# Rozlytrek®

**Entrectinib**
Hard capsules

## 1. NAME OF THE MEDICINAL PRODUCT

Rozlytrek 100 mg
Rozlytrek 200 mg

## 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

NTRK Gene Fusion-Positive Solid Tumors
Rozlytrek is indicated for the treatment of adult and pediatric patients older than 1 month of age with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,

- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or have no satisfactory alternative therapy.

ROS1-Positive Non-Small Cell Lung Cancer
Rozlytrek is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.

## 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 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.

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.

*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 |
|---|---|
| $\leq 0.42$ $m^2$ | 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 |
| $\geq 1.51$ $m^2$ | 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<br>• Resume at reduced dose |
| | Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4) | Permanently discontinue Rozlytrek |
| **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<br>• 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<br>• Resume at reduced dose |
| | Urgent intervention indicated for event (Grade 4) | Permanently discontinue Rozlytrek |
| **Hyperuricemia** | Symptomatic or Grade 4 | • Initiate urate-lowering medication<br>• Withhold Rozlytrek until improvement of signs or symptoms<br>• Resume Rozlytrek at same or reduced dose |
| **QT interval prolongation** | QTc greater than 500 ms | • Withhold Rozlytrek until QTc interval recovers to baseline<br>• Resume at same dose if factors that cause QT prolongation are identified and corrected<br>• 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<br>• Resume at same dose if resolution occurs within 4 weeks<br>• Permanently discontinue if adverse reaction does not resolve within 4 weeks |

| Adverse reaction | Severity* | Dosage modification |
|---|---|---|
| | | • 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<br>• Resume at reduced dose if resolution occurs within 4 weeks<br>• Permanently discontinue if adverse reaction does not resolve within 4 weeks<br>• Permanently discontinue for recurrent Grade 4 events |
| | ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 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<br>• Resume at the same dose or reduced dose, as clinically needed |
| **Vision Disorders** | Grade 2 or above | • Withhold Rozlytrek until improvement or stabilization.<br>• Resume at same dose or reduced dose, as clinically appropriate. |
| **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<br>• Resume at the same or reduced dose, if resolution occurs within 4 weeks<br>• Permanently discontinue if adverse reaction does not resolve within 4 weeks<br>• 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 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 a strong or moderate CYP3A inhibitor for 3 to 5 elimination half-lives, resume the Rozlytrek dose that was taken prior to initiating the CYP3A inhibitor (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 (total bilirubin ≤ 1.5 times ULN) hepatic impairment. Rozlytrek has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) and severe (total bilirubin > 3 times ULN) hepatic impairment.

*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 Patient Information 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

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 |
| **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 |

| System organ class | Adverse reaction | All grades (%) | Frequency category (all grades) | Grade ≥3 (%) |
|---|---|---|---|---|
| | 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%) |

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

| System organ class | Frequency | Infants and toddlers[1] (n=21) | Children[2] (n=55) | Adolescents[3] (n=15) | All paediatric patients (n=91) |
|---|---|---|---|---|---|
| **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%) |
| **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 | Blood creatinine increased (46.7%) | Blood creatinine increased (33%), |

| System organ class | Frequency | Infants and toddlers[1] (n=21) | Children[2] (n=55) | Adolescents[3] (n=15) | All paediatric patients (n=91) |
|---|---|---|---|---|---|
| | | | retention (18.2%) | | 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

### 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.

## 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*

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on mild hepatic impairment (total bilirubin ≤ 1.5 times ULN). The impact of moderate to severe hepatic impairment on the pharmacokinetics of entrectinib is unknown.

*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

Lactose anhydrous
Tartaric acid
Crospovidone
Hypromellose
Microcrystalline cellulose
Magnesium stearate
Colloidal silicon dioxide

Capsule shell

Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172 – 100 mg hard capsule)
FD&C Yellow #6 [Sunset yellow FCF (E110 – 200 mg hard capsule)]

Printing ink

Shellac
Propylene glycol
Strong ammonia solution
FD&C blue #2 aluminium lake

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 below 30°C.

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 Patient Information 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 Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

## 8. MARKETING AUTHORISATION NUMBER(S)

164-36-36185-00
164-37-36186-00

## 9. MANUFACTURER

F.Hoffmann-La Roche, Basel, Switzerland

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