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

Rozlytrek 100 mg hard capsules
Rozlytrek 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rozlytrek 100 mg hard capsules

Each hard capsule contains 100 mg of entrectinib.

Excipients with known effect
Each hard capsule contains 65 mg lactose.

Rozlytrek 200 mg hard capsules

Each hard capsule contains 200 mg of entrectinib.

Excipients with known effect
Each hard capsule contains 130 mg lactose, and 0.6 mg of the azo colouring agent sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Rozlytrek 100 mg hard capsules

Size 2 (18 mm in length), hard capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body.

Rozlytrek 200 mg hard capsules

Size 0 (21.7 mm in length), hard capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients older than 1 month with solid tumours that have a *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 not received a prior *NTRK* inhibitor
- who have no satisfactory treatment options (see sections 4.4 and 5.1).

ROS1 gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult patients with *ROS1*-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

4.2 Posology and method of administration

Treatment with Rozlytrek should be initiated by a physician experienced in the use of anticancer medicinal products.

Patient selection

NTRK gene fusion
A validated assay is required for the selection of patients with *NTRK* gene fusion-positive solid tumours. *NTRK* gene fusion-positive status must be established prior to initiation of Rozlytrek therapy (see section 5.1).

ROS1 gene fusion
A validated assay is required for the selection of adult patients with *ROS1*-positive NSCLC. *ROS1*-positive status must be established prior to initiation of Rozlytrek therapy (see section 5.1).

Posology

Rozlytrek is available as hard capsules or film-coated granules.

The physician should prescribe the most appropriate pharmaceutical form according to the dose required and patient needs.

- Whole capsules are recommended for patients who can swallow whole capsules and where the required dose is 100 mg or a multiple of 100 mg. Patients who have difficulty or are unable to swallow capsules or who require enteral administration (e.g., gastric or nasogastric) may receive treatment with Rozlytrek capsules administered as an oral suspension. Refer to the Method of administration section below and section 6.6.

- Rozlytrek film-coated granules are recommended for paediatric patients who have difficulty, or are unable, to swallow capsules but can swallow soft food and where the required dose is 50 mg or a multiple of 50 mg. Film-coated granules should be sprinkled on soft food. Refer to the Rozlytrek film-coated granules SmPC for prescribing information.

Adults
The recommended dose for adults is 600 mg entrectinib once daily.

Paediatric population

Paediatric population > 6 months of age
The recommended dose for paediatric patients > 6 months of age is based on body surface area (BSA) (see Table 1). Patients who have difficulty or are unable to swallow capsules but can swallow soft food, may receive treatment with Rozlytrek film-coated granules. Refer to the Rozlytrek film-coated granules SmPC for prescribing information.

Table 1: Recommended dosing for paediatric patients > 6 months

Body surface area (BSA)*	Once daily dose
≤ 0.42 m^2	250 mg/m^{2**}
0.43 m^2 to 0.50 m^2	100 mg
0.51 m^2 to 0.80 m^2	200 mg
0.81 m^2 to 1.10 m^2	300 mg
1.11 m^2 to 1.50 m^2	400 mg
≥ 1.51 m^2	600 mg

*BSA categories and recommended dosing in Table 1 are based on closely matching exposures to a target dose of 300 mg/m^2

**To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Method of Administration section below and section 6.6.

Paediatric patients > 1 month to ≤ 6 months of age
The recommended dose for paediatric patients > 1 month to ≤ 6 months of age is 250 mg/m^2 BSA entrectinib once daily, using capsules prepared as an oral suspension.

Capsules administered as an oral suspension (oral or enteral use) enable dosing increments of 10 mg. The daily dose to be administered should be rounded to the nearest 10 mg increment as described in the Method of administration section below and section 6.6.

Duration of treatment
It is recommended that patients are treated with Rozlytrek until disease progression or unacceptable toxicity.

Delayed or missed doses
If a planned dose of Rozlytrek is missed, patients can make up that dose unless the next dose is due within 12 hours.

For whole capsules, if vomiting occurs immediately after taking a dose of Rozlytrek, patients may repeat that dose.

For capsules administered as an oral suspension by individuals other than the healthcare professional (e.g., caregivers or parents) and partial or total vomiting/spitting occurs immediately after taking an administered dose, caregivers should consult the healthcare professional for the next steps.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek, in case of specified adverse reactions (see Table 3) or based on the prescriber's assessment of the patient's safety or tolerability.

Adults
For adults, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability (see Table 2). Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Paediatric population
For paediatric patients older than 1 month, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability (see Table 2).

Table 2: Dose reduction schedule for adult and paediatric patients

Starting dose once daily	**First dose reduction**	**Second dose reduction**	Permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.
250 mg/m^2	Reduce the once daily dose to two thirds of the starting dose*	Reduce the once daily dose to one third of the starting dose*	
100 mg	50 mg or 100 mg once daily, according to schedule**	50 mg once daily	
200 mg	150 mg once daily	100 mg once daily	
300 mg	200 mg once daily	100 mg once daily	
400 mg	300 mg once daily	200 mg once daily	
600 mg	400 mg once daily	200 mg once daily	

*To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Method of administration section below and section 6.6.

**Monday (100 mg), Tuesday (50 mg), Wednesday (100 mg), Thursday (50 mg), Friday (100 mg), Saturday (50 mg), and Sunday (100 mg).

Recommendations for Rozlytrek dose modifications for adult and paediatric patients in case of specific adverse reactions are provided in Table 3 (see sections 4.4 and 4.8).

Table 3: Recommended Rozlytrek dose modifications for adverse reactions in adult and paediatric patients

Adverse reaction	**Severity***	**Dosage modification**
Congestive heart failure	Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
Cognitive disorders	Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
	Severe changes limiting activities of daily living (Grade 3)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose

Adverse reaction	Severity*	Dosage modification
	Urgent intervention indicated for event (Grade 4)	• For prolonged, severe, or intolerable events, discontinue Rozlytrek as clinically appropriate
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
QT interval prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are <u>not</u> identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek
Transaminase elevations	Grade 3	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks
	Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue Rozlytrek
Anaemia or neutropenia	Grade 3 or 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 2 or to baseline • Resume at the same dose or reduced dose, as clinically needed

Adverse reaction	Severity*	Dosage modification
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Rozlytrek until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.		

Strong or moderate CYP3A inhibitors
The concomitant use of strong or moderate CYP3A inhibitors in adult and paediatric patients older than 1 month should be avoided (see section 4.4).

For adults, if co-administration is unavoidable, the use of strong or moderate CYP3A inhibitors with Rozlytrek should be limited to 14 days and the Rozlytrek dose should be reduced as follows:

- 100 mg once daily for use with strong CYP3A inhibitors (see section 4.5)
- 200 mg once daily for use with moderate CYP3A inhibitors.

After discontinuation of the concomitant strong or moderate CYP3A inhibitors, the Rozlytrek dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash-out period may be required for CYP3A4 inhibitors with a long half-life (see section 4.5).

Special populations

Elderly
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see section 5.2). Patients with severe hepatic impairment should be carefully monitored for hepatic function and adverse reactions (see Table 3).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Entrectinib has not been studied in patients with severe renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of entrectinib in paediatric patients 1 month of age and younger have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Rozlytrek is for oral use or enteral use (e.g., gastric or nasogastric).

Rozlytrek can be taken with or without food (see section 5.2) but should not be taken with grapefruit, grapefruit juice, or Seville oranges (see section 4.5).

The hard capsules should be swallowed whole. Do not crush or chew the capsules.

Capsules administered as an oral suspension
For details on preparation of capsules as an oral suspension, see section 6.6.

Rozlytrek should be taken immediately after preparation as an oral suspension. Discard the suspension if not used within 2 hours (see section 6.4).

The patient should drink water after taking the oral suspension to ensure the medicinal product has been completely swallowed. If enteral (e.g., gastric or nasogastric) administration is required, administer the oral suspension via the tube. The tube should be flushed with water or milk after delivering Rozlytrek. Follow the manufacturer's instructions for the enteral tube to administer the medicine, see section 6.6.

Detailed instructions on the administration of the capsules prepared as an oral suspension are given in the Instructions for Use (IFU) at the end of the package leaflet.

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 Rozlytrek has been established in single-arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of Rozlytrek have been shown based on 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 genomic alterations (see section 5.1). For these reasons, Rozlytrek should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted).

Cognitive disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek (see section 4.8). Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes.

Based on the severity of cognitive disorders, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

Patients should be counselled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders (see section 4.7).

Fractures

Fractures have been reported in 29.7% (27/91) of paediatric patients treated with Rozlytrek in clinical trials (see section 4.8). Bone fractures mostly occurred in paediatric patients less than 12 years of age and were localised in the lower extremity (with a predilection for femur, tibia, foot, and fibula). In both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area. Fourteen paediatric patients had more than one occurrence of a fracture. Fractures resolved in the majority of paediatric patients (see section 4.8). Five paediatric patients had Rozlytrek treatment interrupted due to a fracture. Six paediatric patients discontinued treatment due to fractures.

Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly.

Hyperuricemia

Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating Rozlytrek and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. Treatment with urate-lowering medicinal products should be initiated as clinically indicated and Rozlytrek withheld for signs and symptoms of hyperuricemia. Rozlytrek dose should be modified based on severity as described in Table 3 in section 4.2.

Congestive heart failure

Congestive heart failure (CHF) has been reported in 5.4% of patients across clinical trials with Rozlytrek (see section 4.8). These reactions were observed in patients with or without a history of cardiac disease and resolved in 63.0% of those patients upon institution of appropriate clinical management and/or Rozlytrek dose reduction/interruption.

For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Rozlytrek treatment. Patients receiving Rozlytrek should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate.

Based on the severity of CHF, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

QTc interval prolongation

QTc interval prolongation has been observed in patients treated with Rozlytrek in clinical trials (see section 4.8).

Use of Rozlytrek should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval.

Rozlytrek should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. If, in the opinion of the treating physician, the potential benefits of Rozlytrek in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.

Assessment of ECG and electrolytes at baseline and after 1 month of treatment with Rozlytrek are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout Rozlytrek treatment, are also recommended.

Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

Women of childbearing potential

Rozlytrek may cause foetal harm when administered to a pregnant woman. Women of childbearing potential must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of Rozlytrek.

Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with Rozlytrek and for 3 months after the last dose (see sections 4.6 and 5.3).

Drug interactions

Co-administration of Rozlytrek with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations (see section 4.5), which could increase the frequency or severity of adverse reactions. Co-administration of Rozlytrek with a strong or moderate CYP3A inhibitor should be avoided. For adult patients if co-administration is unavoidable, the Rozlytrek dose should be reduced (see section 4.2).

During treatment with Rozlytrek, the consumption of grapefruit, grapefruit products, and Seville oranges should be avoided.

Co-administration of Rozlytrek with a strong or moderate CYP3A or P-gp inducer decreases entrectinib plasma concentrations (see section 4.5), which may reduce efficacy of Rozlytrek, and should be avoided.

Lactose intolerance

Rozlytrek contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sunset yellow FCF (E110)

Rozlytrek 200 mg hard capsules contain sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of entrectinib on other medicinal products

Effect of entrectinib on CYP substrates
Entrectinib is a weak inhibitor of CYP3A4. Co-administration of entrectinib 600 mg once daily with oral midazolam (a sensitive CYP3A substrate) in patients increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21%. Caution is advised when entrectinib is administered together with sensitive CYP3A4 substrates with a narrow therapeutic range (e.g., cisapride, cyclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus), due to the increased risk of adverse drug reactions.

Effect of entrectinib on P-gp substrates
In vitro data suggest that entrectinib has inhibitory potential towards P-glycoprotein (P-gp).

Co-administration of a single 600 mg dose of entrectinib with digoxin (a sensitive P-gp substrate) increased digoxin C_{max} by 28% and AUC by 18%. The renal clearance of digoxin was similar between treatments of digoxin alone and digoxin co-administered with entrectinib, indicating minimal effect of entrectinib on renal clearance of digoxin.

The effect of entrectinib on digoxin absorption is not considered clinically relevant, but it is unknown whether the effect of entrectinib may be larger on more sensitive oral P-gp substrates such as dabigatran etexilate.

Effect of entrectinib on BCRP substrates
Inhibition of BCRP was observed in *in vitro* studies.
The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral BCRP substrates (e.g. methotrexate, mitoxantrone, topotecan, lapatinib) are co-administered with entrectinib, due to the risk of increased absorption.

Effect of entrectinib on other transporter substrates
In vitro data indicate that entrectinib has weak inhibitory potential towards organic anion-transporting polypeptide (OATP)1B1. The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral OATP1B1 substrates (e.g. atorvastatin, pravastatin, rosuvastatin repaglinide, bosentan) are co-administered with entrectinib, due to the risk of increased absorption.

Effect of entrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that entrectinib may induce pregnane X receptor (PXR) regulated enzymes (e.g. CYP2C family and UGT). Co-administration of entrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Oral contraceptives
It is currently unknown whether entrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives are advised to add a barrier method (see section 4.6).

Effects of other medicinal products on entrectinib

Based on *in vitro* data, CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

Effect of CYP3A or P-gp inducers on entrectinib
Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced entrectinib AUC_{inf} by 77% and C_{max} by 56%.

Co-administration of entrectinib with CYP3A/P-gp inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's Wort [*Hypericum perforatum*], apalutamide, ritonavir, dexamethasone) should be avoided.

If co-administration of Rozlytrek with dexamethasone cannot be avoided, dexamethasone dose recommendations should be determined by the healthcare professional.

Effect of CYP3A or P-gp inhibitors on entrectinib
Co-administration of itraconazole, a strong CYP3A4 inhibitor, with a single oral dose of entrectinib increased AUC_{inf} by 600% and C_{max} by 173%. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children as young as 2 years old.

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit, or Seville oranges) should be avoided. If concurrent use of strong or moderate inhibitors of CYP3A4 is unavoidable, dose adjustment of entrectinib is required (see section 4.2).

Although, a marked effect of inhibitory P-gp medicinal products on entrectinib pharmacokinetics is not expected, caution is advised when treatment with strong or moderate P-gp inhibitors (e.g. verapamil, nifedipine, felodipine, fluvoxamine, paroxetine) are co-administered with entrectinib due to risk of increased entrectinib exposure (see section 5.2).

Effect of medicinal products that increase gastric pH on entrectinib
Co-administration of a proton pump inhibitor (PPI), lansoprazole with a single 600 mg entrectinib dose reduced entrectinib AUC by 25% and C_{max} by 23%.

No dose adjustments are required when entrectinib is co-administered with PPIs or other medicines that raise gastric pH (e.g., H2 receptor antagonists or antacids).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Female patients of childbearing potential should have medically supervised pregnancy testing prior to initiating Rozlytrek therapy.

Female patients of childbearing potential must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Rozlytrek.

It is currently unknown whether entrectinib may reduce the effectiveness of systemically acting hormonal contraceptives (see section 4.5). Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Rozlytrek (see section 5.3).

Pregnancy

There are no available data from the use of entrectinib in pregnant women. Based on animal studies and its mechanism of action, entrectinib may cause foetal harm when administered to a pregnant woman (see sections 4.4 and 5.3).

Rozlytrek is not recommended during pregnancy and in women of childbearing potential not using contraception.

Female patients receiving Rozlytrek should be advised of the potential harm to the foetus. Female patients should be advised to contact the doctor, should pregnancy occur.

Breast-feeding

It is unknown whether entrectinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Rozlytrek.

Fertility

No fertility studies in animals have been performed to evaluate the effect of entrectinib (see section 5.3).

4.7 Effects on ability to drive and use machines

Rozlytrek has moderate influence on the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥20%) were fatigue, constipation, diarrhoea, dizziness, dysgeusia, oedema, increased weight, anaemia, increased blood creatinine, nausea, dysaesthesia, pain, vomiting, pyrexia, arthralgia, increased aspartate aminotransferase and dyspnoea, cognitive disorders, cough, and increased alanine aminotransferase. The most frequent serious adverse reactions (≥2%) were lung infection (5.3%), fractures (4.1%), dyspnoea (3.6%), cognitive impairment (2.9%), pleural

effusion (2.5%) and pyrexia (2.5%). Permanent discontinuation due to an adverse reaction occurred in 6.0% of patients.

Tabulated list of adverse reactions

Table 4 summarises the adverse drug reactions (ADRs) occurring in 762 adult and 91 paediatric patients treated with Rozlytrek in three clinical trials in adults (ALKA, STARTRK-1, and STARTRK-2) and one clinical trial in paediatric patients (STARTRK-NG) and one clinical trial in adult and paediatric patients (TAPISTRY). The median duration of exposure was 8.6 months.

Table 5 includes paediatric patients from three clinical studies; STARTRK-NG, STARTRK-2 and TAPISTRY. The median duration of exposure was 11.1 months. Paediatric data in the description of selected adverse reactions reflect exposure to Rozlytrek in this expanded paediatric safety population (n=91). The safety profile observed in the expanded paediatric population was consistent with the known paediatric safety profile from the integrated safety population in Table 4 below.

Adverse drug reactions are listed by MedDRA system organ class. The following categories of frequency have been used: very common ≥1/10, common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000). Within each system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse drug reactions occurring in adult and paediatric patients treated with Rozlytrek in clinical trials (n=853)

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
Infections and infestations	Urinary tract infection	15.7	Very common	2.7
	Lung infection[1]	14.4	Very common	6.1*
Blood and lymphatic system disorders	Anaemia	33.4	Very common	9.7
	Neutropenia[2]	15.8	Very common	6.1
Metabolism and nutritional disorders	Weight increased	34.1	Very common	10.6
	Hyperuricemia	16.4	Very common	2.3
	Decreased appetite	13.0	Very common	0.7
	Dehydration	6.6	Common	1.1
	Tumour lysis syndrome	0.2	Uncommon	0.2*
Nervous system disorders	Dizziness[3]	36.5	Very common	1.9
	Dysgeusia	35.8	Very common	0.2
	Dysaesthesia[4]	24.9	Very common	0.4
	Cognitive disorders[5]	23.3	Very common	3.6
	Peripheral sensory neuropathy[6]	16.2	Very common	1.1
	Headache	16.1	Very common	0.6
	Ataxia[7]	15.1	Very common	1.5
	Sleep disturbances[8]	12.8	Very common	0.4
	Mood disorders[9]	9.4	Common	0.6
	Syncope	5.0	Common	3.5
Eye disorders	Vision blurred[10]	11.7	Very common	0.2
Cardiac disorders	Congestive heart failure[11]	5.4	Common	2.5*
	Electrocardiogram QTc prolonged	3.6	Common	0.9
	Myocarditis	0.2	Uncommon	0.1
Vascular disorders	Hypotension[12]	15.9	Very common	2.3
Respiratory, thoracic and mediastinal disorders	Dyspnoea	23.8	Very common	4.9*
	Cough	21.1	Very common	0.4
	Pleural effusion	6.0	Common	2.2

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
Gastrointestinal disorders	Constipation	42.3	Very common	0.4
	Diarrhoea	37.9	Very common	2.2
	Nausea	30.0	Very common	0.6
	Vomiting	25.1	Very common	1.1
	Abdominal pain	11.6	Very common	0.6
	Dysphagia	10.7	Very common	0.6
Hepatobiliary disorders	AST increased	21.1	Very common	2.9
	ALT increased	20.2	Very common	3.2
Skin and subcutaneous tissue disorders	Rash[13]	13.4	Very common	1.2
	Photosensitivity reaction	1.9	Common	0
Musculoskeletal and connective tissue disorders	Arthralgia	21.0	Very common	0.7
	Myalgia	19.7	Very common	0.8
	Fractures[14]	11.3	Very common	3.4
	Muscular weakness	10.4	Very common	1.3
Renal and urinary disorders	Blood creatinine increased	31.5	Very common	1.2
	Urinary retention[15]	10.4	Very common	0.6
General disorders and administration site conditions	Fatigue[16]	43.5	Very common	5.0
	Oedema[17]	34.3	Very common	1.8
	Pain[18]	25.6	Very common	1.5
	Pyrexia	23.8	Very common	0.9

* Grades 3 to 5, inclusive of fatal adverse reactions (including 4 reactions of pneumonia, 3 reactions of dyspnoea, 1 reaction of cardiac failure, and 1 reaction of tumour lysis syndrome).

[1] Lung infection (bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection)

[2] Neutropenia (neutropenia, neutrophil count decreased)

[3] Dizziness (dizziness, vertigo, dizziness postural)

[4] Dysaesthesia (paresthesia, hyperesthesia, hypoesthesia, dysesthesia)

[5] Cognitive disorders (cognitive disorder, confusional state, memory impairment, disturbance in attention, amnesia, mental status changes, hallucination, delirium, disorientation, brain fog, attention deficit hyperactivity disorder, 'visual hallucination','auditory hallucination', mental impairment, mental disorder)

[6] Periphery sensory neuropathy (neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy)

[7] Ataxia (ataxia, balance disorder, gait disturbances)

[8] Sleep disturbances (hypersomnia, insomnia, sleep disorder, somnolence)

[9] Mood disorders (anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation)

[10] Vision blurred (diplopia, vision blurred, visual impairment)

[11] Congestive heart failure (acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary oedema)

[12] Hypotension (hypotension, orthostatic hypotension)

[13] Rash (rash, rash maculopapular, rash pruritic, rash erythematous, rash papular)

[14] Fractures (acetabulum fracture, ankle fracture, avulsion fracture, bursitis, cartilage injury, clavicle fracture, compression fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, fracture, fractured sacrum, hand fracture, hip fracture, humerus fracture, ilium fracture, jaw fracture, joint injury, limb fracture, lower limb fracture, lumbar vertebral fracture, osteoporotic fracture, pathological fracture, pelvic fracture, rib fracture, spinal compression fracture, spinal fracture, spondylolisthesis, sternal fracture, stress fracture, synovial rupture, thoracic vertebral fracture, tibia fracture, ulna fracture, wrist fracture)

[15] Urinary retention (urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency)

[16] Fatigue (fatigue, asthenia)

[17] Oedema (face oedema, fluid retention, generalised oedema, localised oedema, oedema, oedema peripheral, peripheral swelling)

[18] Pain (back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity)

Table 5: Adverse drug reactions occurring in paediatric patients treated with Rozlytrek in clinical trials (n=91)

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
Infections and infestations	Very common	Lung infection (28.6%), Urinary tract infection (23.8%)	Urinary tract infection (23.6%), Lung infection (16.4%)		Urinary tract infection (19.8%), Lung infection (17.6%)
	Common			Lung infection (6.7%)	
Blood and lymphatic system disorders	Very common	Anaemia (61.9%), Neutropenia (47.6%)	Anaemia (34.5%), Neutropenia (27.3%)	Anaemia (33.3%), Neutropenia (33.3%)	Anaemia (40.7%), Neutropenia (33.0%)
Metabolism and nutritional disorders	Very common	Weight increased (23.8%), Decreased appetite (14.3%)	Weight increased (38.5%), Decreased appetite (29.1%), Dehydration (12.7%)	Weight increased (53.3%), Decreased appetite (13.3%), Hyperuricemia (13.3%)	Weight increased (38.5%), Decreased appetite (23.1%)
	Common	Dehydration (4.8%), Hyperuricemia (4.8%)	Hyperuricemia (3.6%)		Dehydration (8.8%), Hyper-uricemia (5.5%)
Nervous system disorders	Very common		Headache (32.7%), Mood disorders (16.4%), Sleep disturbances (16.4%), Dizziness (14.5%), Ataxia (10.9%)	Dysgeusia (20%), Mood disorders (13.3%), Cognitive disorders (13.3%), Dysaesthesia (13.3%)	Headache (20.9%), Mood disorders (14.3%), Sleep disturbances (13.2%)

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
	Common	Mood disorders (9.5%), Sleep disturbances (9.5%), Cognitive disorders (9.5%), Ataxia (4.8%), Peripheral sensory neuropathy (4.8%), Syncope (4.8%)	Cognitive disorders (9.1%), Dysgeusia (9.1%), Dysaesthesia (5.5%), Syncope (5.5%), Peripheral sensory neuropathy (5.5%)	Headache (6.7%), Sleep disturbances (6.7%), Peripheral sensory neuropathy (6.7%), Syncope (6.7%)	Cognitive disorders (9.9%), Dizziness (8.8%), Dysgeusia (8.8%), Ataxia (7.7%), Dysaesthesia (5.5%), Peripheral sensory neuropathy (5.5%), Syncope (5.5%)
Eye disorders	Common		Vision blurred (7.3%)	Vision blurred (6.7%)	Vision blurred (5.5%)
Cardiac disorders	Common	Congestive heart failure (9.5%), Electro-cardiogram QT prolonged (9.5%)	Congestive heart failure (5.5%), Electro-cardiogram QT prolonged (5.5%)		Congestive heart failure (5.5%), Electro-cardiogram QT prolonged (5.5%)
Vascular disorders	Common	Hypotension (9.5%)	Hypotension (7.3%)	Hypotension (6.7%)	Hypotension (7.7%)
Respiratory, thoracic and mediastinal disorders	Very common	Cough (42.9%)	Cough (40%)	Cough (20%), Dyspnoea (13.3%)	Cough (37.4%)
	Common	Dyspnoea (4.8%)	Dyspnoea (9.1%), Pleural effusion (5.5%)	Pleural effusion (6.7%)	Dyspnoea (8.8%), Pleural effusion (4.4%)
Gastrointestinal disorders	Very common	Vomiting (47.6%), Diarrhoea (42.9%), Constipation (42.9%)	Vomiting (43.6%), Diarrhoea (43.6%), Constipation (36.4%), Nausea (34.5%), Abdominal pain (25.5%)	Nausea (40%), Constipation (33.3%), Vomiting (20%), Diarrhoea (20%), Abdominal pain (13.3%)	Vomiting (40.7%), Diarrhoea (39.6%), Constipation (37.4 %), Nausea (28.6 %), Abdominal pain (19.8%)

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
	Common	Abdominal pain (9.5%), Nausea (4.8%)			
Hepatobiliary disorders	Very common	ALT increased (47.6%), AST increased (42.9%)	AST increased (29.1%), ALT increased (25.5%)	AST increased (53.3%), ALT increased (46.7%)	AST increased (36.3%), ALT increased (34.1%)
Skin and subcutaneous tissue disorders	Very common	Rash (38.1%)	Rash (21.8%)		Rash (22%)
Musculo-skeletal and connective tissue disorders	Very common		Fractures (40%), Arthralgia (16.4%)	Fractures (20%), Muscular weakness (13.3%), Myalgia (13.3%)	Fractures (29.7%), Arthralgia (11.0%)
	Common	Fractures (9.5%)	Muscular weakness (7.3%), Myalgia (7.3%)	Arthralgia (6.7%)	Muscular weakness (6.6%), Myalgia (6.6%)
Renal and urinary disorders	Very common	Blood creatinine increased (19%)	Blood creatinine increased (34.5%), Urinary retention (18.2%)	Blood creatinine increased (46.7%)	Blood creatinine increased (33%), Urinary retention (14.3%)
	Common	Urinary retention (9.5%)		Urinary retention (6.7%)	
General disorders and administration site conditions	Very common	Pyrexia (61.9%)	Pyrexia (50.9%), Fatigue (40%), Pain (30.9%), Oedema (14.5%)	Pain (33.3%), Pyrexia (33.3%), Fatigue (20%)	Fatigue (28.6%), Pain (26.4%), Pyrexia (50.5%), Oedema (11%)
	Common	Pain (9.5%), Oedema (9.5%), Fatigue (4.8%)			

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)

% refers to all grades

[1]Infant/toddlers (≥ 28 days to < 24 months): Grade ≥ 3 reactions reported were neutropenia, weight increased, lung infection, anaemia, AST increased, abdominal pain, and urinary tract infection

[2]Children (≥ 24 months to < 12 years): Grade ≥ 3 reactions reported were neutropenia, weight increased, fractures, lung infection, anaemia, ALT increased, syncope, AST increased, ataxia, dyspnoea, abdominal pain, congestive heart failure, fatigue, headache, pain, pyrexia, urinary tract infection, arthralgia, cognitive disorders, constipation, cough, decreased appetite, dehydration, hypotension, muscular weakness, oedema, and vomiting

[3]Adolescents (≥ 12 to < 18 years of age): Grade ≥ 3 reactions reported were neutropenia, weight increased, fracture, lung infection, and headache

Description of selected adverse reactions

Cognitive disorders
A variety of cognitive symptoms was reported across clinical trials (see section 4.4). These included events reported as cognitive disorders (6.4%), confusional state (6.2%), memory impairment (4.9%), disturbance in attention (4.1%), amnesia (2.3%), mental status changes (0.9%), hallucination (0.8%), delirium (0.8%), disorientation (0.5%), brain fog (0.4%), attention deficit hyperactivity disorder (0.2%), visual hallucination (0.2%), auditory hallucination (0.1%), mental impairment (0.1%) and mental disorder (0.1%). Grade 3 cognitive disorders were reported in 3.6% of patients. Adult patients who had central nervous system (CNS) disease at baseline had a higher frequency of these adverse reactions (30%) compared to those without CNS disease (22.6%). The median time to onset for cognitive disorders was 0.95 months. In the paediatric population, 2.2% (2/91) of patients experienced disturbance in attention of Grade 1 severity and 2.2% (2/91) of patients experienced disturbance in attention of Grade 2 severity.

Fractures
Fractures were experienced by 9.1% (69/762) of adult patients and 29.7% (27/91) of paediatric patients. In general, there was inadequate assessment for tumour involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some adult patients. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft) and some fractures occurred in the setting of a fall or other trauma.

The median time to fracture was 8.11 months (range: 0.26 months to 45.34 months) in adults. Rozlytrek was interrupted in 26.1% of adults that experienced fractures. Eighteen adult patients had Rozlytrek treatment interrupted and 2 adult patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for 2 adult patients due to fractures.

A total of 52 fracture events were reported in 27 paediatric patients, with 14 patients who experienced more than one occurrence of fracture. In paediatric patients, fractures mostly occurred in patients less than 12 years of age. Fractures resolved in 85.2% (23/27) of paediatric patients. The median time to fracture was 4.3 months (range: 2.0 months to 28.65 months) in paediatric patients. Twelve patients experienced Grade 2 fractures and 10 patients experienced Grade 3 fractures. Seven of the Grade 3 fractures were serious. Rozlytrek was interrupted in 18.5% (5/27) of paediatric patients who experienced fractures. Six paediatric patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for one paediatric patient.

Ataxia
Ataxia (including events of ataxia, balance disorder, and gait disturbances) was reported in 15.1% of patients. The median time to onset for ataxia was 0.5 months (range: 0.03 months to 65.48 months) and the median duration was 0.7 months (range: 0.03 months to 11.99 months). The majority of patients (55.8%) recovered from ataxia. Ataxia related adverse reactions were observed more frequently in elderly patients (24.2%) compared to patients below 65 years of age (11.8%).

Syncope
Syncope was reported in 5.0% of patients. In some patients, syncope was reported with concurrent hypotension, dehydration, or QTc prolongation and in other patients no other concurrent related conditions were reported.

QTc interval prolongation
Among the 853 patients who received entrectinib across clinical trials, 47 (7.2%) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting entrectinib, and 27 (4.1%) patients had a QTcF interval of > 500 ms (see section 4.4).

Peripheral sensory neuropathy
Peripheral sensory neuropathy was reported in 16.2% of patients. The median time to onset was 0.71 months (range 0.03 months to 81.97 months) and the median duration was 0.9 months (range: 0.07 months to 41 months). 48.6% of patients recovered from peripheral neuropathy.

Eye disorders
Eye disorders reported across clinical trials included vision blurred (9%), visual impairment (1.9%), and diplopia (1.8%). The median time to onset for eye disorders was 1.9 months (range: 0.03 months to 49.61 months). The median duration of eye disorders was 1.2 months (range 0.03 months to 14.98 months). 54% of patients recovered from the eye disorder adverse reactions.

Paediatric population

The overall safety profile of Rozlytrek in the paediatric population is generally similar to the safety profile in adults.

The safety of Rozlytrek in paediatric patients was established based on data from 91 paediatric patients across 3 clinical trials (STARTRK-NG, STARTRK-2, and TAPISTRY). Of these, 21 patients were 28 days to < 2 years old, 55 patients were ≥ 2 to < 12 years old, 15 patients were ≥ 12 to < 18 years old.

Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increased incidence) in paediatric patients compared to adult patients were neutropenia (19.8% vs 4.5%), weight increased (18.7% vs 9.6%), bone fractures (11% vs 2.5%), and lung infection (11% vs 5.5%). No Grade 5 events were observed in the 91 patients in the expanded paediatric safety population. Grade 3 to 4 events that occurred at a frequency ≥ 5% were neutropenia (19.8%), weight increased (18.7%), fractures (11%), lung infection (11%), and anaemia (8.8%).

The safety profile in each age group (infants and toddlers, children, and adolescents) is similar to the overall safety profile of Rozlytrek in paediatric patients.

Elderly
Among the 853 patients who received entrectinib across clinical trials, 227 (26.6%) patients were 65 years or older and 53 (6.2%) were 75 years or older. The overall safety profile of entrectinib in elderly patients is similar to the safety profile observed in patients younger than 65 years of age. Adverse reactions occurring more frequently (at least a 5% increased incidence) in the elderly compared to patients less than 65 years old were dizziness (44.9% vs 33.4%), blood creatinine increased (35.7% vs 30%), hypotension (19.8% vs 14.5%), and ataxia (24.2% vs 11.8%).

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

Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for entrectinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX14

Mechanism of action

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1, NTRK2* and *NTRK3*, respectively), proto-oncogene tyrosine-protein kinase ROS (*ROS1*), and anaplastic lymphoma kinase (ALK), with IC_{50} values of 0.1 to 2 nM. The major active metabolite of entrectinib, M5, showed similar *in vitro* potency and activity against TRK, ROS1, and ALK.

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib demonstrated *in vitro* and *in vivo* inhibition of cancer cell lines derived from multiple tumour types, including subcutaneous and intracranial tumours, harbouring *NTRK, ROS1,* and *ALK* fusion genes.

Prior treatments with other drugs that inhibit the same kinases may confer resistance to entrectinib. Resistance mutations in the TRK kinase domain identified following entrectinib discontinuation include *NTRK1* (G595R, G667C) and *NTRK3* (G623R, G623E and G623K). Resistance mutations in the ROS1 kinase domain identified following entrectinib discontinuation include G2032R, F2004C and F2004I.

The molecular causes for primary resistance to entrectinib 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.

Clinical efficacy and safety

NTRK gene fusion-positive solid tumours

Efficacy in adult patients
The efficacy of Rozlytrek was evaluated in a pooled sub-group of adult patients with unresectable or metastatic solid tumours with a *NTRK* gene fusion enrolled in one of three multicentre single-arm, open-label clinical trials (ALKA, STARTRK-1, and STARTRK-2) or the multicentre multi-cohort, open-label clinical trial, TAPISTRY. To be included in the pooled subgroup, patients were required to have confirmed *NTRK* gene fusion-positive solid tumours; measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1; at least 12 months of follow-up from the first post-treatment initiation tumour assessment, and no prior therapy with a TRK inhibitor (patients with concomitant driver mutations, where known, were excluded). Patients with primary CNS tumours were assessed separately using Response Assessment in Neuro-Oncology Criteria (RANO). Patients received Rozlytrek 600 mg orally once daily until unacceptable toxicity or disease progression. The primary efficacy endpoints were objective response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy was assessed in 242 adult patients with solid tumours with an *NTRK* gene fusion enrolled in these trials. The baseline demographic and disease characteristics were: 47.5% males, median age of 58 years (range 19 years to 92 years), 37.2% and 9.9% were 65 years or older and 75 years or older

respectively, 49.4% white Caucasian, 36.5% Asian, 3.3% Hispanic or Latino and 61.9% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (42.1%), 1 (50%), or 2 (7.9%). Most patients (95.5%) had metastatic disease [most common sites being lung (62.8%), lymph nodes (49.2%), liver (33.1%), bone (31%), and brain (16.5%)], 4.5% patients had locally advanced disease. 76.9% and 52.5% of patients had received surgery and radiotherapy for their cancer, respectively. 71.5% patients had received prior systemic therapy for their cancer including chemotherapy (61.6%) and 37.2% patients had no prior systemic therapies for metastatic disease. The most common cancers were lung cancer (24.8%), sarcoma (19%), salivary gland tumours (15.7%), thyroid cancer (13.6%), colorectal cancer (7%), and breast cancer (7%). The overall median duration of follow-up was 35.1 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 6.

Table 6: Overall efficacy by BICR in adults with *NTRK* gene fusion-positive solid tumours

Efficacy endpoint	**Rozlytrek n=242**
Primary endpoints *(BICR assessed; RECIST 1.1)*	
Objective response rate	
Number of responses	152/242
ORR% (95% CI[*])	62.8% (56.4, 68.9)
Complete response, n (%)	41 (16.9%)
Partial response, n (%)	111 (45.9%)
Duration of response[**]	
Number (%) of patients with events	86/152 (56.6%)
Median, months (95% CI)	22 (16.6, 30.4)
6-month durable response % (95% CI)	85% (80, 91)
9-month durable response % (95% CI)	78% (71, 84)
12-month durable response % (95% CI)	69% (62, 77)
[*]Confidence Intervals (CI) calculated using the Clopper-Pearson method. [**]Median and event-free rates based on Kaplan-Meier estimates.	

Objective response rate and duration of response by tumour type in adult patients with *NTRK* gene fusion-positive solid tumours is presented in Table 7 below.

Table 7: Efficacy by tumour type in adults with *NTRK* gene fusion-positive solid tumours

Tumour type	Patients (n=242)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	46	29 (63)	(47.6, 76.8)	2.8, 68.6*
Non-small cell lung cancer	60	38 (63.3)	(49.9, 75.4)	3.1, 71.6
Salivary (MASC)	38	32 (84.2)	(68.8, 94)	2.8, 73.5*
Breast cancer (secretory)	12	10 (83.3)	(51.6, 97.9)	5.5, 69.9*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Breast cancer (NOS)	2	NE, NE	NA	NA
Breast cancer (Ductal)	1	PD	NA	NA
Thyroid cancer	33	20 (60.6)	(42.1, 77.1)	5.6, 60.7
Colorectal cancer	17	6 (35.3)	(14.2, 61.7)	5.6*, 24*
Neuroendocrine cancers	8	5 (62.5)	(24.5, 91.5)	7.4, 31.1
Head and neck	5	3 (60.0)	(14.7, 94.7)	4.0, 56.5*
Pancreatic cancer	6	4 (66.7)	(22.3, 95.7)	5.6*, 12.9
Unknown primary cancer	3	1 (33.3)	(0.8, 90.6)	9.1
Ovarian cancer	1	Non CR/PD	NA	NA
Endometrial carcinoma	1	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	CR	NA	30.4
Gastrointestinal cancer (non CRC)	1	PD	NA	NA
Neuroblastoma	1	NE	NA	NA
Prostate cancer	1	PD	NA	NA
Penile cancer	1	PD	NA	NA
Adrenal cancer	1	PD	NA	NA

*Censored
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; NOS: not otherwise specified; CRC: colorectal cancer; CR: complete response; PR: partial response; PD: progressive disease; NE: not estimable.

Due to the rarity of *NTRK* gene fusion-positive cancers, 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.

The ORR in 122 patients that had broad molecular characterisation before Rozlytrek treatment was 59.8% (95% CI: 50.6, 68.6); of those, the ORR in 97 patients who had other genomic alterations in addition to *NTRK* gene fusion was 55.7% (95% CI: 45.2, 65.8) and the ORR in 25 patients without other genomic alterations was 76% (95% CI: 54.9, 90.6).

Intracranial response
A BICR assessment resulted in a subgroup of 36 adult patients with CNS metastases at baseline, including 20 patients with measurable CNS lesions. Intracranial (IC) response assessed by BICR according to RECIST v1.1 was reported in 14 out of these 20 patients (7 CR and 7 PR), for an ORR of 70% (95% CI: 45.7, 88.1) and median DOR of 19.7 months (95% CI: 7.4, 26.6). Five of these 20 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek treatment.

Primary CNS tumour
Across the three trials, 16 adult patients with primary CNS tumours were treated with Rozlytrek with a minimum of 12 months of follow-up. Two out of the 16 adult patients had an objective response assessed by BICR according to RANO.

Efficacy in paediatric patients
Efficacy of Rozlytrek was assessed in 44 paediatric patients with solid tumours that have a *NTRK* gene fusion enrolled in STARTRK-NG or TAPISTRY.

To be included in the analysis, patients were required to have confirmed *NTRK* gene fusion-positive solid tumours; at least 6 months of follow-up, no prior therapy with a TRK inhibitor, received at least one dose of entrectinib and presenting with measurable or evaluable disease at baseline. Patients received Rozlytrek doses from 20 mg to 600 mg once daily. The primary efficacy endpoint was confirmed ORR as evaluated by BICR according to RECIST v1.1 for extracranial tumours and according to RANO for primary CNS tumours. The secondary efficacy outcome measures included duration of confirmed response as evaluated by BICR and time to first confirmed objective response (CR or PR).

The baseline demographic and disease characteristics were: 45.5% males, median age of 4 years (range: 2 months to 15 years), 52.3% white Caucasian, 34.1% Asian, and 9.1% Hispanic or Latino, with a median BSA of 0.73 m^2 (range: 0.2-1.9 m^2). At baseline, 23.8% of patients had metastatic disease, 76.2% of patients had locally advanced disease, and 43.2% of patients had no prior systemic therapies for their cancer. The majority of patients had received treatment for their cancer including surgery (n=24), radiotherapy (n=8) and/or systemic therapy (n=25). The sites for metastatic disease included other (4 patients), brain (3 patients), and lung (3 patients). 45.5% of patients had primary CNS tumours. The overall median duration of follow-up was 24.2 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 8.

Table 8: Overall efficacy by BICR in paediatric patients with *NTRK* gene fusion-positive solid tumours

Efficacy endpoints	Rozlytrek n=44
Primary endpoints**	
Objective response rate	
Number of responses	32/44
ORR% (95% CI***)	72.7% (57.21, 85.04)
Complete response, n (%)	20 (45.5%)
Partial response, n (%)	12 (27.3%)
Secondary endpoints**	
DOR*	
Number (%) of patients with events	6/32 (18.8%)
Median, months (95% CI)	NE (25.4, NE)
6-month durable response % (95% CI)	97% (90, 100)
9-month durable response % (95% CI)	97% (90, 100)
12-month durable response % (95% CI)	84% (70, 99)

NE = not estimable.
*Median and event-free rates based on Kaplan-Meier estimates.
**Includes patients with measurable or evaluable disease. BICR analysis by RECIST v1.1 for solid tumours (24 patients) and by RANO criteria for primary CNS tumours (20 patients).
***Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Objective response rate and duration of response by tumour type in paediatric patients with *NTRK* gene fusion-positive solid tumours is presented in Table 9.

Table 9: Efficacy by tumour type in paediatric patients with *NTRK* gene fusion-positive solid tumours

Tumour type	Patients (n=44)	ORR		DOR
		n (%)	95% CI	Range (months)
Primary CNS	20	10 (50)	(27.2, 72.8)	5.5, 42.3*
Infantile fibrosarcoma	11	10 (90.9)	(58.7, 99.8)	5.7*, 24*
Spindle Cell	8	8 (100.0)	(63.1, 100)	5.4*, 23*
Sarcoma (other)	2	PR; Non-CR/Non-PD	NA	3.7*
Melanoma	1	CR	NA	42.4*
Kidney cancer	1	PR	NA	9.2*
Thyroid cancer	1	CR	NA	11.1*

*Censored
ORR: Objective Response Rate; DOR: Duration of Response; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease

Due to the rarity of NTRK gene fusion-positive cancers, 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.

ROS1-positive NSCLC

The efficacy of Rozlytrek was evaluated in a pooled sub-group of patients with *ROS1*-positive metastatic NSCLC who received Rozlytrek 600 mg orally once daily and were enrolled in one of three multicentre single-arm, open-label clinical trials (ALKA, STARTRK-1, and STARTRK-2). To be included in the pooled sub-group, patients were required to have histologically confirmed, recurrent or metastatic, *ROS1*-positive NSCLC, ECOG performance status ≤ 2, measurable disease per RECIST v1.1, ≥ 6 months of follow-up, and no prior therapy with a ROS1 inhibitor. All patients were assessed for CNS lesions at baseline.

The primary efficacy endpoints were ORR and DOR, as evaluated by BICR according to RECIST v1.1. The secondary efficacy endpoints included PFS, OS, and in patients presenting with CNS metastases at baseline – IC-ORR and IC-DOR (also evaluated by BICR using RECIST v1.1).

Efficacy was assessed in 161 patients with *ROS1*-positive NSCLC. The baseline demographic and disease characteristics were: 35.4% males, median age of 54 years (range 20 years to 86 years), 24.2% and 4.3% were older than 65 years and 75 years of age, respectively, 44.1% white Caucasian, 45.3% Asian, 4.3%, Black, 2.6% Hispanic or Latino and 62.7% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (41%), 1 (49.1%), or 2 (9.9%). Most patients (98.1%) had metastatic disease [most common sites being lymph nodes (69.6%), lung (50.3%) and brain (32.9%)], 1.9% patients had locally advanced disease and 37.3% patients had no prior systemic therapies for metastatic disease. *ROS1* positivity was determined by NGS in 83% of patients, by FISH in 9% of patients, and by RT-PCR in 8% of patients. The overall median duration of follow-up from receipt of the first dose was 15.8 months.

Efficacy results from patients with *ROS1*-positive NSCLC are summarised in Table 10.

Table 10: Overall efficacy by BICR in patients with *ROS1*-positive NSCLC

Efficacy endpoint	Rozlytrek n=161
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
Objective response rate	
Number of responses	108/161
ORR% (95% CI[***])	67.1% (59.25, 74.27)
Complete response, n (%)	14 (8.7%)
Partial response, n (%)	94 (58.4%)
Duration of response[*]	
Number (%) of patients with events	48/108 (44.4%)
Range (months)	1.8[**], 42.3[**]
6-month durable response % (95% CI)	83% (76, 90)
9-month durable response % (95% CI)	75% (67, 84)
12-month durable response % (95% CI)	63% (53, 73)
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
PFS[*]	
Number (%) of patients with events	82/161 (50.9%)
6-month PFS % (95% CI)	77% (70, 84)
9-month PFS % (95% CI)	66% (58, 74)
12-month PFS % (95% CI)	55% (47, 64)
Overall survival[*]	
Number (%) of patients with events	38/161 (23.6%)
6-month OS % (95% CI)	91% (87, 96)
9-month OS % (95% CI)	86% (81, 92)
12-month OS % (95% CI)	81% (74, 87)

[*]Event-free rates based on Kaplan-Meier estimates.
[**]Censored
[***]Confidence Intervals (CI) calculated using the Clopper-Pearson method.

In the ROS1 positive NSCLC efficacy evaluable patients with ≥ 12 months of follow-up (n=94), the ORR was 73.4% (95% CI: 63.3, 82), the median DOR was 16.5 months (95% CI: 14.6, 28.6) and median PFS was 16.8 months (95% CI: 12, 21.4).

Intracranial response
A BICR assessment resulted in a subgroup of 46 ROS1-positive NSCLC patients with CNS metastases at baseline including 24 patients with measurable CNS lesions. Intracranial response assessed by BICR according to RECIST v1.1 was reported in 19 of these 24 patients (3 CR and 16 PR) for an ORR of 79.2% (95% CI: 57.8, 92.9). The percentage of patients (95% CI) with DOR ≥ 6 months, ≥ 9 months and ≥ 12 months was 76% (56, 97), 62% (38, 86), and 55% (29, 80), respectively (Kaplan-Meier estimates). Nine of these 24 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek 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

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5), have been characterised in patients with *NTRK* gene fusion-positive solid tumours and *ROS1*-positive NSCLC and healthy subjects. The pharmacokinetics of entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for entrectinib and two weeks for M5 following daily administration of Rozlytrek.

Entrectinib is a weak P-gp substrate based on *in vitro* data. The exact *in vivo* contribution of P-gp is unknown. M5 is a P-gp substrate. Entrectinib is not a substrate of BCRP but M5 is a substrate of BCRP. Entrectinib and M5 are not substrates of OATP 1B1 or OATP1B3.

Absorption

Following a single 600 mg oral administration of Rozlytrek to patients with *NTRK* gene fusion-positive and *ROS1*-positive NSCLC under fed conditions, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 to 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

No clinically significant effect of food on entrectinib bioavailability was observed.

In healthy adult subjects, the AUC and C_{max} of Rozlytrek in the film-coated granule formulation was similar to that of the capsules. Rozlytrek capsules administered as a suspension with water or milk, given orally, or through a gastric or nasogastric tube, results in similar AUC and C_{max} as capsules swallowed whole.

Distribution

Entrectinib and its major active metabolite M5 are highly bound to human plasma proteins independent of drug concentrations. In human plasma, entrectinib and M5 had similar protein binding with > 99% bound at a clinically relevant concentration.

After a single oral dose of entrectinib, the geometric mean volume of distribution (Vz/F) was 600 L, suggesting extensive distribution of the drug. Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 to 2.2 in multiple animal species (mice, rats, and dogs) at clinically relevant systemic exposures.

Biotransformation

Entrectinib is metabolised predominantly by CYP3A4 (~76%). Minor contributions from several other CYPs and UGT1A4 were estimated at < 25% in total. The active metabolite M5 (formed by CYP3A4) and the direct N-glucuronide conjugate, M11, (formed by UGT1A4) are the two major circulating metabolites identified.

Elimination

The population PK model estimated mean accumulation at steady-state following 600 mg once daily administration of entrectinib was 1.89 (±0.381) and 2.01 (±0.437) for M5. Following administration of a single dose of [^{14}C]-labelled entrectinib, 83% radioactivity was excreted in faeces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at C_{max}, and approximately half of total radioactivity AUC_{inf}.

Population PK analysis estimated apparent clearance CL/F was 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively. The elimination half-lives of entrectinib and M5 were estimated to be 20 hours and 40 hours, respectively.

Linearity/Non-linearity

Entrectinib has linear pharmacokinetics in the dose range of 100 mg to 600 mg.

Pharmacokinetics in special populations

Paediatric population

The pharmacokinetics of entrectinib have been evaluated in 78 paediatric patients above one month of age. In patients from > 1 month to ≤ 6 months the administered dose was 250 mg/m^2; in patients > 6 months, the administered dose was 300 mg/m^2 based on five BSA categories, with a maximum dose of 600 mg for children with ≥ 1.51 m^2 body surface area (BSA).

Data obtained from population pharmacokinetic analyses show that in paediatric patients 6 years and older, 300 mg Rozlytrek once daily dose for BSA range 0.81 m^2 to 1.10 m^2, 400 mg Rozlytrek once daily dose for BSA range 1.11 m^2 to 1.50 m^2, and 600 mg Rozlytrek once daily dose for BSA range ≥ 1.51 m^2 results in a similar systemic exposure attained in adults treated with 600 mg Rozlytrek once daily dose.

Data from non-compartmental analysis in patients from 1 month to < 6 years demonstrated that systemic exposure of the sum of entrectinib and M5 in paediatric patients receiving 250 mg/m^2 or 300 mg/m^2 of Rozlytrek once daily were generally lower than the mean systemic exposure of adult patients treated with 600 mg of Rozlytrek once daily. The recommended dose in this age category is based on available efficacy and safety data.

Elderly

No differences in entrectinib exposure were noted in patients older than 65 years and younger adults based on pharmacokinetic analysis.

Renal impairment

Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3% of the dose) indicating that renal clearance plays a minor role in the elimination of entrectinib. Based on population pharmacokinetic analyses, the pharmacokinetics of entrectinib are not significantly affected in renal impairment. The impact of severe renal impairment on the pharmacokinetics of entrectinib is unknown.

Hepatic impairment

The pharmacokinetics of entrectinib were studied in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, relative to subjects with normal hepatic function. Following administration of a single oral dose of 100 mg entrectinib, the combined AUC_{last} of entrectinib and M5 showed no relevant change in the hepatic impaired groups compared to the normal function group. The AUC_{last} geometric mean ratio (90% CI) was 1.30 (0.889, 1.89) for the mild, 1.24 (0.886, 1.73) for the moderate, and 1.39 (0.988, 1.95) for the severe hepatic impaired groups compared to the normal hepatic function group. For the unbound entrectinib and M5, the $AUC_{last\ (fu)}$ geometric mean ratio (90% CI) was 1.91 (1.21, 3.02) for the mild, 1.57 (1.06, 2.31) for the moderate, and 2.34 (1.57, 3.48) for the severe hepatic impaired groups compared to the normal hepatic function group. Although the effect of hepatic impairment on unbound PK parameters generally followed a similar direction as total PK parameters, due to the high non-specific binding in buffer and high variability, results should be interpreted with caution.

In addition, it was also observed that the variability in systemic exposure was high and observed exposures overlapped across all the study groups (see section 4.2).

Effects of body weight, race and gender

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on sex, race (Asian, Black and White) and body weight (4 kg to 130 kg).

5.3 Preclinical safety data

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of entrectinib.

Genotoxicity

Entrectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but demonstrated a potential for abnormal chromosome segregation (aneugenicity) in cultured human peripheral blood lymphocytes. Entrectinib was not clastogenic or aneugenic in the *in vivo* micronucleus assay in rats and did not induce DNA damage in a comet assay in rats.

Impairment of fertility

Dedicated fertility studies in animals have not been performed to evaluate the effect of entrectinib. No adverse effects of entrectinib on male and female reproductive organs were observed in the repeat-dose toxicology studies in rats and dogs at approximately 2.4-fold and 0.6-fold, respectively, the human exposure by AUC at the recommended human dose.

Reproductive toxicity

In an embryo-foetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and foetal malformations (including body closure defects and malformations of the vertebrae and ribs), were observed at 200 mg/kg/day of entrectinib which represents approximately 2-fold the human exposure by AUC at the recommended dose. Dose-response dependent reduced foetal body weight (low, middle and high dose) and reduced skeletal ossification (middle and high dose) were observed at exposures equivalent to < 2 times the human exposure by AUC at the recommended dose.

Repeat-dose toxicity studies

Entrectinib-related toxicities in repeat-dose studies in adult rats and dogs, and juvenile rats were observed in the central nervous system (convulsions, abnormal gait, tremors) at ≥ 0.2 times the human exposures by C_{max} at the recommended dose, skin (scabs/sores) and decreased red blood cell parameters at ≥ 0.1 times the human exposure by AUC at the recommended dose. In adult rats and dogs, effects on liver (increased ALT and hepatocellular necrosis) were observed at ≥ 0.6 times the human exposure by AUC at the recommended dose. In dogs, diarrhoea at ≥ 0.1 times the human exposure by AUC at the recommended dose and prolongations of QT/QTc interval at ≥ 0.1 times the human exposure by C_{max} at the recommended dose were also observed.

Juvenile rat toxicology study

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood in humans). In addition to CNS effects, ptosis and skin effects, decreased RBC parameters and effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at ≥ 4 mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose). Deficits in neurobehavioural assessments including functional observational battery (decreased

landing foot splay, decreased fore and hind limb grip strength that seemed to manifest later in age) and learning and memory (at ≥ 8 mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose), and decreased femur length (at ≥ 16 mg/kg/day, approximately 0.3 times the human exposure by AUC at the recommended dose) were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Tartaric acid (E334)
Lactose
Hypromellose (E464)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell

Hypromellose (E464)
Titanium dioxide (E171)
Yellow iron oxide (E172 – 100 mg hard capsule)
Sunset yellow FCF (E110 – 200 mg hard capsule)

Printing ink

Shellac (E904)
Propylene glycol (E1520)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

Following preparation as an oral suspension, use immediately. Discard the oral suspension if not used within 2 hours.

6.4 Special precautions for storage

Store in the original package and keep the bottle tightly closed in order to protect from moisture.

Following preparation as an oral suspension, do not store above 30°C and use within 2 hours.

6.5 Nature and contents of container

Rozlytrek 100 mg hard capsules

HDPE bottles containing 30 hard capsules with a child-resistant, tamper-evident closure and silica gel desiccant integrated in the cap.

Rozlytrek 200 mg hard capsules

HDPE bottles containing 90 hard capsules with a child-resistant, tamper-evident closure and silica gel desiccant integrated in the cap.

6.6 Special precautions for disposal and other handling

Preparation as an oral suspension

The capsule(s) should be opened carefully and the contents mixed with room temperature drinking water or milk to prepare an oral suspension (see Table 11). Do not touch your eyes, nose or mouth during the preparation of the oral suspension.

Prior to administration of the first dose, the HCP should indicate to the patient or caregiver the exact volume of water or milk to be added to the capsule(s) content to prepare the oral suspension and the exact volume of the oral suspension to withdraw for reaching the recommended dose based on section 4.2 and Table 11.

Provide the patient or caregiver with a measuring device (e.g., oral syringe). The syringe (with 0.5 mL graduation marks) and a cup (empty and clean) with adequate capacity to contain the suspension volume to be prepared should be available. The syringe and cup are not included in the package.

The syringe and cup could be reused according to the manufacturer's guidelines. The HCP should indicate to the patient or caregiver that the syringe and cup should be exclusively used for Rozlytrek suspension preparation and should be keep out of the sight and reach of children or other persons that are not caregivers or parents.

The oral suspension should be taken immediately. Discard the suspension if not used within 2 hours.

Table 11: Preparation of Rozlytrek capsules as an oral suspension

Prescribed dose of Rozlytrek to be given	Number of 100 mg or 200 mg capsules needed	Amount of water or milk to be mixed with the content of the capsule(s) to prepare the suspension	Amount of suspension to withdraw in order to reach the prescribed dose
20 mg	One 100 mg	5 mL	1 mL
30 mg	One 100 mg	5 mL	1.5 mL
40 mg	One 100 mg	5 mL	2 mL
50 mg	One 100 mg	5 mL	2.5 mL
60 mg	One 100 mg	5 mL	3 mL
70 mg	One 100 mg	5 mL	3.5 mL
80 mg	One 100 mg	5 mL	4 mL
90 mg	One 100 mg	5 mL	4.5 mL
100 mg	One 100 mg	5 mL	5 mL
110 mg	One 200 mg	10 mL	5.5 mL
120 mg	One 200 mg	10 mL	6 mL
130 mg	One 200 mg	10 mL	6.5 mL
140 mg	One 200 mg	10 mL	7 mL
150 mg	One 200 mg	10 mL	7.5 mL
200 mg	One 200 mg	10 mL	10 mL
300 mg	Three 100 mg	15 mL	15 mL
400 mg	Two 200 mg	20 mL	20 mL
600 mg	Three 200 mg	30 mL	30 mL

Detailed instructions on preparation and administration of the capsules as an oral suspension are given in the IFU at the end of the package leaflet.

Enteral tube instructions for use

- Check the manufacturer's instructions for the size and dimensions of the enteral tube.
- For administration through an enteral tube, draw up the suspension with a syringe.
- Dosing volumes of 3 mL or higher should be divided into at least two aliquots, and the tube should be flushed after each administration.
    - An enteral tube size that is 8 FR or higher should be used to deliver aliquots of 3 mL or higher.
    - Between each aliquot, flush the tube with a volume of water or milk that is equal to the aliquot administered.
    - Neonates and children with fluid restrictions may require minimal flushing volumes of 1 mL to 3 mL to deliver Rozlytrek. The aliquots should be adjusted accordingly.
- For a dosing volume of 30 mL, divide into at least three (10 mL) aliquots. Between each aliquot, flush the tube with 10 mL of water or milk.
- The tube should be flushed with water or milk after delivering Rozlytrek.

Any unused medicinal product or waste material, including the remaining suspension (not administered) should be disposed of in accordance with local requirements. The remaining suspension (not administered) should not be discarded in wastewater. These measures will help protect the environment.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/001
EU/1/20/1460/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2020
Date of latest renewal: 16 May 2024

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

Rozlytrek 50 mg film-coated granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 50 mg of entrectinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated granules.

Brownish orange or greyish orange film-coated granules (approximately 2 mm in diameter) in sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neurotrophic tyrosine receptor kinase *(NTRK)* gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients older than 1 month with solid tumours that have a *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 not received a prior *NTRK* inhibitor
- who have no satisfactory treatment options (see sections 4.4 and 5.1).

ROS1 gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult patients with *ROS1*-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

4.2 Posology and method of administration

Treatment with Rozlytrek should be initiated by a physician experienced in the use of anticancer medicinal products.

Patient selection

NTRK gene fusion
A validated assay is required for the selection of patients with *NTRK* gene fusion-positive solid tumours. *NTRK* gene fusion-positive status must be established prior to initiation of Rozlytrek therapy (see section 5.1).

ROS1 gene fusion
A validated assay is required for the selection of adult patients with *ROS1*-positive NSCLC. *ROS1*-positive status must be established prior to initiation of Rozlytrek therapy (see section 5.1).

Posology

Rozlytrek is available as hard capsules or film-coated granules.

The physician should prescribe the most appropriate pharmaceutical form according to the dose required and patient needs.

- Rozlytrek film-coated granules are recommended for paediatric patients who have difficulty, or are unable, to swallow capsules but can swallow soft food and where the required dose is 50 mg or a multiple of 50 mg. Film-coated granules should be sprinkled on soft food.

- Patients who have difficulty or are unable to swallow capsules or who require enteral administration (e.g., gastric or nasogastric) may receive treatment with Rozlytrek capsules administered as an oral suspension. Refer to the Rozlytrek hard capsules SmPC for prescribing information.

Adults
The recommended dose for adults is 600 mg entrectinib once daily.

Paediatric population

Paediatric population > 6 months of age
The recommended dose for paediatric patients > 6 months of age is based on body surface area (BSA) (see Table 1).

Table 1: Recommended dosing for paediatric patients > 6 months

Body surface area (BSA)*	Once daily dose / Number of sachets (granules)
≤ 0.42 m2	250 mg/m2**
0.43 m^2 to 0.50 m^2	100 mg (2 sachets)
0.51 m^2 to 0.80 m^2	200 mg (4 sachets)
0.81 m^2 to 1.10 m^2	300 mg (6 sachets)
1.11 m^2 to 1.50 m^2	400 mg (8 sachets)
≥ 1.51 m^2	600 mg (12 sachets)

*BSA categories and recommended dosing in Table 1 are based on closely matching exposures to a target dose of 300 mg/m^2
**To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Rozlytrek capsule SmPC for prescribing information.

Paediatric patients > 1 month to ≤ 6 months of age
The recommended dose for paediatric patients > 1 month to ≤ 6 months of age is 250 mg/m^2 BSA entrectinib once daily, using capsules prepared as an oral suspension.

Capsules administered as an oral suspension (oral or enteral use) enable dosing increments of 10 mg. The daily dose to be administered should be rounded to the nearest 10 mg increment. Refer to the Rozlytrek hard capsules SmPC for prescribing information.

Duration of treatment
It is recommended that patients are treated with Rozlytrek until disease progression or unacceptable toxicity.

Delayed or missed doses
If a planned dose of Rozlytrek is missed, patients can make up that dose unless the next dose is due within 12 hours.

When Rozlytrek is administered by individuals other than the healthcare professional (e.g., caregivers or parents) and partial or total vomiting/spitting occurs immediately after taking an administered dose, caregivers should consult the healthcare professional for the next steps.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek, in case of specified adverse reactions (see Table 3) or based on the prescriber's assessment of the patient's safety or tolerability.

Adults
For adults, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability (see Table 2). Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Paediatric population
For paediatric patients older than 1 month, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability (see Table 2).

Table 2: Dose reduction schedule for adult and paediatric patients

Starting dose once daily	**First dose reduction**	**Second dose reduction**	Permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.
250 mg/m^2	Reduce the once daily dose to two thirds of the starting dose*	Reduce the once daily dose to one third of the starting dose*	
100 mg	50 mg or 100 mg once daily, according to schedule**	50 mg once daily	
200 mg	150 mg once daily	100 mg once daily	
300 mg	200 mg once daily	100 mg once daily	
400 mg	300 mg once daily	200 mg once daily	
600 mg	400 mg once daily	200 mg once daily	

*To enable dosing increments of 10 mg, capsules prepared as an oral suspension may be used. Refer to the Rozlytrek hard capsules SmPC for prescribing information.

**Monday (100 mg), Tuesday (50 mg), Wednesday (100 mg), Thursday (50 mg), Friday (100 mg), Saturday (50 mg), and Sunday (100 mg).

Recommendations for Rozlytrek dose modifications for adult and paediatric patients in case of specific adverse reactions are provided in Table 3 (see sections 4.4 and 4.8).

Table 3: Recommended Rozlytrek dose modifications for adverse reactions in adult and paediatric patients

Adverse reaction	Severity*	Dosage modification
Congestive heart failure	Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
Cognitive disorders	Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
	Severe changes limiting activities of daily living (Grade 3)	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose
	Urgent intervention indicated for event (Grade 4)	• For prolonged, severe, or intolerable events, discontinue Rozlytrek as clinically appropriate
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
QT interval prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are <u>not</u> identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek

Adverse reaction	Severity*	Dosage modification
Transaminase elevations	Grade 3	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks
	Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue Rozlytrek
Anaemia or neutropenia	Grade 3 or 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 2 or to baseline • Resume at the same dose or reduced dose, as clinically needed
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Rozlytrek until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.		

Strong or moderate CYP3A inhibitors
The concomitant use of strong or moderate CYP3A inhibitors in adult and paediatric patients older than 1 month should be avoided (see section 4.4).

For adults, if co-administration is unavoidable, the use of strong or moderate CYP3A inhibitors with Rozlytrek should be limited to 14 days and the Rozlytrek dose should be reduced as follows:

- 100 mg once daily for use with strong CYP3A inhibitors (see section 4.5)
- 200 mg once daily for use with moderate CYP3A inhibitors.

After discontinuation of the concomitant strong or moderate CYP3A inhibitors, the Rozlytrek dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash-out period may be required for CYP3A4 inhibitors with a long half-life (see section 4.5).

Special populations

Elderly
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see section 5.2). Patients with severe hepatic impairment should be carefully monitored for hepatic function and adverse reactions (see Table 3).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Entrectinib has not been studied in patients with severe renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of entrectinib in paediatric patients 1 month of age and younger have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Rozlytrek is for oral use.

Rozlytrek can be taken with or without food (see section 5.2) but should not be taken with grapefruit, grapefruit juice, or Seville oranges (see section 4.5).

The film-coated granules should be sprinkled on one or more spoonfuls of a soft food (e.g., applesauce, yogurt, pudding) and taken within 20 minutes of mixing.

The patient should drink water after taking the film-coated granules to ensure the medicinal product has been completely swallowed.

Patients should be instructed to not crush or chew the film-coated granules to avoid a bitter taste.

The contents of a sachet of film-coated granules should not be divided to prepare a smaller dose.

Detailed instructions on the administration of the film-coated granules are given in the Instructions for Use (IFU) at the end of the package leaflet.

The film-coated granules are not suitable for enteral administration due to potential for clogging in the tubing. Refer to the Rozlytrek hard capsules SmPC for enteral (e.g., gastric or nasogastric tube) administration.

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 Rozlytrek has been established in single-arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of Rozlytrek have been shown based on 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 genomic alterations (see section 5.1). For these reasons, Rozlytrek should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted).

Cognitive disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek (see section 4.8). Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes.

Based on the severity of cognitive disorders, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

Patients should be counselled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders (see section 4.7).

Fractures

Fractures have been reported in 29.7% (27/91) of paediatric patients treated with Rozlytrek in clinical trials (see section 4.8). Bone fractures mostly occurred in paediatric patients less than 12 years of age and were localised in the lower extremity (with a predilection for femur, tibia, foot, and fibula). In both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area.

Fourteen paediatric patients had more than one occurrence of a fracture. Fractures resolved in the majority of paediatric patients (see section 4.8). Five paediatric patients had Rozlytrek treatment interrupted due to a fracture. Six paediatric patients discontinued treatment due to fractures.

Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly.

Hyperuricemia

Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating Rozlytrek and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. Treatment with urate-lowering medicinal products should be initiated as clinically indicated and Rozlytrek withheld for signs and symptoms of hyperuricemia. Rozlytrek dose should be modified based on severity as described in Table 3 in section 4.2.

Congestive heart failure

Congestive heart failure (CHF) has been reported 5.4% of patients across clinical trials with Rozlytrek (see section 4.8). These reactions were observed in patients with or without a history of cardiac disease and resolved in 63.0% of those patients upon institution of appropriate clinical management and/or Rozlytrek dose reduction/interruption.

For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Rozlytrek treatment. Patients receiving Rozlytrek should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate.

Based on the severity of CHF, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

QTc interval prolongation

QTc interval prolongation has been observed in patients treated with Rozlytrek in clinical trials (see section 4.8).

Use of Rozlytrek should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval.

Rozlytrek should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. If, in the opinion of the treating physician, the potential benefits of Rozlytrek in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.

Assessment of ECG and electrolytes at baseline and after 1 month of treatment with Rozlytrek are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout Rozlytrek treatment, are also recommended.

Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described in Table 3 in section 4.2.

Women of childbearing potential

Rozlytrek may cause foetal harm when administered to a pregnant woman. Women of childbearing potential must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of Rozlytrek.

Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with Rozlytrek and for 3 months after the last dose (see sections 4.6 and 5.3).

Drug interactions

Co-administration of Rozlytrek with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations (see section 4.5), which could increase the frequency or severity of adverse reactions. Co-administration of Rozlytrek with a strong or moderate CYP3A inhibitor should be avoided. For adult patients if co-administration is unavoidable, the Rozlytrek dose should be reduced (see section 4.2).

During treatment with Rozlytrek, the consumption of grapefruit, grapefruit products, and Seville oranges should be avoided.

Co-administration of Rozlytrek with a strong or moderate CYP3A or P-gp inducer decreases entrectinib plasma concentrations (see section 4.5), which may reduce efficacy of Rozlytrek, and should be avoided.

Sodium

This medicinal product contains less than 1mmol sodium (23 mg) per 600 mg dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of entrectinib on other medicinal products

Effect of entrectinib on CYP substrates
Entrectinib is a weak inhibitor of CYP3A4. Co-administration of entrectinib 600 mg once daily with oral midazolam (a sensitive CYP3A substrate) in patients increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21%. Caution is advised when entrectinib is administered together with sensitive CYP3A4 substrates with a narrow therapeutic range (e.g., cisapride, cyclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus), due to the increased risk of adverse drug reactions.

Effect of entrectinib on P-gp substrates
In vitro data suggest that entrectinib has inhibitory potential towards P-glycoprotein (P-gp).

Co-administration of a single 600 mg dose of entrectinib with digoxin (a sensitive P-gp substrate) increased digoxin C_{max} by 28% and AUC by 18%. The renal clearance of digoxin was similar between treatments of digoxin alone and digoxin co-administered with entrectinib, indicating minimal effect of entrectinib on renal clearance of digoxin.

The effect of entrectinib on digoxin absorption is not considered clinically relevant, but it is unknown whether the effect of entrectinib may be larger on more sensitive oral P-gp substrates such as dabigatran etexilate.

Effect of entrectinib on BCRP substrates
Inhibition of BCRP was observed in *in vitro* studies.
The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral BCRP substrates (e.g. methotrexate, mitoxantrone, topotecan, lapatinib) are co-administered with entrectinib, due to the risk of increased absorption.

Effect of entrectinib on other transporter substrates
In vitro data indicate that entrectinib has weak inhibitory potential towards organic anion-transporting polypeptide (OATP)1B1. The clinical relevance of this inhibition is unknown, but caution is advised when sensitive oral OATP1B1 substrates (e.g. atorvastatin, pravastatin, rosuvastatin repaglinide, bosentan) are co-administered with entrectinib, due to the risk of increased absorption.

Effect of entrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that entrectinib may induce pregnane X receptor (PXR) regulated enzymes (e.g. CYP2C family and UGT). Co-administration of entrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Oral contraceptives
It is currently unknown whether entrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives are advised to add a barrier method (see section 4.6).

Effects of other medicinal products on entrectinib

Based on *in vitro* data, CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

Effect of CYP3A or P-gp inducers on entrectinib
Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced entrectinib AUC_{inf} by 77% and C_{max} by 56%.

Co-administration of entrectinib with CYP3A/P-gp inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's Wort [*Hypericum perforatum*], apalutamide, ritonavir, dexamethasone) should be avoided.

If co-administration of Rozlytrek with dexamethasone cannot be avoided, dexamethasone dose recommendations should be determined by the healthcare professional.

Effect of CYP3A or P-gp inhibitors on entrectinib
Co-administration of itraconazole, a strong CYP3A4 inhibitor, with a single oral dose of entrectinib increased AUC_{inf} by 600% and C_{max} by 173%. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children as young as 2 years old.

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit, or Seville oranges) should be avoided. If concurrent use of strong or moderate inhibitors of CYP3A4 is unavoidable, dose adjustment of entrectinib is required (see section 4.2).

Although, a marked effect of inhibitory P-gp medicinal products on entrectinib pharmacokinetics is not expected, caution is advised when treatment with strong or moderate P-gp inhibitors (e.g. verapamil, nifedipine, felodipine, fluvoxamine, paroxetine) are co-administered with entrectinib due to risk of increased entrectinib exposure (see section 5.2).

Effect of medicinal products that increase gastric pH on entrectinib
Co-administration of a proton pump inhibitor (PPI), lansoprazole with a single 600 mg entrectinib dose reduced entrectinib AUC by 25% and C_{max} by 23%.

No dose adjustments are required when entrectinib is co-administered with PPIs or other medicines that raise gastric pH (e.g., H2 receptor antagonists or antacids).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Female patients of childbearing potential should have medically supervised pregnancy testing prior to initiating Rozlytrek therapy.

Female patients of childbearing potential must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Rozlytrek.

It is currently unknown whether entrectinib may reduce the effectiveness of systemically acting hormonal contraceptives (see section 4.5). Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Rozlytrek (see section 5.3).

Pregnancy

There are no available data from the use of entrectinib in pregnant women. Based on animal studies and its mechanism of action, entrectinib may cause foetal harm when administered to a pregnant woman (see sections 4.4 and 5.3).

Rozlytrek is not recommended during pregnancy and in women of childbearing potential not using contraception.

Female patients receiving Rozlytrek should be advised of the potential harm to the foetus. Female patients should be advised to contact the doctor, should pregnancy occur.

Breast-feeding

It is unknown whether entrectinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Rozlytrek.

Fertility

No fertility studies in animals have been performed to evaluate the effect of entrectinib (see section 5.3).

4.7 Effects on ability to drive and use machines

Rozlytrek has moderate influence on the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥20%) were fatigue, constipation, diarrhoea, dizziness, dysgeusia, oedema, increased weight, anaemia, increased blood creatinine, nausea, dysaesthesia, pain, vomiting, pyrexia, arthralgia, increased aspartate aminotransferase and dyspnoea, cognitive disorders, cough, and increased alanine aminotransferase. The most frequent serious adverse reactions (≥2%) were lung infection (5.3%), fractures (4.1%), dyspnoea (3.6%), cognitive impairment (2.9%), pleural effusion (2.5%) and pyrexia (2.5%). Permanent discontinuation due to an adverse reaction occurred in 6.0% of patients.

Tabulated list of adverse reactions

Table 4 summarises the adverse drug reactions (ADRs) occurring in 762 adult and 91 paediatric patients treated with Rozlytrek in three clinical trials in adults (ALKA, STARTRK-1, and STARTRK-2) and one clinical trial in paediatric patients (STARTRK-NG) and one clinical trial in adult and paediatric patients (TAPISTRY). The median duration of exposure was 8.6 months.

Table 5 includes paediatric patients from three clinical studies; STARTRK-NG, STARTRK-2 and TAPISTRY. The median duration of exposure was 11.1 months. Paediatric data in the description of selected adverse reactions reflect exposure to Rozlytrek in this expanded paediatric safety population (n=91). The safety profile observed in the expanded paediatric population was consistent with the known paediatric safety profile from the integrated safety population in Table 4 below.

Adverse drug reactions are listed by MedDRA system organ class. The following categories of frequency have been used: very common ≥1/10, common (≥1/100 to <1/10), uncommon (≥1/1 000 to

<1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000). Within each system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse drug reactions occurring in adult and paediatric patients treated with Rozlytrek in clinical trials (n=853)

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
Infections and infestations	Urinary tract infection	15.7	Very common	2.7
	Lung infection[1]	14.4	Very common	6.1*
Blood and lymphatic system disorders	Anaemia	33.4	Very common	9.7
	Neutropenia[2]	15.8	Very common	6.1
Metabolism and nutritional disorders	Weight increased	34.1	Very common	10.6
	Hyperuricemia	16.4	Very common	2.3
	Decreased appetite	13.0	Very common	0.7
	Dehydration	6.6	Common	1.1
	Tumour lysis syndrome	0.2	Uncommon	0.2*
Nervous system disorders	Dizziness[3]	36.5	Very common	1.9
	Dysgeusia	35.8	Very common	0.2
	Dysaesthesia[4]	24.9	Very common	0.4
	Cognitive disorders[5]	23.3	Very common	3.6
	Peripheral sensory neuropathy[6]	16.2	Very common	1.1
	Headache	16.1	Very common	0.6
	Ataxia[7]	15.1	Very common	1.5
	Sleep disturbances[8]	12.8	Very common	0.4
	Mood disorders[9]	9.4	Common	0.6
	Syncope	5.0	Common	3.5
Eye disorders	Vision blurred[10]	11.7	Very common	0.2
Cardiac disorders	Congestive heart failure[11]	5.4	Common	2.5*
	Electrocardiogram QTc prolonged	3.6	Common	0.9
	Myocarditis	0.2	Uncommon	0.1
Vascular disorders	Hypotension[12]	15.9	Very common	2.3
Respiratory, thoracic and mediastinal disorders	Dyspnoea	23.8	Very common	4.9*
	Cough	21.1	Very common	0.4
	Pleural effusion	6.0	Common	2.2
Gastrointestinal disorders	Constipation	42.3	Very common	0.4
	Diarrhoea	37.9	Very common	2.2
	Nausea	30.0	Very common	0.6
	Vomiting	25.1	Very common	1.1
	Abdominal pain	11.6	Very common	0.6
	Dysphagia	10.7	Very common	0.6
Hepatobiliary disorders	AST increased	21.1	Very common	2.9
	ALT increased	20.2	Very common	3.2
Skin and subcutaneous tissue disorders	Rash[13]	13.4	Very common	1.2
	Photosensitivity reaction	1.9	Common	0

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
Musculoskeletal and connective tissue disorders	Arthralgia	21.0	Very common	0.7
	Myalgia	19.7	Very common	0.8
	Fractures[14]	11.3	Very common	3.4
	Muscular weakness	10.4	Very common	1.3
Renal and urinary disorders	Blood creatinine increased	31.5	Very common	1.2
	Urinary retention[15]	10.4	Very common	0.6
General disorders and administration site conditions	Fatigue[16]	43.5	Very common	5.0
	Oedema[17]	34.3	Very common	1.8
	Pain[18]	25.6	Very common	1.5
	Pyrexia	23.8	Very common	0.9

* Grades 3 to 5, inclusive of fatal adverse reactions (including 4 reactions of pneumonia, 3 reactions of dyspnoea, 1 reaction of cardiac failure, and 1 reaction of tumour lysis syndrome).

[1] Lung infection (bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection)

[2] Neutropenia (neutropenia, neutrophil count decreased)

[3] Dizziness (dizziness, vertigo, dizziness postural)

[4] Dysaesthesia (paresthesia, hyperesthesia, hypoesthesia, dysesthesia)

[5] Cognitive disorders (cognitive disorder, confusional state, memory impairment, disturbance in attention, amnesia, mental status changes, hallucination, delirium, disorientation, brain fog, attention deficit hyperactivity disorder, 'visual hallucination','auditory hallucination', mental impairment, mental disorder)

[6] Periphery sensory neuropathy (neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy)

[7] Ataxia (ataxia, balance disorder, gait disturbances)

[8] Sleep disturbances (hypersomnia, insomnia, sleep disorder, somnolence)

[9] Mood disorders (anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation)

[10] Vision blurred (diplopia, vision blurred, visual impairment)

[11] Congestive heart failure (acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary oedema)

[12] Hypotension (hypotension, orthostatic hypotension)

[13] Rash (rash, rash maculopapular, rash pruritic, rash erythematous, rash papular)

[14] Fractures (acetabulum fracture, ankle fracture, avulsion fracture, bursitis, cartilage injury, clavicle fracture, compression fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, fracture, fractured sacrum, hand fracture, hip fracture, humerus fracture, ilium fracture, jaw fracture, joint injury, limb fracture, lower limb fracture, lumbar vertebral fracture, osteoporotic fracture, pathological fracture, pelvic fracture, rib fracture, spinal compression fracture, spinal fracture, spondylolisthesis, sternal fracture, stress fracture, synovial rupture, thoracic vertebral fracture, tibia fracture, ulna fracture, wrist fracture)

[15] Urinary retention (urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency)

[16] Fatigue (fatigue, asthenia)

[17] Oedema (face oedema, fluid retention, generalised oedema, localised oedema, oedema, oedema peripheral, peripheral swelling)

[18] Pain (back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity)

Table 5: Adverse drug reactions occurring in paediatric patients treated with Rozlytrek in clinical trials (n=91)

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
Infections and infestations	Very common	Lung infection (28.6%), Urinary tract infection (23.8%)	Urinary tract infection (23.6%), Lung infection (16.4%)		Urinary tract infection (19.8%), Lung infection (17.6%)
	Common			Lung infection (6.7%)	
Blood and lymphatic system disorders	Very common	Anaemia (61.9%), Neutropenia (47.6%)	Anaemia (34.5%), Neutropenia (27.3%)	Anaemia (33.3%), Neutropenia (33.3%)	Anaemia (40.7%), Neutropenia (33.0%)
Metabolism and nutritional disorders	Very common	Weight increased (23.8%), Decreased appetite (14.3%)	Weight increased (38.5%), Decreased appetite (29.1%), Dehydration (12.7%)	Weight increased (53.3%), Decreased appetite (13.3%), Hyperuricemia (13.3%)	Weight increased (38.5%), Decreased appetite (23.1%)
	Common	Dehydration (4.8%), Hyperuricemia (4.8%)	Hyperuricemia (3.6%)		Dehydration (8.8%), Hyperuricemia (5.5%)
Nervous system disorders	Very common		Headache (32.7%), Mood disorders (16.4%), Sleep disturbances (16.4%), Dizziness (14.5%), Ataxia (10.9%)	Dysgeusia (20%), Mood disorders (13.3%), Cognitive disorders (13.3%), Dysaesthesia (13.3%)	Headache (20.9%), Mood disorders (14.3%), Sleep disturbances (13.2%)
	Common	Mood disorders (9.5%), Sleep disturbances (9.5%), Cognitive disorders (9.5%), Ataxia (4.8 %), Peripheral sensory	Cognitive disorders (9.1%), Dysgeusia (9.1 %), Dysaesthesia (5.5 %), Syncope (5.5 %), Peripheral sensory neuropathy (5.5%)	Headache (6.7%), Sleep disturbances (6.7%), Peripheral sensory neuropathy (6.7 %), Syncope (6.7%)	Cognitive disorders (9.9%), Dizziness (8.8%), Dysgeusia (8.8%), Ataxia (7.7 %), Dysaesthesia (5.5%), Peripheral sensory

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
		neuropathy (4.8 %), Syncope (4.8 %)			neuropathy (5.5 %), Syncope (5.5%)
Eye disorders	Common		Vision blurred (7.3%)	Vision blurred (6.7%)	Vision blurred (5.5%)
Cardiac disorders	Common	Congestive heart failure (9.5%), Electrocardiogram QT prolonged (9.5%)	Congestive heart failure (5.5%), Electrocardiogram QT prolonged (5.5%)		Congestive heart failure (5.5%), Electrocardiogram QT prolonged (5.5 %)
Vascular disorders	Common	Hypotension (9.5%)	Hypotension (7.3%)	Hypotension (6.7%)	Hypotension (7.7%)
Respiratory, thoracic and mediastinal disorders	Very common	Cough (42.9%)	Cough (40%)	Cough (20%), Dyspnoea (13.3%)	Cough (37.4%)
	Common	Dyspnoea (4.8%)	Dyspnoea (9.1%), Pleural effusion (5.5%)	Pleural effusion (6.7%)	Dyspnoea (8.8%), Pleural effusion (4.4%)
Gastrointestinal disorders	Very common	Vomiting (47.6%), Diarrhoea (42.9%), Constipation (42.9%)	Vomiting (43.6%), Diarrhoea (43.6%), Constipation (36.4%), Nausea (34.5%), Abdominal pain (25.5%)	Nausea (40%), Constipation (33.3%), Vomiting (20 %), Diarrhoea (20%), Abdominal pain (13.3 %)	Vomiting (40.7%), Diarrhoea (39.6%), Constipation (37.4 %), Nausea (28.6 %), Abdominal pain (19.8%)
	Common	Abdominal pain (9.5%), Nausea (4.8%)			
Hepatobiliary disorders	Very common	ALT increased (47.6%), AST increased (42.9%)	AST increased (29.1%), ALT increased (25.5%)	AST increased (53.3%), ALT increased (46.7%)	AST increased (36.3%), ALT increased (34.1%)

System organ class	Frequency	Infants and toddlers[1] (n=21)	Children[2] (n=55)	Adolescents[3] (n=15)	All paediatric patients (n=91)
Skin and subcutaneous tissue disorders	Very common	Rash (38.1%)	Rash (21.8%)		Rash (22%)
Musculo-skeletal and connective tissue disorders	Very common		Fractures (40%), Arthralgia (16.4%)	Fractures (20%), Muscular weakness (13.3%), Myalgia (13.3%)	Fractures (29.7%), Arthralgia (11.0%)
	Common	Fractures (9.5%)	Muscular weakness (7.3%), Myalgia (7.3%)	Arthralgia (6.7%)	Muscular weakness (6.6%), Myalgia (6.6%)
Renal and urinary disorders	Very common	Blood creatinine increased (19%)	Blood creatinine increased (34.5%), Urinary retention (18.2%)	Blood creatinine increased (46.7%)	Blood creatinine increased (33%), Urinary retention (14.3%)
	Common	Urinary retention (9.5%)		Urinary retention (6.7%)	
General disorders and administration site conditions	Very common	Pyrexia (61.9%)	Pyrexia (50.9%), Fatigue (40%), Pain (30.9%), Oedema (14.5%)	Pain (33.3%), Pyrexia (33.3%), Fatigue (20%)	Fatigue (28.6%), Pain (26.4%), Pyrexia (50.5%), Oedema (11%)
	Common	Pain (9.5%), Oedema (9.5%), Fatigue (4.8%)			

% refers to all grades

[1]Infant/toddlers (≥ 28 days to < 24 months): Grade ≥ 3 reactions reported were neutropenia, weight increased, lung infection, anaemia, AST increased, abdominal pain, and urinary tract infection

[2]Children (≥ 24 months to < 12 years): Grade ≥ 3 reactions reported were neutropenia, weight increased, fractures, lung infection, anaemia, ALT increased, syncope, AST increased, ataxia, dyspnoea, abdominal pain, congestive heart failure, fatigue, headache, pain, pyrexia, urinary tract infection, arthralgia, cognitive disorders, constipation, cough, decreased appetite, dehydration, hypotension, muscular weakness, oedema, and vomiting

[3]Adolescents (≥ 12 to < 18 years of age): Grade ≥ 3 reactions reported were neutropenia, weight increased, fracture, lung infection, and headache

Description of selected adverse reactions

Cognitive disorders

A variety of cognitive symptoms was reported across clinical trials (see section 4.4). These included events reported as cognitive disorders (6.4%), confusional state (6.2%), memory impairment (4.9%), disturbance in attention (4.1%), amnesia (2.3%), mental status changes (0.9%), hallucination (0.8%), delirium (0.8%), disorientation (0.5%), brain fog (0.4%), attention deficit hyperactivity disorder

(0.2%), visual hallucination (0.2%), auditory hallucination (0.1%), mental impairment (0.1%) and mental disorder (0.1%). Grade 3 cognitive disorders were reported in 3.6% of patients. Adult patients who had central nervous system (CNS) disease at baseline had a higher frequency of these adverse reactions (30%) compared to those without CNS disease (22.6%). The median time to onset for cognitive disorders was 0.95 months. In the paediatric population, 2.2% (2/91) of patients experienced disturbance in attention of Grade 1 severity and 2.2% (2/91) of patients experienced disturbance in attention of Grade 2 severity.

Fractures
Fractures were experienced by 9.1% (69/762) of adult patients and 29.7% (27/91) of paediatric patients. In general, there was inadequate assessment for tumour involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some adult patients. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft) and some fractures occurred in the setting of a fall or other trauma.

The median time to fracture was 8.11 months (range: 0.26 months to 45.34 months) in adults. Rozlytrek was interrupted in 26.1% of adults that experienced fractures. Eighteen adult patients had Rozlytrek treatment interrupted and 2 adult patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for 2 adult patients due to fractures.

A total of 52 fracture events were reported in 27 paediatric patients, with 14 patients who experienced more than one occurrence of fracture. In paediatric patients, fractures mostly occurred in patients less than 12 years of age. Fractures resolved in 85.2% (23/27) of paediatric patients. The median time to fracture was 4.3 months (range: 2.0 months to 28.65 months) in paediatric patients. Twelve patients experienced Grade 2 fractures and 10 patients experienced Grade 3 fractures. Seven of the Grade 3 fractures were serious. Rozlytrek was interrupted in 18.5% (5/27) of paediatric patients who experienced fractures. Six paediatric patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for one paediatric patient.

Ataxia
Ataxia (including events of ataxia, balance disorder, and gait disturbances) was reported in 15.1% of patients. The median time to onset for ataxia was 0.5 months (range: 0.03 months to 65.48 months) and the median duration was 0.7 months (range: 0.03 months to 11.99 months). The majority of patients (55.8%) recovered from ataxia. Ataxia related adverse reactions were observed more frequently in elderly patients (24.2%) compared to patients below 65 years of age (11.8%).

Syncope
Syncope was reported in 5.0% of patients. In some patients, syncope was reported with concurrent hypotension, dehydration, or QTc prolongation and in other patients no other concurrent related conditions were reported.

QTc interval prolongation
Among the 853 patients who received entrectinib across clinical trials, 47 (7.2%) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting entrectinib, and 27 (4.1%) patients had a QTcF interval of > 500 ms (see section 4.4).

Peripheral sensory neuropathy
Peripheral sensory neuropathy was reported in 16.2% of patients. The median time to onset was 0.71 months (range 0.03 months to 81.97 months) and the median duration was 0.9 months (range: 0.07 months to 41 months). 48.6% of patients recovered from peripheral neuropathy.

Eye disorders
Eye disorders reported across clinical trials included vision blurred (9%), visual impairment (1.9%), and diplopia (1.8%). The median time to onset for eye disorders was 1.9 months (range: 0.03 months

to 49.61 months). The median duration of eye disorders was 1.2 months (range 0.03 months to 14.98 months). 54% of patients recovered from the eye disorder adverse reactions.

Paediatric population

The overall safety profile of Rozlytrek in the paediatric population is generally similar to the safety profile in adults.

The safety of Rozlytrek in paediatric patients was established based on data from 91 paediatric patients across 3 clinical trials (STARTRK-NG, STARTRK-2, and TAPISTRY). Of these, 21 patients were 28 days to < 2 years old, 55 patients were ≥ 2 to < 12 years old, 15 patients were ≥ 12 to < 18 years old.

Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increased incidence) in paediatric patients compared to adult patients were neutropenia (19.8% vs 4.5%), weight increased (18.7% vs 9.6%), bone fractures (11% vs 2.5%), and lung infection (11% vs 5.5%). No Grade 5 events were observed in the 91 patients in the expanded paediatric safety population. Grade 3 to 4 events that occurred at a frequency ≥ 5% were neutropenia (19.8%), weight increased (18.7%), fractures (11%), lung infection (11%), and anaemia (8.8%).

The safety profile in each age group (infants and toddlers, children, and adolescents) is similar to the overall safety profile of Rozlytrek in paediatric patients.

Elderly

Among the 853 patients who received entrectinib across clinical trials, 227 (26.6%) patients were 65 years or older and 53 (6.2%) were 75 years or older. The overall safety profile of entrectinib in elderly patients is similar to the safety profile observed in patients younger than 65 years of age. Adverse reactions occurring more frequently (at least a 5% increased incidence) in the elderly compared to patients less than 65 years old were dizziness (44.9% vs 33.4%), blood creatinine increased (35.7% vs 30%), hypotension (19.8% vs 14.5%), and ataxia (24.2% vs 11.8%).

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

Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for entrectinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX14

Mechanism of action

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1*, *NTRK2 and NTRK3*, respectively), proto-oncogene tyrosine-protein kinase ROS (*ROS1*), and anaplastic lymphoma kinase

(ALK), with IC_{50} values of 0.1 to 2 nM. The major active metabolite of entrectinib, M5, showed similar *in vitro* potency and activity against TRK, ROS1, and ALK.

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib demonstrated *in vitro* and *in vivo* inhibition of cancer cell lines derived from multiple tumour types, including subcutaneous and intracranial tumours, harbouring *NTRK, ROS1,* and *ALK* fusion genes.

Prior treatments with other drugs that inhibit the same kinases may confer resistance to entrectinib. Resistance mutations in the TRK kinase domain identified following entrectinib discontinuation include *NTRK1* (G595R, G667C) and *NTRK3* (G623R, G623E and G623K). Resistance mutations in the ROS1 kinase domain identified following entrectinib discontinuation include G2032R, F2004C and F2004I.

The molecular causes for primary resistance to entrectinib 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.

Clinical efficacy and safety

NTRK gene fusion-positive solid tumours

Efficacy in adult patients
The efficacy of Rozlytrek was evaluated in a pooled sub-group of adult patients with unresectable or metastatic solid tumours with a *NTRK* gene fusion enrolled in one of three multicentre single-arm, open-label clinical trials (ALKA, STARTRK-1, and STARTRK-2) or the multicentre multi-cohort, open-label clinical trial, TAPISTRY. To be included in the pooled subgroup, patients were required to have confirmed *NTRK* gene fusion-positive solid tumours; measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1; at least 12 months of follow-up from the first post-treatment initiation tumour assessment, and no prior therapy with a TRK inhibitor (patients with concomitant driver mutations, where known, were excluded). Patients with primary CNS tumours were assessed separately using Response Assessment in Neuro-Oncology Criteria (RANO). Patients received Rozlytrek 600 mg orally once daily until unacceptable toxicity or disease progression. The primary efficacy endpoints were objective response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy was assessed in 242 adult patients with solid tumours with an *NTRK* gene fusion enrolled in these trials. The baseline demographic and disease characteristics were: 47.5% males, median age of 58 years (range 19 years to 92 years), 37.2% and 9.9% were 65 years or older and 75 years or older respectively, 49.4% white Caucasian, 36.5% Asian, 3.3% Hispanic or Latino and 61.9% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (42.1%), 1 (50%), or 2 (7.9%). Most patients (95.5%) had metastatic disease [most common sites being lung (62.8%), lymph nodes (49.2%), liver (33.1%), bone (31%), and brain (16.5%)], 4.5% patients had locally advanced disease. 76.9% and 52.5% of patients had received surgery and radiotherapy for their cancer, respectively. 71.5% patients had received prior systemic therapy for their cancer including chemotherapy (61.6%) and 37.2% patients had no prior systemic therapies for metastatic disease. The most common cancers were lung cancer (24.8%), sarcoma (19%), salivary gland tumours (15.7%), thyroid cancer (13.6%), colorectal cancer (7%), and breast cancer (7%). The overall median duration of follow-up was 35.1 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 6.

Table 6: Overall efficacy by BICR in adults with *NTRK* gene fusion-positive solid tumours

Efficacy endpoint	Rozlytrek n=242
Primary endpoints *(BICR assessed; RECIST 1.1)*	
Objective response rate	
Number of responses	152/242
ORR% (95% CI[*])	62.8% (56.4, 68.9)
Complete response, n (%)	41 (16.9%)
Partial response, n (%)	111 (45.9%)
Duration of response[**]	
Number (%) of patients with events	86/152 (56.6%)
Median, months (95% CI)	22 (16.6, 30.4)
6-month durable response % (95% CI)	85% (80, 91)
9-month durable response % (95% CI)	78% (71, 84)
12-month durable response % (95% CI)	69% (62, 77)

[*]Confidence Intervals (CI) calculated using the Clopper-Pearson method.
[**]Median and event-free rates based on Kaplan-Meier estimates.

Objective response rate and duration of response by tumour type in adult patients with *NTRK* gene fusion-positive solid tumours is presented in Table 7 below.

Table 7: Efficacy by tumour type in adults with *NTRK* gene fusion-positive solid tumours

Tumour type	Patients (n=242)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	46	29 (63)	(47.6, 76.8)	2.8, 68.6[*]
Non-small cell lung cancer	60	38 (63.3)	(49.9, 75.4)	3.1, 71.6
Salivary (MASC)	38	32 (84.2)	(68.8, 94)	2.8, 73.5[*]
Breast cancer (secretory)	12	10 (83.3)	(51.6, 97.9)	5.5, 69.9[*]
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Breast cancer (NOS)	2	NE, NE	NA	NA
Breast cancer (Ductal)	1	PD	NA	NA
Thyroid cancer	33	20 (60.6)	(42.1, 77.1)	5.6, 60.7
Colorectal cancer	17	6 (35.3)	(14.2, 61.7)	5.6[*], 24[*]
Neuroendocrine cancers	8	5 (62.5)	(24.5, 91.5)	7.4, 31.1
Head and neck	5	3 (60.0)	(14.7, 94.7)	4.0, 56.5[*]
Pancreatic cancer	6	4 (66.7)	(22.3, 95.7)	5.6[*], 12.9
Unknown primary cancer	3	1 (33.3)	(0.8, 90.6)	9.1
Ovarian cancer	1	Non CR/PD	NA	NA
Endometrial carcinoma	1	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	CR	NA	30.4
Gastrointestinal cancer (non CRC)	1	PD	NA	NA
Neuroblastoma	1	NE	NA	NA
Prostate cancer	1	PD	NA	NA
Penile cancer	1	PD	NA	NA
Adrenal cancer	1	PD	NA	NA

[*]Censored
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; NOS: not otherwise specified; CRC: colorectal cancer; CR: complete response; PR: partial response; PD: progressive disease; NE: not estimable.

Due to the rarity of *NTRK* gene fusion-positive cancers, 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.

The ORR in 122 patients that had broad molecular characterisation before Rozlytrek treatment was 59.8% (95% CI: 50.6, 68.6); of those, the ORR in 97 patients who had other genomic alterations in addition to *NTRK* gene fusion was 55.7% (95% CI: 45.2, 65.8) and the ORR in 25 patients without other genomic alterations was 76% (95% CI: 54.9, 90.6).

Intracranial response
A BICR assessment resulted in a subgroup of 36 adult patients with CNS metastases at baseline, including 20 patients with measurable CNS lesions. Intracranial (IC) response assessed by BICR according to RECIST v1.1 was reported in 14 out of these 20 patients (7 CR and 7 PR), for an ORR of 70% (95% CI: 45.7, 88.1) and median DOR of 19.7 months (95% CI: 7.4, 26.6). Five of these 20 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek treatment.

Primary CNS tumour
Across the three trials, 16 adult patients with primary CNS tumours were treated with Rozlytrek with a minimum of 12 months of follow-up. Two out of the 16 adult patients had an objective response assessed by BICR according to RANO.

Efficacy in paediatric patients
Efficacy of Rozlytrek was assessed in 44 paediatric patients with solid tumours that have a *NTRK* gene fusion enrolled in STARTRK-NG or TAPISTRY.

To be included in the analysis, patients were required to have confirmed *NTRK* gene fusion-positive solid tumours; at least 6 months of follow-up, no prior therapy with a TRK inhibitor, received at least one dose of entrectinib and presenting with measurable or evaluable disease at baseline. Patients received Rozlytrek doses from 20 mg to 600 mg once daily. The primary efficacy endpoint was confirmed ORR as evaluated by BICR according to RECIST v1.1 for extracranial tumours and according to RANO for primary CNS tumours. The secondary efficacy outcome measures included duration of confirmed response as evaluated by BICR and time to first confirmed objective response (CR or PR).

The baseline demographic and disease characteristics were: 45.5% males, median age of 4 years (range: 2 months to 15 years), 52.3% white Caucasian, 34.1% Asian, and 9.1% Hispanic or Latino, with a median BSA of 0.73 m^2 (range: 0.2-1.9 m^2). At baseline, 23.8% of patients had metastatic disease, 76.2% of patients had locally advanced disease, and 43.2% of patients had no prior systemic therapies for their cancer. The majority of patients had received treatment for their cancer including surgery (n=24), radiotherapy (n=8) and/or systemic therapy (n=25). The sites for metastatic disease included other (4 patients), brain (3 patients), and lung (3 patients). 45.5% of patients had primary CNS tumours. The overall median duration of follow-up was 24.2 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 8.

Table 8: Overall efficacy by BICR in paediatric patients with *NTRK* gene fusion-positive solid tumours

Efficacy endpoints	Rozlytrek n=44
Primary endpoints**	
Objective response rate	
Number of responses	32/44
ORR% (95% CI***)	72.7% (57.21, 85.04)
Complete response, n (%)	20 (45.5%)
Partial response, n (%)	12 (27.3%)
Secondary endpoints**	
DOR*	
Number (%) of patients with events	6/32 (18.8%)
Median, months (95% CI)	NE (25.4, NE)
6-month durable response % (95% CI)	97% (90, 100)
9-month durable response % (95% CI)	97% (90, 100)
12-month durable response % (95% CI)	84% (70, 99)

NE = not estimable.
*Median and event-free rates based on Kaplan-Meier estimates.
**Includes patients with measurable or evaluable disease. BICR analysis by RECIST v1.1 for solid tumours (24 patients) and by RANO criteria for primary CNS tumours (20 patients).
***Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Objective response rate and duration of response by tumour type in paediatric patients with *NTRK* gene fusion-positive solid tumours is presented in Table 9.

Table 9: Efficacy by tumour type in paediatric patients with *NTRK* gene fusion-positive solid tumours

Tumour type	Patients (n=44)	ORR		DOR
		n (%)	95% CI	Range (months)
Primary CNS	20	10 (50)	(27.2, 72.8)	5.5, 42.3*
Infantile fibrosarcoma	11	10 (90.9)	(58.7, 99.8)	5.7*, 24*
Spindle Cell	8	8 (100.0)	(63.1, 100)	5.4*, 23*
Sarcoma (other)	2	PR; Non-CR/Non-PD	NA	3.7*
Melanoma	1	CR	NA	42.4*
Kidney cancer	1	PR	NA	9.2*
Thyroid cancer	1	CR	NA	11.1*

*Censored
ORR: Objective Response Rate; DOR: Duration of Response; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease

Due to the rarity of NTRK gene fusion-positive cancers, 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.

ROS1-positive NSCLC

The efficacy of Rozlytrek was evaluated in a pooled sub-group of patients with *ROS1*-positive metastatic NSCLC who received Rozlytrek 600 mg orally once daily and were enrolled in one of three multicentre single-arm, open-label clinical trials (ALKA, STARTRK-1, and STARTRK-2). To be

included in the pooled sub-group, patients were required to have histologically confirmed, recurrent or metastatic, *ROS1*-positive NSCLC, ECOG performance status ≤ 2, measurable disease per RECIST v1.1, ≥ 6 months of follow-up, and no prior therapy with a ROS1 inhibitor. All patients were assessed for CNS lesions at baseline.

The primary efficacy endpoints were ORR and DOR, as evaluated by BICR according to RECIST v1.1. The secondary efficacy endpoints included PFS, OS, and in patients presenting with CNS metastases at baseline – IC-ORR and IC-DOR (also evaluated by BICR using RECIST v1.1).

Efficacy was assessed in 161 patients with *ROS1*-positive NSCLC. The baseline demographic and disease characteristics were: 35.4% males, median age of 54 years (range 20 years to 86 years), 24.2% and 4.3% were older than 65 years and 75 years of age, respectively, 44.1% white Caucasian, 45.3% Asian, 4.3%, Black, 2.6% Hispanic or Latino and 62.7% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (41%), 1 (49.1%), or 2 (9.9%). Most patients (98.1%) had metastatic disease [most common sites being lymph nodes (69.6%), lung (50.3%) and brain (32.9%)], 1.9% patients had locally advanced disease and 37.3% patients had no prior systemic therapies for metastatic disease. *ROS1* positivity was determined by NGS in 83% of patients, by FISH in 9% of patients, and by RT-PCR in 8% of patients. The overall median duration of follow-up from receipt of the first dose was 15.8 months.

Efficacy results from patients with *ROS1*-positive NSCLC are summarised in Table 10.

Table 10: Overall efficacy by BICR in patients with *ROS1*-positive NSCLC

Efficacy endpoint	Rozlytrek n=161
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
Objective response rate	
Number of responses	108/161
ORR% (95% CI***)	67.1% (59.25, 74.27)
Complete response, n (%)	14 (8.7%)
Partial response, n (%)	94 (58.4%)
Duration of response*	
Number (%) of patients with events	48/108 (44.4%)
Range (months)	1.8**, 42.3**
6-month durable response % (95% CI)	83% (76, 90)
9-month durable response % (95% CI)	75% (67, 84)
12-month durable response % (95% CI)	63% (53, 73)
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
PFS*	
Number (%) of patients with events	82/161 (50.9%)
6-month PFS % (95% CI)	77% (70, 84)
9-month PFS % (95% CI)	66% (58, 74)
12-month PFS % (95% CI)	55% (47, 64)
Overall survival*	
Number (%) of patients with events	38/161 (23.6%)
6-month OS % (95% CI)	91% (87, 96)
9-month OS % (95% CI)	86% (81, 92)
12-month OS % (95% CI)	81% (74, 87)

*Event-free rates based on Kaplan-Meier estimates.
**Censored
***Confidence Intervals (CI) calculated using the Clopper-Pearson method.

In the ROS1 positive NSCLC efficacy evaluable patients with ≥ 12 months of follow-up (n=94), the ORR was 73.4% (95% CI: 63.3, 82), the median DOR was 16.5 months (95% CI: 14.6, 28.6) and median PFS was 16.8 months (95% CI: 12, 21.4).

Intracranial response
A BICR assessment resulted in a subgroup of 46 *ROS1*-positive NSCLC patients with CNS metastases at baseline including 24 patients with measurable CNS lesions. Intracranial response assessed by BICR according to RECIST v1.1 was reported in 19 of these 24 patients (3 CR and 16 PR) for an ORR of 79.2% (95% CI: 57.8, 92.9). The percentage of patients (95% CI) with DOR ≥ 6 months, ≥ 9 months and ≥ 12 months was 76% (56, 97), 62% (38, 86), and 55% (29, 80), respectively (Kaplan-Meier estimates). Nine of these 24 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek 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

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5), have been characterised in patients with *NTRK* gene fusion-positive solid tumours and *ROS1*-positive NSCLC and healthy subjects. The pharmacokinetics of entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for entrectinib and two weeks for M5 following daily administration of Rozlytrek.

Entrectinib is a weak P-gp substrate based on *in vitro* data. The exact *in vivo* contribution of P-gp is unknown. M5 is a P-gp substrate. Entrectinib is not a substrate of BCRP but M5 is a substrate of BCRP. Entrectinib and M5 are not substrates of OATP 1B1 or OATP1B3.

Absorption

Following a single 600 mg oral administration of Rozlytrek to patients with *NTRK* gene fusion-positive and *ROS1*-positive NSCLC under fed conditions, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 to 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

No clinically significant effect of food on entrectinib bioavailability was observed.

In healthy adult subjects, the AUC and C_{max} of Rozlytrek in the film-coated granule formulation was similar to that of the capsules. Rozlytrek capsules administered as a suspension with water or milk, given orally, or through a gastric or nasogastric tube, results in similar AUC and C_{max} as capsules swallowed whole.

Distribution

Entrectinib and its major active metabolite M5 are highly bound to human plasma proteins independent of drug concentrations. In human plasma, entrectinib and M5 had similar protein binding with > 99% bound at a clinically relevant concentration.

After a single oral dose of entrectinib, the geometric mean volume of distribution (Vz/F) was 600 L, suggesting extensive distribution of the drug. Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 to 2.2 in multiple animal species (mice, rats, and dogs) at clinically relevant systemic exposures.

Biotransformation

Entrectinib is metabolised predominantly by CYP3A4 (~76%). Minor contributions from several other CYPs and UGT1A4 were estimated at < 25% in total. The active metabolite M5 (formed by CYP3A4) and the direct N-glucuronide conjugate, M11, (formed by UGT1A4) are the two major circulating metabolites identified.

Elimination

The population PK model estimated mean accumulation at steady-state following 600 mg once daily administration of entrectinib was 1.89 (±0.381) and 2.01 (±0.437) for M5. Following administration of a single dose of [^{14}C]-labelled entrectinib, 83% radioactivity was excreted in faeces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at C_{max}, and approximately half of total radioactivity AUC_{inf}.

Population PK analysis estimated apparent clearance CL/F was 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively. The elimination half-lives of entrectinib and M5 were estimated to be 20 hours and 40 hours, respectively.

Linearity/Non-linearity

Entrectinib has linear pharmacokinetics in the dose range of 100 mg to 600 mg.

Pharmacokinetics in special populations

Paediatric population

The pharmacokinetics of entrectinib have been evaluated in 78 paediatric patients above one month of age. In patients from > 1 month to ≤ 6 months the administered dose was 250 mg/m^2; in patients > 6 months, the administered dose was 300 mg/m^2 based on five BSA categories, with a maximum dose of 600 mg for children with ≥ 1.51 m^2 body surface area (BSA).

Data obtained from population pharmacokinetic analyses show that in paediatric patients 6 years and older, 300 mg Rozlytrek once daily dose for BSA range 0.81 m^2 to 1.10 m^2, 400 mg Rozlytrek once daily dose for BSA range 1.11 m^2 to 1.50 m^2, and 600 mg Rozlytrek once daily dose for BSA range ≥ 1.51 m^2 results in a similar systemic exposure attained in adults treated with 600 mg Rozlytrek once daily dose.

Data from non-compartmental analysis in patients from 1 month to < 6 years demonstrated that systemic exposure of the sum of entrectinib and M5 in paediatric patients receiving 250 mg/m^2 or 300 mg/m^2 of Rozlytrek once daily were generally lower than the mean systemic exposure of adult patients treated with 600 mg of Rozlytrek once daily. The recommended dose in this age category is based on available efficacy and safety data.

Elderly

No differences in entrectinib exposure were noted in patients older than 65 years and younger adults based on pharmacokinetic analysis.

Renal impairment

Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3% of the dose) indicating that renal clearance plays a minor role in the elimination of entrectinib. Based on population pharmacokinetic analyses, the pharmacokinetics of entrectinib are not significantly affected in renal impairment. The impact of severe renal impairment on the pharmacokinetics of entrectinib is unknown.

Hepatic impairment

The pharmacokinetics of entrectinib were studied in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, relative to subjects with normal hepatic function. Following administration of a single oral dose of 100 mg entrectinib, the combined AUC_{last} of entrectinib and M5 showed no relevant change in the hepatic impaired groups compared to the normal function group. The AUC_{last} geometric mean ratio (90% CI) was 1.30 (0.889, 1.89) for the mild, 1.24 (0.886, 1.73) for the moderate, and 1.39 (0.988, 1.95) for the severe hepatic impaired groups compared to the normal hepatic function group. For the unbound entrectinib and M5, the $AUC_{last\ (fu)}$ geometric mean ratio (90% CI) was 1.91 (1.21, 3.02) for the mild, 1.57 (1.06, 2.31) for the moderate, and 2.34 (1.57, 3.48) for the severe hepatic impaired groups compared to the normal hepatic function group. Although the effect of hepatic impairment on unbound PK parameters generally followed a similar direction as total PK parameters, due to the high non-specific binding in buffer and high variability, results should be interpreted with caution.

In addition, it was also observed that the variability in systemic exposure was high and observed exposures overlapped across all the study groups (see section 4.2).

Effects of body weight, race and gender

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on sex, race (Asian, Black and White) and body weight (4 kg to 130 kg).

5.3 Preclinical safety data

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of entrectinib.

Genotoxicity

Entrectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but demonstrated a potential for abnormal chromosome segregation (aneugenicity) in cultured human peripheral blood lymphocytes. Entrectinib was not clastogenic or aneugenic in the *in vivo* micronucleus assay in rats and did not induce DNA damage in a comet assay in rats.

Impairment of fertility

Dedicated fertility studies in animals have not been performed to evaluate the effect of entrectinib. No adverse effects of entrectinib on male and female reproductive organs were observed in the repeat-dose toxicology studies in rats and dogs at approximately 2.4-fold and 0.6-fold, respectively, the human exposure by AUC at the recommended human dose.

Reproductive toxicity

In an embryo-foetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and foetal malformations (including body closure defects and malformations of the vertebrae and ribs), were observed at 200 mg/kg/day of entrectinib which represents approximately

2-fold the human exposure by AUC at the recommended dose. Dose-response dependent reduced foetal body weight (low, middle and high dose) and reduced skeletal ossification (middle and high dose) were observed at exposures equivalent to < 2 times the human exposure by AUC at the recommended dose.

Repeat-dose toxicity studies

Entrectinib-related toxicities in repeat-dose studies in adult rats and dogs, and juvenile rats were observed in the central nervous system (convulsions, abnormal gait, tremors) at ≥ 0.2 times the human exposures by C_{max} at the recommended dose, skin (scabs/sores) and decreased red blood cell parameters at ≥ 0.1 times the human exposure by AUC at the recommended dose. In adult rats and dogs, effects on liver (increased ALT and hepatocellular necrosis) were observed at ≥ 0.6 times the human exposure by AUC at the recommended dose. In dogs, diarrhoea at ≥ 0.1 times the human exposure by AUC at the recommended dose and prolongations of QT/QTc interval at ≥ 0.1 times the human exposure by C_{max} at the recommended dose were also observed.

Juvenile rat toxicology study

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood in humans). In addition to CNS effects, ptosis and skin effects, decreased RBC parameters and effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at ≥ 4 mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose). Deficits in neurobehavioural assessments including functional observational battery (decreased landing foot splay, decreased fore and hind limb grip strength that seemed to manifest later in age) and learning and memory (at ≥ 8 mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose), and decreased femur length (at ≥ 16 mg/kg/day, approximately 0.3 times the human exposure by AUC at the recommended dose) were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule core

Microcrystalline cellulose (E460)
Tartaric acid (E334)
Silica, colloidal anhydrous (E551)
Croscarmellose sodium (E468)
Sodium stearyl fumarate
Mannitol (E421)
Magnesium stearate (E470b)

Film-coating

Titanium dioxide (E171)
Talc
Yellow iron oxide (E172)
Red iron oxide (E172)
Black iron oxide (E172)
Polyethylene glycol 3350
Polyvinyl alcohol (partially hydrolysed)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Rozlytrek film-coated granules are packaged in a PET/Alu/PE laminated foil sachet. Each carton contains 42 sachets.

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

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2020
Date of latest renewal: 16 May 2024

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(S) 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

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

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

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomised controlled trial versus crizotinib in treatment naïve *ROS1* NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with CNS metastases at baseline. The clinical study report should be submitted by:	31 December 2027

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

This being a conditional marketing authorisation and pursuant to Article 14a(4) 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 entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of *NTRK* fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol. The MAH should submit the results of an interim safety and efficacy analysis of the *NTRK* efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.	31 March 2027
In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.	31 March 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rozlytrek 100 mg hard capsules
entrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg entrectinib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rozlytrek 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

Rozlytrek 100 mg hard capsules
entrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg entrectinib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

30 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

Rozlytrek 200 mg hard capsules
entrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg entrectinib.

3. LIST OF EXCIPIENTS

Contains lactose and azo colouring agent sunset yellow FCF (E110). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rozlytrek 200 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

Rozlytrek 200 mg hard capsules
entrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg entrectinib.

3. LIST OF EXCIPIENTS

Contains lactose and azo colouring agent sunset yellow FCF (E110). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

90 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

Rozlytrek 50 mg film-coated granules in sachet
entrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of film-coated granules contains 50 mg of entrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated granules in sachet

42 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Store in the original package in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rozlytrek 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINUMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rozlytrek 50 mg film-coated granules in sachet
entrectinib
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Roche

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rozlytrek 100 mg hard capsules
Rozlytrek 200 mg hard capsules
entrectinib

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

1. What Rozlytrek is and what it is used for

What Rozlytrek is

Rozlytrek is a cancer medicine that contains the active substance 'entrectinib'.

What Rozlytrek is used for

Rozlytrek is used to treat either:
- adults, adolescents, and children older than 1 month with solid tumours (cancer) in various parts of the body that are caused by a change in a gene called 'neurotrophic tyrosine receptor kinase' (*NTRK*), or
- adults with a type of lung cancer called 'non-small cell lung cancer' (NSCLC) that is caused by a change in a gene called '*ROS1*'.

This medicine is used for solid tumour cancers when:
- a test has shown that your cancer cells have a change in genes called '*NTRK*' (see 'How Rozlytrek works' below), and
- your cancer has spread within the affected organ or to other organs in your body or if surgery to remove the cancer is likely to cause severe complications, and
- you have not previously been given medicines called '*NTRK* inhibitors'
- other treatments have not worked or are not suitable for you.

This medicine is used if your lung cancer (NSCLC):
- is '*ROS1*-positive' – this means that your cancer cells have a change in a gene called '*ROS1*' (see 'How Rozlytrek works' below), and
- is advanced – for example, has spread to other parts of your body (metastatic), and
- you have not previously been given medicines called '*ROS1* inhibitors'.

How Rozlytrek works

Rozlytrek works by blocking the action of faulty enzymes. These faulty enzymes are caused by a change in the *NTRK* or *ROS1* genes that make them. The faulty enzymes make the cancer cells grow.

Rozlytrek may slow down or stop the growth of the cancer. It may also help to shrink your cancer.

2. What you need to know before you take Rozlytrek

Do not take Rozlytrek

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

If you are not sure, talk to your doctor, pharmacist or nurse before taking Rozlytrek.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Rozlytrek if:
- you have recently had memory loss, confusion, hallucinations, or mental status changes
- you have had fractured bones, or conditions which may increase your risk of breaking bones, called 'osteoporosis' or 'osteopaenia'
- you take medicine to lower the uric acid in your blood
- you have heart failure (when your heart struggles to pump blood to supply oxygen to the body) – signs can include cough, feeling short of breath, or swelling in your legs or arms
- you have ever had heart problems or a heart conduction problem called 'prolonged QTc interval' – this is shown on an 'electro-cardiogram' (ECG), or by low levels of electrolytes in your blood
- you have an inherited problem called 'galactose intolerance', 'congenital lactase deficiency' or 'glucose-galactose malabsorption'.

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

Other medicines and Rozlytrek

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

In particular, tell your doctor or pharmacist if you are taking any of the following medicines for:
- fungal infections (anti-fungals) – such as ketoconazole, itraconazole, voriconazole, posaconazole
- AIDS/HIV infection – such as ritonavir or saquinavir
- depression – such as paroxetine, fluvoxamine, or a herbal medicine for depression – St. John's Wort
- stopping seizures or fits – such as phenytoin, carbamazepine, or phenobarbital
- tuberculosis – such as rifampicin or rifabutin

- solid cancers and blood cancer – topotecan, lapatinib, mitoxantrone, apalutamide, or methotrexate
- inflamed joints or joint autoimmune disease (rheumatoid arthritis) – methotrexate
- migraines – ergotamine
- severe pain – fentanyl
- mental illness (psychoses) or Tourette Syndrome – pimozide
- irregular heart rate – quinidine
- stopping the formation of blood clots – warfarin or dabigatran etexilate
- gastric reflux (heartburn) – cisapride or omeprazole
- lowering blood cholesterol – atorvastatin, pravastatin, or rosuvastatin
- suppressing your body's immune system, or stopping your body from rejecting an organ transplant – sirolimus, tacrolimus, or cyclosporin
- lowering blood sugar levels – repaglinide or tolbutamide
- high blood pressure – bosentan, felodipine, nifedipine, or verapamil
- inflammation or nausea – dexamethasone

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

Rozlytrek with food and drink

Do not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with this medicine. It may increase the amount of the medicine in your blood to a harmful level.

Women and contraception

You must avoid becoming pregnant while taking this medicine because it could harm the baby. If you are able to become pregnant, you must use highly effective contraception:
- while on treatment, and
- for at least 5 weeks after stopping treatment.

It is not known if Rozlytrek can reduce the effect of birth control medicines (contraceptive pills or implanted hormonal contraceptives). You should use another reliable method of birth control such as a barrier method (such as a condom).

Talk to your doctor about the right methods of contraception for you and your partner.

Men and contraception

Your female partner must avoid becoming pregnant while you are taking this medicine because it could harm the baby. If your female partner is able to become pregnant, you must use highly effective contraception:
- while on treatment, and
- for at least 3 months after stopping treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy

- Do not take Rozlytrek if you are pregnant. This is because it may harm your baby.
- If you become pregnant when taking the medicine or during the 5 weeks after taking your last dose, tell your doctor straight away.

Breast-feeding

Do not breast-feed while taking this medicine. This is because it is not known if Rozlytrek can pass over into breast milk and could therefore harm your baby.

Driving, cycling and using machines

Rozlytrek may affect your ability to drive, ride a bicycle, or use machines. Rozlytrek may cause you to:

- have blurred vision
- feel tired, dizzy, or pass out
- have changes in your mental status, feel confused or see things that are not there (hallucinations).

If this happens, you should not drive, ride a bicycle, or operate heavy machines until you feel better. Talk to your doctor or pharmacist about whether it is okay for you to drive, ride a bicycle, or use machines.

Rozlytrek contains:

- **lactose -** a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- **sunset yellow FCF (E110) in 200 mg hard capsules only.** This is a colouring agent, which may cause allergic reactions.

3. How to take Rozlytrek

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

How much to take

For adults:

- The recommended dose is 3 capsules of 200 mg once a day (total amount 600 mg).
- If you feel unwell, your doctor may lower your dose, stop treatment for a short time or stop treatment completely.

For adolescents and children older than 1 month:

- Your child’s doctor will work out the correct dose to use – based on the height and weight of the child.
- Your child’s doctor will review the dose and change it as needed.

Rozlytrek is also available as film-coated granules in a sachet for patients who cannot swallow the capsules but are able to swallow soft food.

How to take

Rozlytrek can be taken with or without food.

There are two ways your doctor may tell you to take Rozlytrek capsules:

- Swallow each capsule whole by mouth. Do not crush or chew the capsules.

- Take it prepared as an oral suspension by mouth (using an oral syringe) or through a feeding tube, if needed.

Read the 'Instructions for Use' at the end of this leaflet

Read and follow the '**Instructions for Use**' at the end of this leaflet carefully on how to take or give Rozlytrek. It shows you details on how to prepare, measure, and take or give Rozlytrek prepared as an oral suspension:
- by mouth, or
- through a feeding tube (such as a gastric or nasogastric tube).

If you vomit after taking Rozlytrek

For whole capsules

If you vomit immediately after taking a dose of Rozlytrek, take another dose.

For capsules administered as an oral suspension

If partial or total vomiting or spitting occurs immediately after giving an administered dose to the patient, consult the patient's doctor or pharmacist for the next steps.

If you take more Rozlytrek than you should

If you take more Rozlytrek than you should, talk to a doctor or go to hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take Rozlytrek

- If your next dose is more than 12 hours later, take the missed dose as soon as you remember.
- If there are less than 12 hours until your next dose, do not take the missed dose. Take your next dose at the usual time.
- Do not take a double dose to make up for a missed dose.

If you stop taking Rozlytrek

Do not stop taking this medicine without talking to your doctor first. It is important to take this medicine every day for as long as your doctor prescribes it for you.

If you have any 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. The following side effects may happen with this medicine.

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects. Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely if:
- you have cough, feel short of breath, or swelling in your legs or arms (fluid retention) – these can be signs of heart problems (congestive heart failure)
- you feel confused, have mood changes, memory problems or see things that are not there (hallucinations)

- you feel dizzy or light-headed, or feel your heart beating irregularly or fast – this may be a sign of an abnormal heartbeat
- you notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures
- you have kidney problems or arthritis – you may have high uric acid levels in your blood

Tell your doctor straight away if you notice any of the side effects above.

Other side effects

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:
- feeling tired
- changes in taste
- feeling unsteady or dizzy
- blurred vision
- swelling
- diarrhoea or constipation
- being or feeling sick
- difficulty swallowing
- abnormal sense of touch which feels like itching, tingling or burning sensation
- rash
- feeling short of breath
- cough or fever
- headache
- weight gain
- vomiting
- muscle pain or weakness
- pain including back pain, neck pain, musculoskeletal pain, pain in limbs
- stomach pain
- joint pain
- abnormal unpleasant sensation in your arms or legs
- loss of muscle coordination, being unsteady when walking
- disturbance in normal sleep patterns
- lung infection
- urinary tract infection
- cannot empty your bladder completely
- loss of appetite
- low blood pressure
- decreased number of a type of white blood cell called neutrophils
- lack of enough red blood cells (anaemia)
- increased blood levels of certain liver enzymes (AST/ALT)
- increased blood level of creatinine (something normally removed by the kidneys into the urine)

Common: may affect up to 1 in 10 people:
- mood disorders
- dehydration
- fluid around your lungs
- fainting
- skin being more sensitive to sunlight

Uncommon: may affect less than 1 in 100 people:
- changes in certain chemicals in your blood caused by fast breakdown of tumour cells – this may cause damage to organs, including the kidneys, heart, and liver.
- inflammation of the heart muscle

Tell your doctor, pharmacist or nurse if you notice any of the side effects above.

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 Rozlytrek

- 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 after EXP. The expiry date refers to the last day of that month.
- Store the capsules in the original package and keep the bottle tightly closed in order to protect from moisture.
- Following preparation as an oral suspension, store below 30°C and use within 2 hours of preparation.
- Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rozlytrek contains

The active substance is entrectinib.
Rozlytrek 100 mg: each capsule contains 100 mg entrectinib
Rozlytrek 200 mg: each capsule contains 200 mg entrectinib

The other ingredients are:
- *Capsule content:* tartaric acid (E334), lactose (see section 2 'Rozlytrek contains lactose'), hypromellose (E464), crospovidone (E1202), microcrystalline cellulose (E460), silica, colloidal anhydrous (E551), magnesium stearate (E470b).
- *Capsule shell:* hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172; for Rozlytrek 100 mg capsule), sunset yellow FCF (E110; for Rozlytrek 200 mg capsule). See section 2 'Rozlytrek contains sunset yellow FCF (E110)'.
- *Printing ink:* shellac, propylene glycol, indigo carmine aluminium lake (E132).

What Rozlytrek looks like and contents of the pack

Rozlytrek 100 mg hard capsules are opaque yellow with ENT 100 imprinted in blue on the body.

Rozlytrek 200 mg hard capsules are opaque orange with ENT 200 imprinted in blue on the body.

The capsules are provided in bottles containing either:
- 30 hard capsules of Rozlytrek 100 mg, or
- 90 hard capsules of Rozlytrek 200 mg.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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

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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.

Other sources of information

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

7. Instructions for use

Rozlytrek
(entrectinib)
Capsules for oral use
(administered as whole capsules or as an oral suspension)

These Instructions for Use contain information on how to prepare, take and give Rozlytrek capsules.

Rozlytrek capsules can be swallowed whole or prepared as a suspension and taken or given by mouth or through gastric or nasogastric tube.

Before starting

- **Read these Instructions for Use** before taking or giving Rozlytrek capsules.
- Ask your healthcare professional to show you how to use Rozlytrek before treatment is started.
- If you have any further questions on the use of Rozlytrek, ask your healthcare professional.

Important Information You Need to Know Before Preparing and Taking or Giving Rozlytrek

- Your healthcare professional should show you how to correctly prepare and take or give a dose of Rozlytrek capsules. Always take or give Rozlytrek capsules exactly as your healthcare professional tells you.
- **Do not take or** give Rozlytrek to someone else, until you have been shown how to properly prepare and take or give Rozlytrek.
- Wash your hands before and after using Rozlytrek. **Do not** touch your eyes, nose or mouth during the preparation of the oral suspension.
- Check the expiry date and the product for damage before use. **Do not** use if expired or damaged.
- For whole capsules, if you vomit immediately after taking a dose of Rozlytrek, take another dose.
- For capsules administered as an oral suspension, if partial or total vomiting or spitting occurs immediately after giving an administered dose to the patient, consult the patient's doctor or pharmacist for the next steps.
- The oral suspension should be administered **within 2 hours** of preparing.

Rozlytrek administration as a whole capsule by mouth

Your healthcare professional will decide the right daily dose of Rozlytrek for you or your child.

- Swallow whole capsules, with or without food, with some drinking water, as directed by your healthcare professional.
- Do not crush or chew the capsules.

Rozlytrek administration as a liquid suspension – orally or via gastric/nasogastric tube

If you or your child cannot swallow capsules whole, Rozlytrek capsules can be prepared as a suspension (in water or milk) and taken or given by mouth or through a feeding tube.

Your healthcare provider will tell you the number of capsules to use, the exact amount of liquid (water or milk) to be mixed with the contents of capsule(s) needed to prepare the suspension, AND the exact amount of suspension (mL) to withdraw in order to reach the prescribed dose of Rozlytrek to be taken or given.

Table 1 shows the prescribed dose, the number and strength of capsules needed, the amount of water or milk to be mixed with the contents of the capsule(s) and prepare the suspension, AND the amount of suspension to withdraw in order to reach the prescribed dose to be taken or given.

You may need to measure a smaller amount of suspension than you prepared to take or give the correct prescribed dose of Rozlytrek.

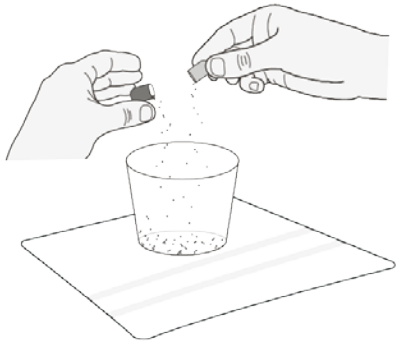
Table 1. Preparation of Rozlytrek capsules as a suspension

Prescribed dose of Rozlytrek to be given	Number of 100 mg or 200 mg capsules needed	Amount of water or milk to be mixed with the content of the capsule(s) to prepare the suspension	Amount of suspension to withdraw in order to reach the prescribed dose
20 mg	One 100 mg	5 mL	1 mL
30 mg	One 100 mg	5 mL	1.5 mL
40 mg	One 100 mg	5 mL	2 mL
50 mg	One 100 mg	5 mL	2.5 mL
60 mg	One 100 mg	5 mL	3 mL
70 mg	One 100 mg	5 mL	3.5 mL
80 mg	One 100 mg	5 mL	4 mL
90 mg	One 100 mg	5 mL	4.5 mL
100 mg	One 100 mg	5 mL	5 mL
110 mg	One 200 mg	10 mL	5.5 mL
120 mg	One 200 mg	10 mL	6 mL
130 mg	One 200 mg	10 mL	6.5 mL
140 mg	One 200 mg	10 mL	7 mL
150 mg	One 200 mg	10 mL	7.5 mL
200 mg	One 200 mg	10 mL	10 mL
300 mg	Three 100 mg	15 mL	15 mL
400 mg	Two 200 mg	20 mL	20 mL
600 mg	Three 200 mg	30 mL	30 mL

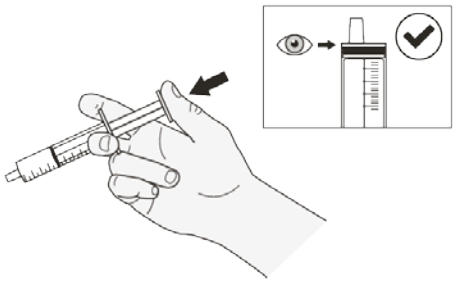
To prepare the suspension you will need:

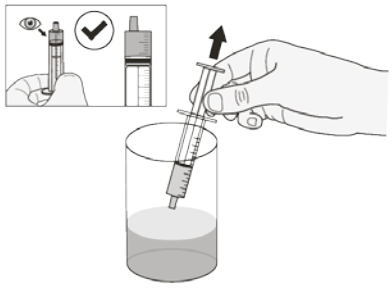
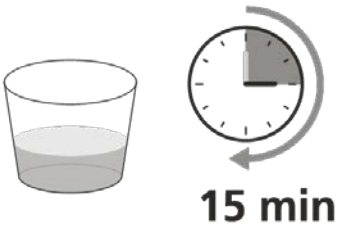
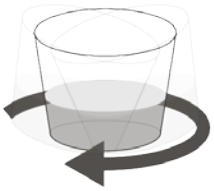
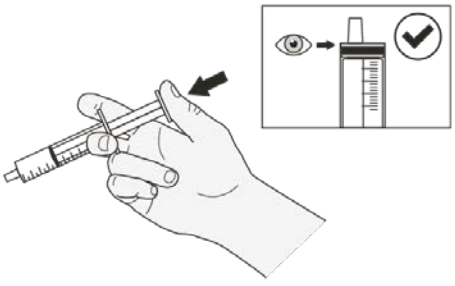
- The number of capsules indicated by your healthcare professional
- A clean empty cup (not included in the package)
- A cup of room temperature (below 30°C) drinking water or milk
- An oral syringe (provided by your pharmacist) with 0.5 mL graduation marks
- A paper towel

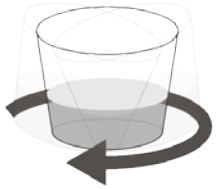
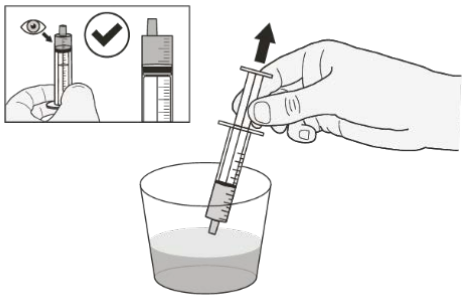
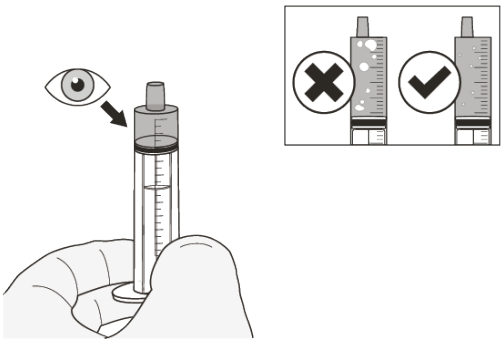
Preparing a suspension of Rozlytrek

<table>
<tr><td colspan="2">Step 1. Wash your hands.</td></tr>
<tr><td colspan="2">Step 2. Count the number of capsules indicated by your healthcare professional to prepare the suspension.</td></tr>
<tr><td>Step 3. Place a clean empty cup on a paper towel.</td><td rowspan="4"> 
Figure A</td></tr>
<tr><td>Step 4. Tap the capsule to loosen the contents inside.</td></tr>
<tr><td>Step 5. Hold the capsule above the clean empty cup to avoid spilling.</td></tr>
<tr><td>Step 6. Open the capsule by gently pressing in on the capsule and gently twisting both sides apart.

Pour the contents into the clean cup (Figure A).</td></tr>
<tr><td colspan="2">Step 7. Tap both sides of the capsule shell and check to ensure all contents have gone into the cup.

• If the contents of the capsule are spilled outside of the cup, empty the cup contents, and use another capsule. Go to Step C1 for clean-up instructions and then start over at Step 1.</td></tr>
<tr><td>Step 8. Push the syringe plunger all the way down to remove any air in the oral syringe (Figure B).</td><td> 
Figure B</td></tr>
</table>

• **Step 9.** Take the cup of room temperature (below 30°C) drinking water or milk. Using the syringe, withdraw the exact volume* of room temperature drinking water or milk from the cup (**Figure C**). **Your healthcare professional will tell you how much liquid to use.* **Do not** use any other type of liquid.	 **Figure C**
Step 10. Add the drinking water or milk from the syringe to the cup with the content of the capsule(s) (**Figure D**).	 **Figure D**
Step 11. Let the suspension sit for 15 minutes (**Figure E**). **Note:** It is important to do this to get an even suspension, otherwise you may not get the correct dose.	 **Figure E**
Step 12. Swirl the suspension several times to evenly mix the medicine in the liquid (**Figure F**). **Note**: The suspension will be cloudy if you have used water.	 **Figure F**
Step 13. Push the plunger of the syringe all the way down to remove any air in the syringe (**Figure G**).	 **Figure G**

Step 14. Swirl the medicine cup again before placing the syringe in the cup (**Figure H**).	 **Figure H**
Step 15. Immediately place the syringe into the cup and slowly pull back the plunger and withdraw the exact volume of suspension to reach your prescribed dose of Rozlytrek (**Figure I**). • Your healthcare professional will tell you how much suspension to withdraw for the prescribed dose. • **Do not** wait to withdraw the suspension. If it sits for too long, the medicine may settle to the bottom, and you may not get the correct dose.	 **Figure I**
Step 16. Check the amount in the syringe (**Figure J**). With the tip of the syringe pointing up, check: • you have withdrawn the correct volume of suspension • there are no large bubbles **Note:** If you have not withdrawn the correct volume, or if there are large bubbles inside: • put the syringe into the cup again • push the medicine back into the cup • then withdraw the medicine again (start at Step15) Shake the syringe quickly. Give Rozlytrek immediately after it is drawn up into the syringe. If not taken **within 2 hours**, throw away the medicine from the syringe. Go to Step C1 for clean-up instructions and then start at Step 2 to remix a new dose.	 **Figure J**

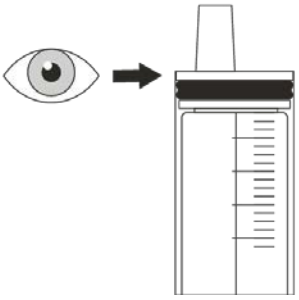
Administration by mouth

<table>
<tr>
<td>Step A1. Sit the patient upright when giving a dose of Rozlytrek by mouth (Figure K).

Place the oral syringe into the mouth with the tip along either cheek.

Slowly push the plunger all the way down.

Note: Giving Rozlytrek too fast may cause choking.</td>
<td> 
Figure K</td>
</tr>
<tr>
<td>Step A2. Check that there is no medicine left in the oral syringe (Figure L).

If some suspension remains in the oral syringe, repeat step A1.</td>
<td> 
Figure L</td>
</tr>
<tr>
<td colspan="2">Step A3. Give some water right after giving the prescribed dose of Rozlytrek.

In case of a strong aftertaste, the child can be breast-fed or given milk.</td>
</tr>
</table>

Administration through a gastric or nasogastric tube

You can take or give the suspension through a nasogastric or gastric tube placed by the healthcare professional. Check the manufacturer's instructions for the size and dimensions of the enteral tube. Make sure that the tube size is at least 8 French or higher to prevent clogging of the tube if your aliquots (amount of suspension) is 3 mL or higher.

To take or give Rozlytrek doses of 3 mL or higher, split the dose and give it in at least 2 parts. Flush the tube with same amount of water or milk after giving each part.

Neonates and children with fluid restrictions may require minimal flushing volumes of 1 mL to 3 mL to deliver Rozlytrek. The aliquots should be adjusted accordingly.

To take or give Rozlytrek doses of 30 mL, split the dose into at least three 10 mL parts. Flush the tube with the same amount of water or milk after giving each part. The tube should be flushed with water or milk after delivering Rozlytrek.

In case of any questions consult your healthcare professional.

Step B1

Place the syringe tip into the nasogastric/gastric tube.

Slowly press the plunger all the way down to give the full dose of Rozlytrek (**Figure M1 and M2**).

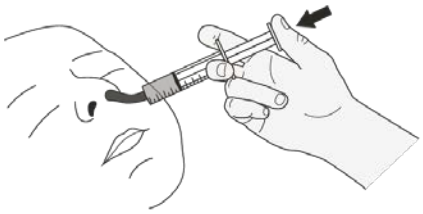


Figure M1

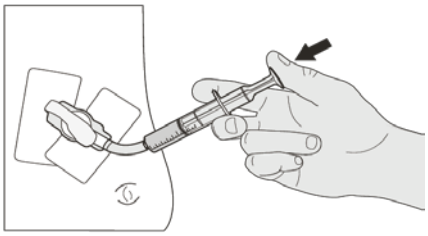


Figure M2

Step B2

Check that there is no medicine left in the syringe (**Figure N**).

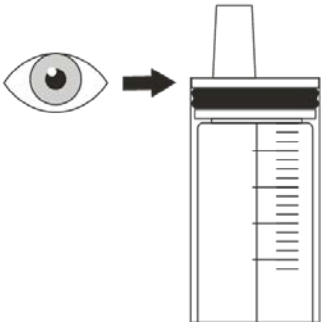


Figure N

Step B3

Flush the nasogastric/gastric tube with water or milk* right after giving the prescribed dose (**Figure O1 and O2**).

**Your healthcare professional will tell you how much water or milk to flush with.*

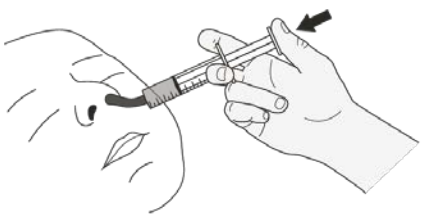


Figure O1

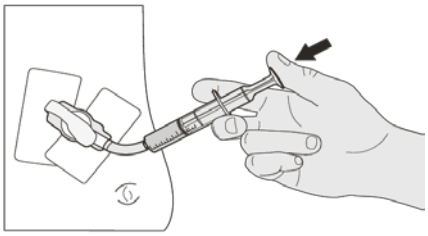


Figure O2

Step C1

- Wash your hands and all the items used to give Rozlytrek.
- Remove the syringe plunger from the syringe barrel.
- Use only clean water to rinse the syringe parts and the cup used to prepare the suspension. Let all items dry before the next use.
- Put the syringe plunger back into the syringe barrel when dry.
- Any unused medicinal product or waste material, including the remaining suspension (not administered) should be disposed of in accordance with local requirements. The remaining suspension (not administered) should not be discarded in wastewater.
- Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Storing Rozlytrek

- Store below 30°C in the original container and keep the bottle tightly closed to protect it from moisture.
- Throw away Rozlytrek if exposed to temperatures higher than 30°C and follow the instructions for disposal reported in Step C1 and section 5 of the leaflet.
- Following preparation as an oral suspension, store below 30°C and use within 2 hours of preparation.
- Always keep Rozlytrek out of sight and reach of children.

Package leaflet: Information for the patient

Rozlytrek 50 mg film-coated granules in sachet
entrectinib

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

1. What Rozlytrek is and what it is used for

What Rozlytrek is

Rozlytrek is a cancer medicine that contains the active substance 'entrectinib'.

What Rozlytrek is used for

Rozlytrek is used to treat either:
- adults, adolescents, and children older than 1 month with solid tumours (cancer) in various parts of the body that are caused by a change in a gene called 'neurotrophic tyrosine receptor kinase' (*NTRK*), or
- adults with a type of lung cancer called 'non-small cell lung cancer' (NSCLC) that is caused by a change in a gene called '*ROS1*'.

This medicine is used for solid tumour cancers when:
- a test has shown that your cancer cells have a change in genes called '*NTRK*' (see 'How Rozlytrek works' below), and
- your cancer has spread within the affected organ or to other organs in your body or if surgery to remove the cancer is likely to cause severe complications, and
- you have not previously been given medicines called '*NTRK* inhibitors'
- other treatments have not worked or are not suitable for you.

This medicine is used if your lung cancer (NSCLC):
- is '*ROS1*-positive' – this means that your cancer cells have a change in a gene called '*ROS1*' (see 'How Rozlytrek works' below), and
- is advanced – for example, has spread to other parts of your body (metastatic), and
- you have not previously been given medicines called '*ROS1* inhibitors'.

How Rozlytrek works

Rozlytrek works by blocking the action of faulty enzymes. These faulty enzymes are caused by a change in the *NTRK* or *ROS1* genes that make them. The faulty enzymes make the cancer cells grow.

Rozlytrek may slow down or stop the growth of the cancer. It may also help to shrink your cancer.

2. What you need to know before you take Rozlytrek

Do not take Rozlytrek

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

If you are not sure, talk to your doctor, pharmacist or nurse before taking Rozlytrek.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Rozlytrek if:
- you have recently had memory loss, confusion, hallucinations, or mental status changes
- you have had fractured bones, or conditions which may increase your risk of breaking bones, called 'osteoporosis' or 'osteopaenia'
- you take medicine to lower the uric acid in your blood
- you have heart failure (when your heart struggles to pump blood to supply oxygen to the body) – signs can include cough, feeling short of breath, or swelling in your legs or arms
- you have ever had heart problems or a heart conduction problem called 'prolonged QTc interval' – this is shown on an 'electro-cardiogram' (ECG), or by low levels of electrolytes in your blood
- you have an inherited problem called 'galactose intolerance', 'congenital lactase deficiency' or 'glucose-galactose malabsorption'.

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

Other medicines and Rozlytrek

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

In particular, tell your doctor or pharmacist if you are taking any of the following medicines for:
- fungal infections (anti-fungals) – such as ketoconazole, itraconazole, voriconazole, posaconazole
- AIDS/HIV infection – such as ritonavir or saquinavir
- depression – such as paroxetine, fluvoxamine, or a herbal medicine for depression – St. John's Wort
- stopping seizures or fits – such as phenytoin, carbamazepine, or phenobarbital
- tuberculosis – such as rifampicin or rifabutin

- solid cancers and blood cancer – topotecan, lapatinib, mitoxantrone, apalutamide, or methotrexate
- inflamed joints or joint autoimmune disease (rheumatoid arthritis) – methotrexate
- migraines – ergotamine
- severe pain – fentanyl
- mental illness (psychoses) or Tourette Syndrome – pimozide
- irregular heart rate – quinidine
- stopping the formation of blood clots – warfarin or dabigatran etexilate
- gastric reflux (heartburn) – cisapride or omeprazole
- lowering blood cholesterol – atorvastatin, pravastatin, or rosuvastatin
- suppressing your body's immune system, or stopping your body from rejecting an organ transplant – sirolimus, tacrolimus, or cyclosporin
- lowering blood sugar levels – repaglinide or tolbutamide
- high blood pressure – bosentan, felodipine, nifedipine, or verapamil
- inflammation or nausea – dexamethasone

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

Rozlytrek with food and drink

Do not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with this medicine. It may increase the amount of the medicine in your blood to a harmful level.

Women and contraception

You must avoid becoming pregnant while taking this medicine because it could harm the baby. If you are able to become pregnant, you must use highly effective contraception:
- while on treatment, and
- for at least 5 weeks after stopping treatment.

It is not known if Rozlytrek can reduce the effect of birth control medicines (contraceptive pills or implanted hormonal contraceptives). You should use another reliable method of birth control such as a barrier method (such as a condom).

Talk to your doctor about the right methods of contraception for you and your partner.

Men and contraception

Your female partner must avoid becoming pregnant while you are taking this medicine because it could harm the baby. If your female partner is able to become pregnant, you must use highly effective contraception:
- while on treatment, and
- for at least 3 months after stopping treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy

- Do not take Rozlytrek if you are pregnant. This is because it may harm your baby.
- If you become pregnant when taking the medicine or during the 5 weeks after taking your last dose, tell your doctor straight away.

Breast-feeding

Do not breast-feed while taking this medicine. This is because it is not known if Rozlytrek can pass over into breast milk and could therefore harm your baby.

Driving, cycling and using machines

Rozlytrek may affect your ability to drive, ride a bicycle, or use machines. Rozlytrek may cause you to:

- have blurred vision
- feel tired, dizzy, or pass out
- have changes in your mental status, feel confused or see things that are not there (hallucinations).

If this happens, you should not drive, ride a bicycle, or operate heavy machines until you feel better. Talk to your doctor or pharmacist about whether it is okay for you to drive, ride a bicycle, or use machines.

Rozlytrek contains sodium

This medicinal product contains less than 1mmol sodium (23 mg) per 600 mg dose, that is to say essentially 'sodium-free'. See section 6.

3. How to take Rozlytrek

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

How much to take

For adults:

- The recommended dose is 12 sachets once a day (total amount 600 mg). Each individual sachet is 50 mg.
- If you feel unwell, your doctor may lower your dose, stop treatment for a short time or stop treatment completely.

For adolescents and children older than 1 month:

- Your child's doctor will work out the correct dose to use – based on the height and weight of the child.
- Your child's doctor will review the dose and change it as needed.

Rozlytrek is also available as hard capsules for patients who are able to swallow capsules whole. Capsules may also be prepared as an oral suspension for patients who are unable to swallow soft food or need to use a feeding tube.

How to take

Take Rozlytrek film-coated granules by mouth – sprinkled on soft food.

- **Do not** divide the content of a sachet of film-coated granules to prepare a smaller dose.
- Film-coated granules should be sprinkled on one or more spoonfuls of a soft food (such as applesauce, yogurt, or pudding) and taken within 20 minutes of mixing.

- **Do not** crush or chew film-coated granules to avoid a bitter taste.
- Drink water after taking the medicine.
- Film-coated granules are not to be used with a feeding tube – they could block the tubing.

Read the 'Instructions for Use' at the end of this leaflet

Read and follow the '**Instructions for Use**' at the end of this leaflet carefully on how to take or give Rozlytrek. It shows you details on how to prepare a dose using film-coated granules and soft food.

If you vomit after taking Rozlytrek

If partial or total vomiting or spitting occurs immediately after giving an administered dose to the patient, consult the patient's doctor or pharmacist for the next steps.

If you take more Rozlytrek than you should

If you take more Rozlytrek than you should, talk to a doctor or go to hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take Rozlytrek

- If your next dose is more than 12 hours later, take the missed dose as soon as you remember.
- If there are less than 12 hours until your next dose, do not take the missed dose. Take your next dose at the usual time.
- Do not take a double dose to make up for a missed dose.

If you stop taking Rozlytrek

Do not stop taking this medicine without talking to your doctor first. It is important to take this medicine every day for as long as your doctor prescribes it for you.

If you have any 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. The following side effects may happen with this medicine.

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects. Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely if:
- you have cough, feel short of breath, or swelling in your legs or arms (fluid retention) – these can be signs of heart problems (congestive heart failure)
- you feel confused, have mood changes, memory problems or see things that are not there (hallucinations)
- you feel dizzy or light-headed, or feel your heart beating irregularly or fast – this may be a sign of an abnormal heartbeat
- you notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures
- you have kidney problems or arthritis – you may have high uric acid levels in your blood

Tell your doctor straight away if you notice any of the side effects above.

Other side effects

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:
- feeling tired
- changes in taste
- feeling unsteady or dizzy
- blurred vision
- swelling
- diarrhoea or constipation
- being or feeling sick
- difficulty swallowing
- abnormal sense of touch which feels like itching, tingling or burning sensation
- rash
- feeling short of breath
- cough or fever
- headache
- weight gain
- vomiting
- muscle pain or weakness
- pain including back pain, neck pain, musculoskeletal pain, pain in limbs
- stomach pain
- joint pain
- abnormal unpleasant sensation in your arms or legs
- loss of muscle coordination, being unsteady when walking
- disturbance in normal sleep patterns
- lung infection
- urinary tract infection
- cannot empty your bladder completely
- loss of appetite
- low blood pressure
- decreased number of a type of white blood cell called neutrophils
- lack of enough red blood cells (anaemia)
- increased blood levels of certain liver enzymes (AST/ALT)
- increased blood level of creatinine (something normally removed by the kidneys into the urine)

Common: may affect up to 1 in 10 people:
- mood disorders
- dehydration
- fluid around your lungs
- fainting
- skin being more sensitive to sunlight

Uncommon: may affect less than 1 in 100 people:
- changes in certain chemicals in your blood caused by fast breakdown of tumour cells – this may cause damage to organs, including the kidneys, heart, and liver.
- inflammation of the heart muscle

Tell your doctor, pharmacist or nurse if you notice any of the side effects above.

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 Rozlytrek

- 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 sachet after EXP. The expiry date refers to the last day of that month.
- Store the film-coated granules in the original package in order to protect from moisture.
- After addition to soft food, use within 20 minutes of preparation.
- Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rozlytrek contains

The active substance is entrectinib. Each sachet contains 50 mg of entrectinib.

The other ingredients are:
- *Granule core:* microcrystalline cellulose (E460), tartaric acid (E334), silica, colloidal anhydrous (E551), croscarmellose sodium (E468), sodium stearyl fumarate, mannitol (E421), magnesium stearate (E470b).
- *Film-coating:* titanium dioxide (E171), talc, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), polyethylene glycol 3350, polyvinyl alcohol (partially hydrolysed).

What Rozlytrek looks like and contents of the pack

Rozlytrek 50 mg film-coated granules are brownish orange or greyish orange granules and contained in a sachet. Each carton contains 42 sachets.

Marketing Authorisation Holder

Roche Registration GmbH
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Germany

Manufacturer

Roche Pharma AG
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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.

Other sources of information

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

7. Instructions for use

Rozlytrek
(entrectinib)
Film-coated granules for oral use

These Instructions for Use contain information on how to prepare, take and give Rozlytrek film-coated granules.

Before starting

- **Read these Instructions for Use** before taking or giving Rozlytrek film-coated granules.
- Ask your healthcare professional to show you how to use Rozlytrek before treatment is started.
- If you have any further questions on the use of Rozlytrek, ask your healthcare professional.

Important Information You Need to Know Before Preparing and Taking or Giving Rozlytrek

- Your healthcare professional should show you how to correctly prepare and take or give a daily dose of Rozlytrek film-coated granules. Always take or give Rozlytrek film-coated granules exactly as your healthcare professional tells you.
- **Do not** take or give Rozlytrek to someone else until you have been shown how to properly prepare and take or give Rozlytrek.
- Wash your hands before and after using Rozlytrek.
- Check the expiry date and the product for damage before use. **Do not** use if expired or damaged.
- If partial or total vomiting or spitting occurs immediately after giving an administered dose to the patient, consult the patient's doctor or pharmacist for the next steps.
- Give within 20 minutes of preparation.

Dosing Rozlytrek film-coated granules

Your healthcare professional will decide the right dose of Rozlytrek for you or your child.

- Each sachet contains 50 mg of Rozlytrek.
- **Do not** divide the content of a sachet of film-coated granules to prepare a smaller dose.
- Take Rozlytrek film-coated granules by mouth – sprinkled on soft food. The film-coated granules should be sprinkled on one or more spoonfuls of a soft food (such as applesauce, yogurt, or pudding) and taken within 20 minutes of preparation.
- **Do not** crush or chew the film-coated granules to avoid a bitter taste.
- Drink water after taking the medicine.
- Film-coated granules **must not** be used with a feeding tube – they could block the tubing.

Preparing to give Rozlytrek

Step 1. Wash your hands.

Step 2. To give a dose, you will need:

- the number of sachets needed for your prescribed dose
- a paper towel or clean plate
- a clean spoon
- soft food (for example, applesauce, yoghurt, or pudding)

Step 3. Count the number of sachets (50 mg each) you will need to give the prescribed dose (**Figure A**).

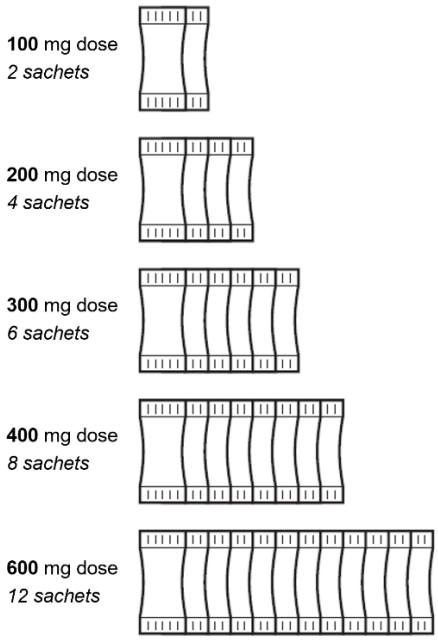


Figure A

Step 4. Tap the sachet to ensure the film-coated granules are on one side of the sachet.

Hold the side of the sachet where the film-coated granules are tapped and open the sachet by hand or with scissors (**Figure B**).

Note: Take care not to cut the film-coated granules with scissors.

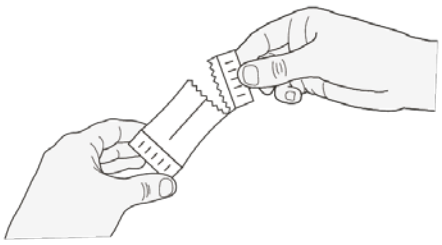


Figure B

Step 5. Get a spoonful of the soft food and hold the spoonful above a paper towel or clean plate.

Sprinkle the prescribed number of sachets on the spoonful of soft food (**Figure C**).

Tap the sachets to make sure all film-coated granules are sprinkled on the food.

Note: You may need to use more than 1 spoonful of soft food to give the prescribed dose.

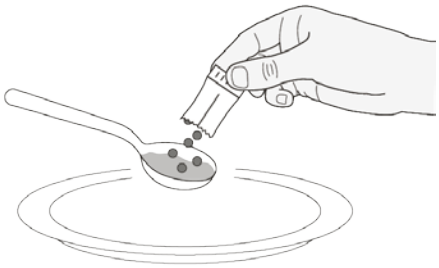
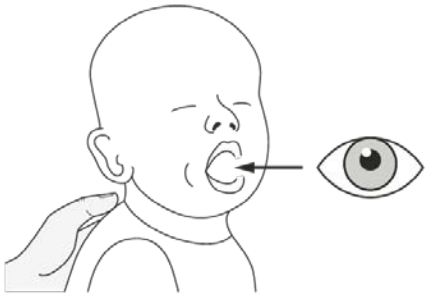


Figure C

Step 6. Take or give the spoonful of food with the film-coated granules sprinkled on it right away (**Figure D**). Take or give the spoonful of soft food within 20 minutes after sprinkling the film-coated granules on it if you cannot take or give it right way. **Note: Do not** crush or chew to avoid a bitter taste. If you leave the film-coated granules in the soft food for too long it may dissolve the coating and cause a bitter taste. If not taken **within 20 minutes**, throw away the soft food with the film-coated granules sprinkled on it and prepare a new dose (start at **Step 2**).	 **Figure D**
Step 7. Give patients some water after giving Rozlytrek to make sure all the film-coated granules are swallowed (**Figure E**). Patients can be given any meal or drink of their choice after giving Rozlytrek to improve the taste.	 **Figure E**
Step 8. Check the mouth to make sure that all of the film-coated granules were swallowed properly (**Figure F**). If not all of the film-coated granules were swallowed, give some water.	 **Figure F**
Step 9. Wash your hands and the items used to give Rozlytrek. Throw away the disposable items according to your local requirements.	

Storing Rozlytrek

- Store below 30°C and keep film-coated granules in the original package to protect from moisture.
- Throw away Rozlytrek if exposed to temperatures higher than 30°C and see section 5 of the leaflet.
- Always keep Rozlytrek out of sight and reach of children.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for entrectinib, the scientific conclusions of PRAC are as follows:

In view of available data on myocarditis from clinical trial(s), the literature, spontaneous reports including in nine cases a close temporal relationship and a positive de-challenge, the PRAC considers a causal relationship between entrectinib and myocarditis is at least a reasonable possibility. The PRAC concluded that the product information of products containing entrectinib should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for entrectinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing entrectinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.