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

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have not received a prior *NTRK* inhibitor

- who have no satisfactory treatment options (see sections 4.4 and 5.1).

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-positive solid tumours
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-positive non-small cell lung cancer
A validated assay is required for the selection of patients with *ROS1*-positive NSCLC. *ROS1*-positive status must be established prior to initiation of Rozlytrek therapy (see section 5.1).

Posology

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

Paediatric population
The recommended dose for paediatric patients 12 years of age and older is 300 mg/m^2 body surface area (BSA) entrectinib once daily (see Table 1).

Table 1: Recommended dosing for paediatric patients

Body surface area (BSA)	Once daily dose
1.11 m^2 to 1.50 m^2	400 mg
$\geq$ 1.51m^2	600 mg

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. If vomiting occurs immediately after taking a dose of Rozlytrek, patients may repeat that dose.

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 4) 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.

Table 2: Dose reduction schedule for adult patients

Dose reduction schedule	Dose level
Recommended dose	600 mg once daily
First dose reduction	400 mg once daily
Second dose reduction	200 mg once daily

Paediatric population
For paediatric patients 12 years of age and older, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability (see Table 3).

For some patients an intermittent dosing schedule is required to achieve the recommended reduced total weekly paediatric dose. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 3: Dose reduction schedule for paediatric patients

Action	**BSA of 1.11 m^2 to1.50 m^2** (once/day)	**BSA ≥ 1.51 m^2** (once/day)
Recommended dose	400 mg	600 mg
First dose reduction	300 mg	400 mg
Second dose reduction	200 mg, for 5 days each week*	200 mg
*5 days each week: Monday, Wednesday, Friday, Saturday, and Sunday		

Recommendations for Rozlytrek dose modifications for adult and paediatric patients in case of specific adverse reactions are provided in Table 4 (see sections 4.4 and 4.8).

Table 4: 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

Adverse reaction	Severity*	Dosage modification
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 adults and paediatric patients 12 years and older, should be avoided (see section 4.4).

For adults, if coadministration 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 hepatic impairment. Entrectinib has not been studied in patients with moderate and severe hepatic impairment (see section 5.2).

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 children below 12 years of age 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. The hard capsules should be swallowed whole and must not be opened or dissolved since the contents of the capsule are very bitter. Rozlytrek can be taken with or without food (see section 5.2) but should not be taken with grapefruit or grapefruit juice (see section 4.5).

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 4 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 21.9% (7/32) paediatric patients treated with Rozlytrek in clinical trials (see section 4.8). Bone fractures were reported in patients less than 12 years of age and were localised in the lower extremity (with a predilection for hip, femur and tibia). Bone fractures in paediatric patients generally occurred with minimal or no trauma. Three patients had more than one occurrence of a fracture and 3 patients had Rozlytrek treatment interrupted due to a fracture. All patients continued Rozlytrek treatment and all but one event of fracture recovered.

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 4 in section 4.2.

Congestive heart failure

Congestive heart failure (CHF) has been reported 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 upon treatment with diuretics 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 4 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 4 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. In adult and paediatric patients 12 years and older, 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 and grapefruit products 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) should be avoided.

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%.

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 drugs that raise gastric pH (e.g., H2 receptor antagonists or antacids).

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 the 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, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%). Permanent discontinuation due to an adverse reaction occurred in 4.4% of patients.

Tabulated list of adverse reactions

Tables 5 and 6 summarise the adverse drug reactions (ADRs) occurring in adult and paediatric patients treated with Rozlytrek in three clinical trials in adults (ALKA, STARTRK-1, STARTRK-2) and one clinical trial in pediatric patients (STARTRK-NG). The median duration of exposure was 5.5 months.

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 <1/1000), very rare (<1/10,000). Within each system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 5: Adverse drug reactions occurring in adult and paediatric patients treated with Rozlytrek in clinical trials (N=504)

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
Infections and infestations	Lung infection[1]	13.1	Very common	6.0*
	Urinary tract infection	12.7	Very common	2.6
Blood and lymphatic system disorders	Anaemia	28.2	Very common	9.7
	Neutropenia[2]	11.3	Very common	4.4
Metabolism and nutritional disorders	Weight increased	26.4	Very common	7.3
	Decreased appetite	11.9	Very common	0.2
	Hyperuricemia	9.1	Common	1.8
	Dehydration	7.9	Common	1.0
	Tumour lysis syndrome	0.2	Uncommon	0.2*
Nervous system disorders	Dysgeusia	42.3	Very common	0.4
	Dizziness[3]	39.7	Very common	1.2
	Dysaesthesia[4]	29.0	Very common	0.2
	Cognitive disorders[5]	24.2	Very common	4.4
	Headache	17.5	Very common	1.0
	Peripheral sensory neuropathy[6]	15.7	Very common	1.0
	Ataxia[7]	15.7	Very common	0.8
	Sleep disturbances[8]	13.5	Very common	0.4
	Mood disorders[9]	9.1	Common	0.6
	Syncope	4.6	Common	3.0
Eye disorders	Vision blurred[10]	11.9	Very common	0.4
Cardiac disorders	Congestive heart failure[11]	3.0	Common	2.2
	Electrocardiogram QTc prolonged	2.0	Common	0.6
Vascular disorders	Hypotension[12]	16.5	Very common	2.4
Respiratory, thoracic and mediastinal disorders	Dyspnoea	27.0	Very common	5.8*
	Cough	21.4	Very common	0.6
	Pleural effusion	6.9	Common	2.8
Gastrointestinal disorders	Constipation	42.9	Very common	0.4
	Diarrhoea	33.5	Very common	2.6
	Nausea	32.1	Very common	0.8
	Vomiting	23.2	Very common	1.2
	Abdominal pain	11.1	Very common	0.6
	Dysphagia	10.1	Very common	0.4
Hepatobiliary disorders	AST increased	17.5	Very common	3.6
	ALT increased	16.1	Very common	3.4
Skin and subcutaneous tissue disorders	Rash[13]	11.5	Very common	1.4
	Photosensitivity reaction	2.8	Common	0
Musculoskeletal and connective tissue disorders	Myalgia	19.6	Very common	0.6
	Arthralgia	19.0	Very common	0.6
	Muscular weakness	12.3	Very common	1.2
	Fractures[14]	6.2	Common	2.4
Renal and urinary disorders	Blood creatinine increased	25.4	Very common	0.6
	Urinary retention[15]	10.9	Very common	0.6

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade ≥3 (%)
General disorders and administration site conditions	Fatigue[16]	45.0	Very common	5.0
	Oedema[17]	37.3	Very common	1.4
	Pain[18]	24.4	Very common	1.6
	Pyrexia	20.0	Very common	0.8

* Grades 3 to 5, inclusive of fatal adverse reactions (including 2 reactions of pneumonia, 2 reactions of dyspnoea, 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, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'visual hallucination' and 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 (ankle fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, fracture, humerus fracture, jaw fracture, lower limb fracture, pathological fracture, rib fracture, spinal compression fracture, spinal fracture, stress fracture, tibia 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, localized oedema, oedema, oedema peripheral, peripheral swelling)
[18] Pain (back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity)

Table 6: Adverse drug reactions occurring in paediatric patients treated with Rozlytrek in clinical trials

System organ class	Frequency	Adolescents[1] (N=7)	All paediatric patients (N=32)
Infections and infestations	Very common		Urinary tract infection (18.8%), Lung infection (12.5%),
Blood and lymphatic system disorders	Very common	Anaemia (57.1%), Neutropenia (42.9%)	Anaemia (59.4%), Neutropenia (43.8%)
Metabolism and nutritional disorders	Very common	Weight increased (57.1%), Decreased appetite (14.3%)	Weight increased (50%), Decreased appetite (31.3%), Dehydration (25%)
Nervous system disorders	Very common	Dysgeusia (42.9%), Dysaesthesia (28.6%), Mood disorders (28.6%), Cognitive disorders (14.3%), Headache (14.3%), Syncope (14.3%), Peripheral sensory neuropathy (14.3%), Sleep disturbances (14.3%)	Headache (31.3%), Dysgeusia (21.9%), Mood disorders (28.1%), Ataxia (15.6%), Sleep disturbances (13.3%), Dizziness (12.5%), Peripheral sensory neuropathy (12.5%),
Eye disorders	Very common	Vision blurred (14.3%)	
Vascular disorders	Very common	Hypotension (14.3%)	Hypotension (18.8%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea (28.6%), Cough (28.6%)	Dyspnoea (18.8%), Cough (50%), Pleural effusion (12.5%)
Gastrointestinal disorders	Very common	Nausea (71.4%), Abdominal pain (28.6%), Constipation (28.6%)	Nausea (46.9%), Abdominal pain (28.1%), Constipation (43.8%), Vomiting (34.4%), Diarrhoea (37.5%)
Hepatobiliary disorders	Very common	AST increased (57.1%), ALT increased (42.9%)	AST increased (50%), ALT increased (50%)
Skin and subcutaneous tissue disorders	Very common		Rash (25%)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia (14.3%), Myalgia (14.3%)	Fractures (21.9%)
	Very common	Muscular weakness (28.6%)	Muscular weakness (18.8%)
Renal and urinary disorders	Very common	Blood creatinine increased (57.1%)	Blood creatinine increased (43.8%), Urinary retention (21.9%)
General disorders and administration site conditions	Very common	Fatigue (42.9%), Pain (57.1%), Pyrexia (57.1%)	Fatigue (43.8%), Pain (46.9%), Pyrexia (56.3%), Oedema (18.8%)

% refers to all grades
[1]Adolescents (12 to <18 years of age): Grade ≥3 reactions reported were neutropenia and headache

Description of selected adverse reactions

Cognitive disorders
A variety of cognitive symptoms was reported across clinical trials (section 4.4). These included events reported as cognitive disorders (6.3%), confusional state (7.3%), disturbance in attention (3.8%), memory impairment (4.2%), amnesia (2.8%), mental status changes (1.2%), hallucination (1.0%), delirium (0.8%), visual hallucination (0.4%) and mental disorder (0.2%). Grade 3 cognitve disorders were reported in 4.4% of patients. Adult patients who had CNS disease at baseline had a higher frequency of these adverse reactions (29.7%) compared to those without CNS disease (23.1%). The median time to onset for cognitive disorders was 0.92 months.

Fractures
Fractures were experienced by 5.3% (25/475) of adult patients and 21.8% (7/32) 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 2 paediatric patients, bilateral femoral neck fractures occurred. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). No patients discontinued Rozlytrek due to fractures.

In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area. The median time to fracture was 3.4 months (range: 0.26 months to 18.5 months) in adults. Rozlytrek was interrupted in 36.0% of adults that experienced fractures.

In paediatric patients all fractures occurred in patients with minimal or no trauma. A total of 11 adverse reactions of fractures were reported in the 7 paediatric patients. The median time to fracture was 4.3 months (range: 2.46 months to 7.39 months) in paediatric patients. Rozlytrek was interrupted in 42.9% (3/7) of paediatric patients that experienced fractures. Three of the fractures were Grade 2 and 4 fractures were Grade 3. Three of the Grade 3 fractures were serious. There were no reports of tumour involvement at the site of the fracture. All but one event of fracture recovered.

Ataxia
Ataxia (including events of ataxia, balance disorder, and gait disturbances) was reported in 15.7% of patients. The median time to onset for ataxia was 0.4 months (range: 0.03 months to 28.19 months) and the median duration was 0.7 months (range: 0.03 months to 11.99 months). The majority of patients (67.1%) recovered from ataxia. Ataxia related adverse reactions were observed more frequently in elderly patients (23.8%) compared to patients below 65 years of age (12.8%).

Syncope
Syncope was reported in 4.6% 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 504 patients who received entrectinib across clinical trials, 17 (4.0%) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of >60 ms after starting entrectinib, and 12 (2.8%) patients had a QTcF interval of ≥500 ms (section 4.4).

Peripheral sensory neuropathy
Peripheral sensory neuropathy was reported in 15.7% of patients. The median time to onset was 0.49 months (range 0.03 months to 20.93 months) and the median duration was 0.8 months (range: 0.07 months to 6.01 months). The majority of patients (55.7%) recovered from peripheral neuropathy.

Eye disorders
Eye disorders reported across clinical trials included vision blurred (8.5%), diplopia (2.6%), and visual impairment (1.6%). The median time to onset for eye disorders was 1.9 months (range: 0.03 months to 21.59 months). The median duration of eye disorders was 1 month (range 0.03 months to 14.49 months). The majority of patients (61.7%) recovered from the eye disorder adverse reactions.

Paediatric population

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

The safety of Rozlytrek in paediatric patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harbouring an *NTRK* gene fusion (ALKA, STARTRK-1 and STARTRK-2), and data from 32 paediatric patients (30 patients enrolled in STARTRK-NG, and 2 patients enrolled in STARTRK-2). Of these, 2 patients were less than 2 years old, 23 patients were 2 to 11 years old, 7 patients were 12 to 17 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 (28.1% vs. 3.4%), weight increased (21.9% vs 6.9%), headache (6.3% vs 0.6%) and bone fractures (12.5% vs 1.9%).

There are limited safety data in adolescents, however, the safety profile in adolescents is similar to the overall safety profile of Rozlytrek. Adverse reactions Grade ≥3 reported in adolescents were neutropenia and headache.

Elderly
Among the 504 patients who received entrectinib across clinical trials, 130 (25.8%) patients were 65 years or older and 34 (6.7%) were 75 years or older. The overall safety profile of entrectinib in the elderly patients is similar to the safety profile observed in patients younger than 65 years of age. Adverse reactions occurring more frequently in the elderly compared to patients less than 65 years old were dizziness (48.5% vs 36.6%), blood creatinine increased (31.5% vs 23.3%), and hypotension (21.5% vs 14.7%), ataxia (23.8% vs 12.8%).

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: L01XE56

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). 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 6 months of follow-up after the first dose of Rozlytrek 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 by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy was assessed in 74 adult patients with solid tumours with an *NTRK* gene fusion enrolled in these trials. The baseline demographic and disease characteristics were: 47.3% males, median age of 57 years (range 21 years to 83 years), 35% and 14.9% were older than 65 years and 75 years of age, respectively, 70% white Caucasian, 17.6% Asian, 5.5% Hispanic or Latino and 59.7% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (40.5%), 1 (45.9%), or 2 (13.5%). Most patients (97.3%) had metastatic disease [most common sites being lung (60.8%), lymph nodes (52.7%) and brain (25.7%)], 2.7% patients had locally advanced disease. 86.5% patients had received prior treatment for their cancer including surgery (82.4%), radiotherapy (63.5%), chemotherapy (81.1%) and 27% patients had no prior systemic therapies for metastatic disease. The most common cancers were sarcoma (21.6%), lung cancer (17.6%), salivary gland tumours (17.6%), thyroid cancer (9.5%) colorectal cancer (9.5%) and breast cancer (8.1%). Most patients (97.3%) had an *NTRK* gene fusion detected by next-generation sequencing (NGS) and 2.7% had a *NTRK* gene fusion detected by other nucleic acid-based tests. The overall median duration of follow-up from receipt of first dose was 14.2 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 7.

Table 7: Overall efficacy by BICR in adults with *NTRK*-fusion positive solid tumours

Efficacy endpoint	Rozlytrek N = 74
Primary endpoints *(BICR assessed; RECIST 1.1)*	
Objective Response Rate Number of Responses ORR% (95% CI) Complete Response, n (%) Partial Response, n (%)	 47/74 63.5% (51.5, 74.4) 5 (6.8%) 42 (56.8%)
Duration of Response* Number (%) of patients with events Median, months (95% CI) 6-month durable response % (95% CI) 9-month durable response % (95% CI) 12-month durable response % (95% CI)	 21/47 (44.7%) 12.9 (9.3, NE) 71% (58, 85) 65% (51,80) 55% (39,72)
NE = not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method. *Median and percentiles 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 8 below.

Table 8: Efficacy by tumour type, in adults with *NTRK* gene fusion-positive solid tumours

Tumour type	Patients (N = 74)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	16	9 (56.3)	(29.9, 80.3)	2.8, 15.1
Non-small cell lung cancer	13	9 (69.2)	(38.6, 90.9)	1.4*, 25.9*
Salivary (MASC)	13	12 (92.3)	(64.0, 99.8)	2.8, 22.1*
Breast cancer (secretory)	4	4 (100)	(39.8, 100)	5.5, 20.2*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Thyroid cancer	7	3 (42.9)	(9.9, 81.6)	5.6, 10.9*
Colorectal cancer	7	2 (28.6)	(3.7, 71)	7.9*, 15.2
Neuroendocrine cancers	4	2 (50.0)	(6.8, 93.2)	1.9*, 9.2*
Pancreatic cancer	3	2 (66.7)	(9.4, 99.2)	7.1, 12.9
Ovarian cancer	1	Non CR/PD	NA	26.0*
Endometrial carcinoma	1	PR	NA	26.0*
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	PR	NA	5.6*
Neuroblastoma	1	NE	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; 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 30 patients that had broad molecular characterisation before Rozlytrek treatment was 56.7% [37.4, 74.5]; of those, the ORR in 24 patients who had other genomic alterations in addition to *NTRK* gene fusion was 50% [29.1, 70.9] and the ORR in 6 patients without other genomic alterations was 83.3% [35.9, 99.6].

Intracranial response
A BICR assessment resulted in a subgroup of 16 adult patients with CNS metastases at baseline, including 8 patients with measureable CNS lesions. Intracranial (IC) response assessed by BICR according to RECIST v1.1 was reported in 5 out of these 8 patients (1 CR and 4 PR), for an ORR of 62.5% (95% CI: 24.5, 91.5) and DOR of NE (5.0, NE). Four of these 8 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek treatment.

Primary CNS tumour
Across the three trials, seven adult patients with CNS primary tumours were treated with Rozlytrek with a minimum of 6 months of follow-up. One out of the seven adult patients had an objective response assessed by BICR according to RANO.

Efficacy in paediatric patients
The efficacy of Rozlytrek in paediatric patients 12 years and older was based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harbouring a *NTRK* gene fusion (ALKA, STARTRK-1 and STARTRK-2), and efficacy and pharmacokinetic data in paediatric patients enrolled in STARTRK-NG. The best overall response as evaluated by BICR in 5 paediatric patients, (all patients were less than 12 years of age and had more than 6 months of follow up; 3 patients had solid tumours and 2 patients had primary CNS tumours) showed 2 complete responses (epithelioid glioblastoma and infantile fibrosarcoma) and 3 partial responses (high-grade glioma, infantile fibrosarcoma and metastatic melanoma). The responses in 4 out of 5 paediatric patients were ongoing at the time of data cut-off (see section 4.2).

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 9.

Table 9: 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)

NE = not estimable.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.
* Event-free rates based on Kaplan-Meier estimates
** Censored

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 measureable 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 of 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rozlytrek in one or more subsets of the paediatric population in the treatment with *NTRK* gene fusion-positive locally advanced or metastatic solid tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5), have been characterized in patients with *NTRK* gene fusion-positive solid tumours and *ROSI*-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.

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

Data obtained from population pharmacokinetic analyses show that in paediatric patients 12 years and older, a dose of 400 mg Rozlytrek once daily for BSA range 1.11 m^2 to 1.50 m^2, and a dose of 600 mg Rozlytrek once daily for BSA range ≥1.51 m^2 results in a similar systemic exposure attained in adults treated with 600 mg of Rozlytrek, once daily.

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

As elimination of entrectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite M5. Limited clinical data is available in patients with hepatic impairment.

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on mild hepatic impairment. The impact of moderate to severe hepatic impairment on the pharmacokinetics of entrectinib is unknown.

Effects of age, body weight, race and gender

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on age (4 years to 86 years), sex, race (Asian, Black and White) and body weight (32 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 CNS (convulsions, abnormal gait, tremors) at ≥0.2 times the human exposures by C_{max} at the recommended dose, skin (scabs/sores) and decreased RBC 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 neurobehavioral 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 ≥8mg/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
Lactose
Hypromellose
Crospovidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Capsule shell

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

Printing ink

Shellac
Propylene glycol
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

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

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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 the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The 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

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

Batch

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

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

Batch

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1460/002

13. BATCH NUMBER

Batch

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

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

Batch

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

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.

What is in this leaflet

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 and children 12 years of age and older with solid tumour (cancer) in various parts of the body that is caused by a change in the neurotrophic tyrosine receptor kinase (*NTRK*) gene, or
- adults with a type of lung cancer called ‘non-small cell lung cancer’ (NSCLC) that is caused by a change in the *ROS1* gene.

<u>*NTRK* gene fusion-positive solid tumour cancer</u>

It is used when:
- a test has shown that your cancer cells have a change in genes called ‘*NTRK*’ and has spread within the affected organ or to other organs in your body or if surgery to remove the cancer is likely to result in severe complications (see ‘How Rozlytrek works’ below), and
- you have not received treatment with medicines called *NTRK* inhibitors
- other treatments have not worked or are not suitable for you.

ROS1-positive non -small cell lung cancer (NSCLC)

It is used if your lung cancer:
- is '*ROS1*-positive' – this means that your cancer cells have a change in a gene called '*ROS1*' (see 'How Rozlytrek works' below),
- has spread to other parts of your body (metastatic), and
- you have not received treatment with medicines called ROS1 inhibitors.

How Rozlytrek works

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

Rozlytrek may slow down or stop the cancer growing. 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 experienced memory loss, confusion, hallucinations, or mental status changes
- you have a history of fractured bones, or conditions which may increase your risk of breaking bones, called 'osteoporosis' or 'osteopaenia'
- you take medication to lower the levels of uric acid in your blood
- you have heart failure (an inability for your heart to adequately pump blood to supply oxygen to the body) – signs can include cough, shortness of breath, and swelling in your legs or arms
- you have or had heart disorders or a heart conduction problem called 'prolonged QTc interval' – this is shown on an 'electro-cardiogram' (ECG), or low levels of electrolytes (potassium, magnesium, calcium or phosphorus) in your blood
- you have an inherited problem called 'galactose intolerance', 'congenital lactase deficiency' or 'glucose-galactose malabsorption'.

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:
- medicines for fungal infections (anti-fungals) – such as ketoconazole, itraconazole, voriconazole, posaconazole
- medicines to treat Acquired Immune Deficiency Syndrome (AIDS)/Human immunodeficiency virus (HIV) infection – such as ritonavir or saquinavir
- a herbal medicine for depression – St. John's Wort
- medicines to stop seizures or fits (anti-epileptics) – such as phenytoin, carbamazepine, or phenobarbital
- medicines for tuberculosis – such as rifampicin, rifabutin
- medicines to treat solid cancers and blood cancer – topotecan, lapatinib, mitoxantrone, apalutamide, methotrexate

- a medicine for inflammation of joints or joint autoimmune disease (rheumatoid arthritis) – methotrexate
- a medicine for migraine-type headaches – ergotamine
- a medicine for relief of severe pain – fentanyl
- a medicine for mental illness (psychoses) or involuntary movements and sounds, also called Tourette Syndrome – pimozide
- a medicine for irregular heart rate –quinidine
- medicines to prevent formation of blood clots – warfarin, dabigatran etexilate
- medicines for gastric reflux (heartburn) – cisapride, omeprazole
- medicines to reduce blood cholesterol – atorvastatin, pravastatin, rosuvastatin
- medicines to suppress your body's immune system, or prevent the body from rejecting an organ transplant – sirolimus, tacrolimus, cyclosporin,
- medicines for depression – paroxetine, fluvoxamine
- medicines to reduce blood sugar levels – repaglinide, tolbutamide
- medicines for high blood pressure – bosentan, felodipine, nifedipine, verapamil.

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 Rozlytrek. It may increase the amount of the medicine in your blood to a harmful level.

Pregnancy, breast-feeding and fertility

Women and contraception

You should not become 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 (pills or implanted hormonal contraceptives). You should use another reliable method of birth control such as a barrier method (e.g. condom) so you do not become pregnant while you are taking Rozlytrek and for 5 weeks after you stop treatment.

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

Men and contraception

Your female partner should not become 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 and using machines

Rozlytrek may affect your ability to drive or use machines. Rozlytrek may cause you to:
- have blurred vision
- feel dizzy
- pass out (lose consciousness)
- feel tired
- have changes in your mental status, feel confused or see things that are not there (hallucinations).

If this happens, you should not drive, use a bicycle, or operate heavy machinery until your symptoms resolve. Talk to your doctor or pharmacist about whether it is okay for you to drive 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

Adults

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

Children

- Rozlytrek can be used in children 12 years of age and older.
- Your doctor will work out the correct dose to use – this will depend on the height and weight of the child.

How to take

Take Rozlytrek by mouth – with or without food. Swallow each capsule whole. Do not open or dissolve the capsules since the contents of the capsule are very bitter.

If you vomit after taking Rozlytrek

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

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. Then 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 Rozlytrek 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 after having taken Rozlytrek. Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely:
- you have cough, shortness of breath, and swelling in your legs or arms (fluid retention). These can be signs of heart problems
- you feel confused, have changes in mood, memory problems or hallucinations (see things that are not there)
- you feel dizzy or light-headed, or feel your heart beating irregularly or fast, as this may be a sign of an abnormal heart rhythm
- you notice any joint pain, bone pain, deformities or changes in your ability to move
- you have kidney problems or arthritis, as this may be the result of high uric acid levels in your blood.

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
- constipation
- changes in taste
- feeling unsteady or dizzy
- swelling
- diarrhoea
- feeling sick
- abnormal sense of touch which feels like itching, tingling or burning sensation
- lack of enough red blood cells (anaemia)
- shortness of breath
- weight gain
- increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- pain including back pain, neck pain, musculoskeletal pain, pain in limbs
- vomiting
- cough
- fever
- muscle pain
- joint pain
- headache

- low blood pressure
- increased blood levels of certain liver enzymes (AST/ALT)
- 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
- muscle weakness
- decreased appetite
- blurred vision
- rash
- decreased number of a type of white blood cell called neutrophils
- stomach pain
- inability to empty your bladder completely
- difficulty swallowing.

Common: may affect up to 1 in 10 people:
- mood disorders
- dehydration
- fluid in your lungs
- fainting

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

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.
- This medicine does not require any special storage conditions
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help 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, lactose (see section 2 'Rozlytrek contains lactose'), hypromellose, crospovidone, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate.
- *Capsule shell:* hypromellose, 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

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.