods of contraception while taking VITRAKVI and for at least 1 month after the last dose, if

- you are able to become pregnant. If you use hormonal contraceptives, you should also use a barrier method, such as a condom.
- you have sex with a woman able to become pregnant.

Ask your doctor about the best method of contraception for you.

Driving, cycling and using machines

VITRAKVI may make you feel dizzy or tired. If this happens, do not drive, cycle or use any tools or machines.

VITRAKVI contains:

- **sucrose:** it may be harmful to the teeth. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- 22 mg **sorbitol** in 1 mL. Sorbitol is a source of fructose. If your doctor has told you that you or your child have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you or your child take or receive this medicine.
- less than 1 mmol (or 23 mg) of **sodium** per 5 mL, that is to say essentially 'sodium free'.
- 1.2 mg **propylene glycol** in 1 mL. If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.
- **parahydroxybenzoate:** it may cause allergic reactions (possibly delayed).

3. How to take VITRAKVI

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

How much to take

Adults (from 18 years)

- The recommended dose of VITRAKVI is 100 mg (5 mL), two times a day.
- Your doctor will review your dose and change it as needed.

Children and adolescents

- Your child's doctor will work out the right dose for your child based on their height and weight.
- The maximum recommended dose is 100 mg (5 mL), two times a day.
- Your child's doctor will review the dose and change it as needed.

How to take this medicine

- VITRAKVI can be taken with or without food.
 - Do not eat grapefruit or drink grapefruit juice while taking this medicine.
 - Along with this medicine you need a bottle adapter (28 mm diameter) and a syringe that can be used to give medicines by mouth. Use a 1 mL syringe with 0.1 mL marks for doses less than 1 mL. Use a 5 mL syringe with 0.2 mL marks for doses of 1 mL or more.
 - Press the bottle cap and turn it anti-clockwise to open the bottle.
 - Put the bottle adapter into the bottle neck and make sure it is well fixed.
 - Push the plunger fully into the syringe and then put the syringe in the adapter opening. Turn the bottle upside down.
 - Fill the syringe with a small amount of solution by pulling the plunger down, then push the plunger upwards to remove any large bubbles that are in the syringe.
 - Pull the plunger down to the mark equal to the dose in mL prescribed by your doctor.
 - Turn the bottle the right way up and take the syringe out of the adapter.
 - Put the syringe in the mouth, pointing towards the inside of the cheek – this will help you swallow the medicine naturally. Slowly press the plunger in.
 - Put the bottle cap on and tightly close the bottle - leave the adapter in the bottle.
- If necessary, VITRAKVI may be administered via a nasogastric feeding tube. For details how to do so, please ask your doctor, pharmacist or nurse.

If you take more VITRAKVI than you should

Talk to your doctor, pharmacist or nurse or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you miss a dose of VITRAKVI

Do not take a double dose to make up for a forgotten dose or if you vomit after taking this medicine. Take your next dose at the usual time.

If you stop taking VITRAKVI

Do not stop taking this medicine without talking to your doctor first. It is important to take VITRAKVI for as long as your doctor tells you.

If you are not able to take the medicine as your doctor prescribed talk to your doctor straight away. If you have further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

You should **immediately contact your doctor** if you experience any of the following **serious side effects**:

- feeling dizzy (very common side effect, may affect more than 1 in 10 people), tingling, feeling numb, or a burning feeling in your hands and feet, difficulty walking normally (common side effect, may affect up to 1 in 10 people). This could be symptoms of **nervous system problems**. Your doctor may decide to lower the dose, or pause or stop the treatment.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):

- you may look pale and feel your heart pumping, which could be symptoms of low red blood cells (anaemia)
- flu like symptoms including fever, which could be symptoms of low white blood cells (neutropenia, leukopenia)
- feeling or being sick (nausea or vomiting)
- constipation
- muscle pain (myalgia)
- feeling tired (fatigue)
- increased amount of liver enzymes in blood tests
- weight increase.

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

- change in how things taste (dysgeusia)
- muscle weakness
- increased amount of “alkaline phosphatase” in blood tests (very common in children).

Reporting of side effects

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

5. How to store VITRAKVI

- 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 carton and the bottle label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C).
- Do not freeze.
- Once the bottle is open, you must use your medicine within 30 days of opening.
- Do not take the medicine if the bottle or bottle cap looks damaged or like it has leaked.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VITRAKVI contains

The active substance is larotrectinib.

Each mL of oral solution contains 20 mg of larotrectinib (as sulfate).

The other ingredients are:

- Purified water
- Sucrose
- Hydroxypropylbetadex
- Glycerol (E 422)
- Sorbitol (E 420)
- Sodium citrate (E 331)
- Sodium dihydrogen phosphate dihydrate (E 339)
- Citric acid (E 330)
- Propylene glycol (E 1520)
- Potassium sorbate (E 202)
- Methyl parahydroxybenzoate (E 218)
- Citrus fruit flavour
- Natural flavour

See “VITRAKVI contains” in section 2 for more information.

What VITRAKVI looks like and the contents of the bottle

VITRAKVI is a clear yellow to orange oral solution.

Each carton contains 1 child-resistant glass bottle containing 100 mL oral solution.

Marketing Authorisation Holder

Bayer AG
51368 Leverkusen
Germany

Manufacturer

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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

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