

# Rozlytrek<sup>®</sup>



**Entrectinib**  
Hard capsules

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## 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

Rozlytrek is indicated for the treatment of adults 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.

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-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.

###### *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 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.

**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

Recommendations for Rozlytrek dose modifications for adult 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 patients**

<b>Adverse reaction</b>	<b>Severity*</b>	<b>Dosage modification</b>
<b>Congestive heart failure</b>	Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovered to less than or equal to Grade 1</li> <li>• Resume at reduced dose</li> </ul>
	Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	Permanently discontinue Rozlytrek
<b>Cognitive disorders</b>	Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline</li> <li>• Resume at same dose or reduced dose, as clinically needed</li> </ul>
	Severe changes limiting activities of daily living (Grade 3)	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline</li> <li>• Resume at reduced dose</li> </ul>
	Urgent intervention indicated for event (Grade 4)	Permanently discontinue Rozlytrek
<b>Hyperuricemia</b>	Symptomatic or Grade 4	<ul style="list-style-type: none"> <li>• Initiate urate-lowering medication</li> <li>• Withhold Rozlytrek until improvement of signs or symptoms</li> <li>• Resume Rozlytrek at same or reduced dose</li> </ul>
<b>QT interval prolongation</b>	QTc greater than 500 ms	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until QTc interval recovers to baseline</li> <li>• Resume at same dose if factors that cause QT prolongation are identified and corrected</li> <li>• Resume at reduced dose if other factors that cause QT prolongation are <u>not</u> identified</li> </ul>
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Permanently discontinue Rozlytrek
<b>Transaminase elevations</b>	Grade 3	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline</li> <li>• Resume at same dose if resolution occurs within 4 weeks</li> <li>• Permanently discontinue if adverse reaction does not resolve within 4 weeks</li> <li>• Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline</li> </ul>

<b>Adverse reaction</b>	<b>Severity*</b>	<b>Dosage modification</b>
		<ul style="list-style-type: none"> <li>• Resume at reduced dose if resolution occurs within 4 weeks</li> <li>• Permanently discontinue if adverse reaction does not resolve within 4 weeks</li> <li>• Permanently discontinue for recurrent Grade 4 events</li> </ul>
	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
<b>Anaemia or neutropenia</b>	Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until recovery to less than or equal to Grade 2</li> <li>• Resume at the same dose or reduced dose, as clinically needed</li> </ul>
<b>Vision Disorders</b>	Grade 2 or above	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until improvement or stabilization.</li> <li>• Resume at same dose or reduced dose, as clinically appropriate.</li> </ul>
<b>Other clinically relevant adverse reactions</b>	Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold Rozlytrek until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline</li> <li>• Resume at the same or reduced dose, if resolution occurs within 4 weeks</li> <li>• Permanently discontinue if adverse reaction does not resolve within 4 weeks</li> <li>• Permanently discontinue for recurrent Grade 4 events</li> </ul>
* 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 patients, should be avoided (see section 4.4).

For adults, if coadministration 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  $\geq 65$  years of age (see section 5.2).

### *Hepatic impairment*

No dose adjustment is recommended for patients with mild (total bilirubin  $\leq$  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*

Rozlytrek is not indicated for patients less than 18 years of age.

### Method of administration

Rozlytrek is for oral use. The hard capsules should be swallowed whole and must not be opened, crushed, chewed 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**

### 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 25.0% (19/76) 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. Thirteen paediatric patients had more than one occurrence of a fracture and 3 paediatric patients had Rozlytrek treatment interrupted due to a fracture. The majority of fracture events experienced by the paediatric patients resolved. Five 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 less than 5% 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 70% 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. In adult patients, 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<sub>inf</sub> by 77% and C<sub>max</sub> 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<sub>inf</sub> by 600% and C<sub>max</sub> 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<sub>max</sub> by 23%.

No dose adjustments are required when entrectinib is co-administered with PPIs or other drugs that raise gastric pH (e.g., H<sub>2</sub> 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 ( $\geq 20\%$ ) 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 ( $\geq 2\%$ ) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), pleural effusion (3.0%) and fractures (3.8%). Permanent discontinuation due to an adverse reaction occurred in 4.6% of patients.

### Tabulated list of adverse reactions

Table 4 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  $\geq 1/10$ , common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ), 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=504)**

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade $\geq 3$ (%)
<b>Infections and infestations</b>	Lung infection <sup>1</sup>	13.1	Very common	6.0*
	Urinary tract infection	12.7	Very common	2.6
<b>Blood and lymphatic system disorders</b>	Anaemia	28.2	Very common	9.7
	Neutropenia <sup>2</sup>	11.3	Very common	4.4
<b>Metabolism and nutritional disorders</b>	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*
<b>Nervous system disorders</b>	Dysgeusia	42.3	Very common	0.4
	Dizziness <sup>3</sup>	39.7	Very common	1.2
	Dysaesthesia <sup>4</sup>	29.0	Very common	0.2
	Cognitive disorders <sup>5</sup>	24.2	Very common	4.4
	Headache	17.5	Very common	1.0
	Peripheral sensory neuropathy <sup>6</sup>	15.7	Very common	1.0
	Ataxia <sup>7</sup>	15.7	Very common	0.8
	Sleep disturbances <sup>8</sup>	13.5	Very common	0.4
	Mood disorders <sup>9</sup>	9.1	Common	0.6
	Syncope	4.6	Common	3.0
<b>Eye disorders</b>	Vision blurred <sup>10</sup>	11.9	Very common	0.4
<b>Cardiac disorders</b>	Congestive heart failure <sup>11</sup>	3.0	Common	2.2
	Electrocardiogram QTc prolonged	2.0	Common	0.6
<b>Vascular disorders</b>	Hypotension <sup>12</sup>	16.5	Very common	2.4
<b>Respiratory, thoracic and mediastinal disorders</b>	Dyspnoea	27.0	Very common	5.8*
	Cough	21.4	Very common	0.6
	Pleural effusion	6.9	Common	2.8
<b>Gastrointestinal disorders</b>	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
<b>Hepatobiliary disorders</b>	AST increased	17.5	Very common	3.6
	ALT increased	16.1	Very common	3.4
<b>Skin and subcutaneous tissue disorders</b>	Rash <sup>13</sup>	11.5	Very common	1.4
	Photosensitivity reaction	2.8	Common	0
<b>Musculoskeletal and connective tissue disorders</b>	Myalgia	19.6	Very common	0.6
	Arthralgia	19.0	Very common	0.6
	Muscular weakness	12.3	Very common	1.2
	Fractures <sup>14,15</sup>	10.5	Very common	3.3
<b>Renal and urinary disorders</b>	Blood creatinine increased	25.4	Very common	0.6
	Urinary retention <sup>16</sup>	10.9	Very common	0.6

System organ class	Adverse reaction	All grades (%)	Frequency category (all grades)	Grade $\geq$ 3 (%)
<b>General disorders and administration site conditions</b>	Fatigue <sup>17</sup>	45.0	Very common	5.0
	Oedema <sup>18</sup>	37.3	Very common	1.4
	Pain <sup>19</sup>	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).

<sup>1</sup> Lung infection (bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection)

<sup>2</sup> Neutropenia (neutropenia, neutrophil count decreased)

<sup>3</sup> Dizziness (dizziness, vertigo, dizziness postural)

<sup>4</sup> Dysaesthesia (paresthesia, hyperesthesia, hypoesthesia, dysesthesia)

<sup>5</sup> Cognitive disorders (cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'visual hallucination' and mental disorder)

<sup>6</sup> Periphery sensory neuropathy (neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy)

<sup>7</sup> Ataxia (ataxia, balance disorder, gait disturbances)

<sup>8</sup> Sleep disturbances (hypersomnia, insomnia, sleep disorder, somnolence)

<sup>9</sup> Mood disorders (anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation)

<sup>10</sup> Vision blurred (diplopia, vision blurred, visual impairment)

<sup>11</sup> Congestive heart failure (acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary oedema)

<sup>12</sup> Hypotension (hypotension, orthostatic hypotension)

<sup>13</sup> Rash (rash, rash maculopapular, rash pruritic, rash erythematous, rash papular)

<sup>14</sup> 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)

<sup>15</sup> Data based on 798 safety evaluable patients from 02 Aug 2022 data cut-off

<sup>16</sup> Urinary retention (urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency)

<sup>17</sup> Fatigue (fatigue, asthenia)

<sup>18</sup> Oedema (face oedema, fluid retention, generalised oedema, localized oedema, oedema, oedema peripheral, peripheral swelling)

<sup>19</sup> Pain (back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity)

## 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 cognitive 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 9.0% (65/722) of adult patients and 25.0% (19/76) 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 8.1 months (range: 0.26 months to 45.34 months) in adults. Rozlytrek was interrupted in 26.2% of adults that experienced fractures. Seventeen adult patients had Rozlytrek treatment interrupted and none had treatment discontinued due to fractures.

A total of 47 fracture events were reported in the 19 paediatric patients. The median time to fracture was 4.3 months (range: 2.0 months to 28.65 months) in paediatric patients. Rozlytrek was interrupted

in 15.8% (3/19) of paediatric patients who experienced fractures. Nine of the fractures were Grade 2 and 8 of the fractures were Grade 3. Six of the Grade 3 fractures were serious. There were no reports of tumour involvement at the site of the fracture.

#### *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  $\geq$ 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.

#### 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.

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<sub>50</sub> 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 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 150 adult patients with solid tumours with an *NTRK* gene fusion enrolled in these trials. The baseline demographic and disease characteristics were: 49.3% males, median age of 59 years (range 21 years to 88 years), 38% and 12% were 65 years or older and 75 years or older respectively, 58.7% white Caucasian, 26% Asian, 5.4% Hispanic or Latino and 63% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (41.3%), 1 (50%), or 2 (8.7%). Most patients (95.3%) had metastatic disease [most common sites being lung (60.7%), lymph nodes (54.7%), bone (27.3%), liver (36%) and brain (20%)], 4.7% patients had locally advanced disease. 81.3% and 60.7% of patients had received surgery and radiotherapy for their cancer, respectively. 77.3% patients had received prior systemic therapy for their cancer including

chemotherapy (69.3%) and 34% patients had no prior systemic therapies for metastatic disease. The most common cancers were sarcoma (21.3%), lung cancer (20.7%), salivary gland tumours (17.3%), thyroid cancer (10.7%) colorectal cancer (7.3%) and breast cancer (6%). Most patients (87.3%) had an *NTRK* gene fusion detected by next-generation sequencing (NGS) and 12.7% had a *NTRK* gene fusion detected by other nucleic acid-based tests. The overall median duration of follow-up was 30.6 months.

Efficacy results from patients with *NTRK* gene fusion-positive solid tumours are summarised in Table 5.

**Table 5: Overall efficacy by BICR in adults with *NTRK* gene fusion-positive solid tumours**

Efficacy endpoint	Rozlytrek N = 150
<b>Primary endpoints (BICR assessed; RECIST 1.1)</b>	
Objective Response Rate	
Number of Responses	92/150
ORR% (95% CI)	61.3% (53.0, 69.2)
Complete Response, n (%)	25 (16.7%)
Partial Response, n (%)	67 (44.7%)
Duration of Response*	
Number (%) of patients with events	50/92 (54.3%)
Median, months (95% CI)	20 (13.2, 31.1)
6-month durable response % (95% CI)	83% (75, 91)
9-month durable response % (95% CI)	77% (68, 86)
12-month durable response % (95% CI)	66% (56, 76)
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 6 below.

**Table 6: Efficacy by tumour type, in adults with *NTRK* gene fusion-positive solid tumours**

Tumour type	Patients (N = 150)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	32	19 (59.4)	(40.6, 76.3)	2.8, 44.6*
Non-small cell lung cancer	31	20 (64.5)	(45.4, 80.8)	3.7, 58.8*
Salivary (MASC)	26	22 (84.6)	(65.1, 95.6)	2.8, 49.7*
Breast cancer (secretory)	6	5 (83.3)	(35.9, 99.6)	5.5, 53.4*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Breast cancer (NOS)	1	NE	NA	NA
Thyroid cancer	16	10 (62.5)	(35.4, 84.8)	5.6, 44.2*
Colorectal cancer	11	3 (27.3)	(6.0, 61.0)	1.9*, 20.0
Neuroendocrine cancers	5	2 (40.0)	(5.3, 85.3)	11.1, 31.1
Head and neck	5	3 (60.0)	(14.7, 94.7)	4.0, 32.6*
Pancreatic cancer	4	3 (75.0)	(19.4, 99.4)	7.1, 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
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; 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 78 patients that had broad molecular characterisation before Rozlytrek treatment was 53.8% [42.2, 65.2]; of those, the ORR in 61 patients who had other genomic alterations in addition to *NTRK* gene fusion was 47.5% [34.6, 60.7] and the ORR in 17 patients without other genomic alterations was 76.5% [50.1, 93.2].

#### *Intracranial response*

A BICR assessment resulted in a subgroup of 22 adult patients with CNS metastases at baseline, including 13 patients with measurable CNS lesions. Intracranial (IC) response assessed by BICR according to RECIST v1.1 was reported in 9 out of these 13 patients (3 CR and 6 PR), for an ORR of 69.2% (95% CI: 38.6, 90.9) and median DOR of 17.2 (7.4, NE). Five of these 13 patients had received intracranial radiotherapy to the brain within 2 months prior to starting Rozlytrek treatment.

#### *Primary CNS tumour*

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

#### *Efficacy in paediatric patients*

Rozlytrek is not indicated for patients less than 18 years of age.

### 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  $\leq 2$ , measurable disease per RECIST v1.1,  $\geq 6$  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 7.

**Table 7: Overall efficacy by BICR in patients with *ROS1*-positive NSCLC**

Efficacy endpoint	Rozlytrek N = 161
<b>Primary endpoints (BICR-assessed, RECIST 1.1)</b>	
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)
<b>Secondary endpoints (BICR-assessed, RECIST 1.1)</b>	
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  $\geq 12$  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  $\geq 6$  months,  $\geq 9$  months and  $\geq 12$  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 characterized 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.

### 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 ( $V_z/F$ ) 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 ( $\pm 0.381$ ) and 2.01 ( $\pm 0.437$ ) for M5. Following administration of a single dose of [ $^{14}\text{C}$ ]-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  $C_{\text{max}}$ , and approximately half of total radioactivity  $\text{AUC}_{\text{inf}}$ .

Population PK analysis estimated apparent clearance  $\text{CL}/F$  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<sup>2</sup> to 1.50 m<sup>2</sup>, and a dose of 600 mg Rozlytrek once daily for BSA range  $\geq 1.51$  m<sup>2</sup> 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

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on mild hepatic impairment (total bilirubin  $\leq 1.5$  times ULN). 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  $\geq 0.2$  times the human exposures by  $C_{\max}$  at the recommended dose, skin (scabs/sores) and decreased RBC parameters at  $\geq 0.1$  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  $\geq 0.6$  times the human exposure by AUC at the recommended dose. In dogs, diarrhoea at  $\geq 0.1$  times the human exposure by AUC at the recommended dose and prolongations of QT/QTc interval at  $\geq 0.1$  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  $\geq 4$  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  $\geq 8$  mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose), and decreased femur length (at  $\geq 16$  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.

### **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.

### **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 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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