

Date: 17 December 2020

Swissmedic, Swiss Agency for Therapeutic Products

## ***Swiss Public Assessment Report***

### **ROZLYTREK**

**International non-proprietary name:** entrectinib

**Pharmaceutical form:** hard capsules

**Dosage strength:** 100 mg, 200 mg

**Route(s) of administration:** oral

**Marketing Authorisation Holder:** Roche Pharma (Schweiz) AG

**Marketing Authorisation No.:** 67280

**Decision and Decision date:** approved on 05 November 2020

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

**About Swissmedic**

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

**About the Swiss Public Assessment Report (SwissPAR)**

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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## 1 Terms, Definitions, Abbreviations

|                      |  |
|----------------------|--|
| ADA                  | Anti-drug antibody   |
| ADME                 | Absorption, Distribution, Metabolism, Elimination                              |
| AE                   | Adverse event  |
| ALK                  | Anaplastic lymphoma kinase   |
| ALT                  | Alanine aminotransferase   |
| API                  | Active pharmaceutical ingredient   |
| AST                  | Aspartate aminotransferase   |
| ATC                  | Anatomical Therapeutic Chemical Classification System                          |
| AUC                  | Area under the plasma concentration-time curve                                 |
| AUC <sub>0-24h</sub> | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| CI                   | Confidence interval  |
| C <sub>max</sub>     | Maximum observed plasma/serum concentration of drug                            |
| CNS                  | Central nervous system   |
| CYP                  | Cytochrome P450  |
| DLT                  | Dose limiting toxicity   |
| DOR                  | Duration of response   |
| ERA                  | Environmental Risk Assessment  |
| ETV6                 | ETS Variant 6  |
| GC                   | Gas Chromatography   |
| GLP                  | Good Laboratory Practice   |
| HDPE                 | High-density polyethylene  |
| HPLC                 | High Performance Liquid Chromatography   |
| IC                   | Intracranial   |
| IC <sub>50</sub>     | Half maximal inhibitory concentration  |
| ICH                  | International Council for Harmonisation  |
| Ig                   | Immunoglobulin   |
| IL                   | Interleukin  |
| INN                  | International Nonproprietary Name  |
| IR                   | Infrared   |
| LoQ                  | List of Questions  |
| MAH                  | Marketing Authorisation Holder   |
| MASC                 | Mammary analogue secretory carcinoma   |
| Max                  | Maximum  |
| Min                  | Minimum  |
| MRHD                 | Maximum recommended human dose   |
| N/A                  | Not applicable   |
| NO(A)EL              | No Observed (Adverse) Effect Level   |
| NSCLC                | Non-small cell lung cancer   |
| NTRK                 | Neurotrophic tropomyosin (or tyrosine) receptor kinase                         |
| ORR                  | Objective response rate  |
| OS                   | Overall survival   |
| PD                   | Pharmacodynamics   |
| PFS                  | Progression-free survival  |
| PIP                  | Paediatric Investigation Plan (EMA)  |
| PK                   | Pharmacokinetics   |
| PopPK                | Population PK  |
| PND                  | Postnatal day  |
| PR                   | Partial remission  |
| PSP                  | Pediatric Study Plan (US-FDA)  |
| PT                   | Preferred terms  |
| RBC                  | Red blood cell   |
| RMP                  | Risk Management Plan   |

|          |  |
|----------|--|
| ROS      | Receptor tyrosine kinase   |
| SAE      | Serious adverse event  |
| SOC      | System organ class   |
| SwissPAR | Swiss Public Assessment Report   |
| TEAE     | Treatment emergent adverse event   |
| TPA      | Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO      | Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)                 |
| TRK      | Tropomyosin (or tyrosine) receptor kinase  |
| UV       | Ultraviolet  |
| XRPD     | X-ray powder diffraction   |

## 2 Background Information on the Procedure

### 2.1 Applicant's Request(s)

#### **New Active Substance status**

The applicant requested the status of a new active entity for the active substance entrectinib of the medicinal product mentioned above.

#### **Orphan drug status**

The applicant requested Orphan Drug Status in accordance with Article 4<sup>a</sup> <sup>decies</sup> no. 2 of the TPA. The Orphan Status was granted on 26 March 2019.

#### **Temporary authorisation for human medical products**

The applicant requested a temporary authorisation in accordance with Art. 9a TPA. .

### 2.2 Indication and Dosage

#### 2.2.1 Requested Indication

##### *Solid tumours*

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies.

##### *Non-small cell lung cancer (NSCLC)*

Rozlytrek as monotherapy is indicated for the treatment of patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC).

#### 2.2.2 Approved Indication

##### *Solid tumours*

Rozlytrek is indicated as monotherapy for the treatment of adult and paediatric patients aged  $\geq 12$  with solid tumours:

- who have a tumour with NTRK (neurotrophic tyrosine receptor kinase) gene fusion without a known NTRK resistance mutation and
- whose tumour is metastatic or in whom surgical resection will probably cause severe morbidity and
- for whom no satisfactory therapeutic options are available or in whom progression has occurred after prior therapy.

Rozlytrek is not indicated for the treatment of lymphomas and primary CNS tumours (see "Warnings and precautions" and "Properties/Effects").

##### *Non-small cell lung cancer (NSCLC)*

Rozlytrek is indicated as monotherapy for the treatment of adult patients with ROS1-positive, metastatic NSCLC (see "Properties/Effects").

#### 2.2.3 Requested Dosage

##### *For Adult Patients*

The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily.

##### *For Paediatric Patients*

The recommended dose of Rozlytrek for paediatric patients who have the ability to swallow capsules is 300 mg/m<sup>2</sup> orally, once daily.

**2.2.4 Approved Dosage**

(see appendix)

**2.3 Regulatory History (Milestones)**

|                               |                   |
|-------------------------------|-------------------|
| Application                   | 20 May 2019       |
| Formal control completed      | 14 June 2019      |
| List of Questions (LoQ)       | 8 October 2019    |
| Answers to LoQ                | 5 April 2020      |
| Predecision                   | 30 June 2020      |
| Answers to Predecision        | 30 July 2020      |
| Second Predecision            | 28 September 2020 |
| Answers to second Predecision | 16 October 2020   |
| Final Decision                | 05 November 2020  |
| Decision                      | approval          |

### 3 Medical Context

Entrectinib is an inhibitor of 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; encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK).

#### NTRK Fusion Protein-Positive Solid Tumours

TRKs serve as signal receptors for neurotrophins and play a pivotal role in the physiology, development, and function of the peripheral and central nervous system. Activated kinases promote cell proliferation, differentiation, and survival by triggering downstream intracellular signal transduction pathways. NTRK gene fusions encoding the receptor tyrosine kinases promote tumorigenesis and are infrequent but recurrent events observed in various types of congenital and acquired cancers. The estimated prevalence varies among histological subtypes and fusion partners, ranging from approximately 0.2% in patients with NSCLC up to 90-100% in patients with congenital fibrosarcoma and mammary analogue secretory carcinoma (MASC) of the salivary gland.

Treatment options available for patients with advanced NTRK fusion-positive tumours are those used to treat patients irrespective of the presence of targetable oncogenic drivers. The prognosis for these patients is poor, particularly when there is CNS involvement.

#### ROS1 Fusion-Positive NSCLC

Oncogenic fusion kinases resulting from chromosomal rearrangements involving ROS1 have been identified and have become an established therapeutic target in lung cancer. They are present in approximately 1-2% of NSCLCs and define a distinct molecular subgroup. The exact mechanism of ROS1 kinase activation in the fusion proteins has not been established.

Approved treatment options for patients with ROS1-positive NSCLC in Switzerland include tyrosine kinase inhibitors or platinum-based chemotherapy.

### 4 Quality Aspects

#### 4.1 Drug Substance

INN: Entrectinib

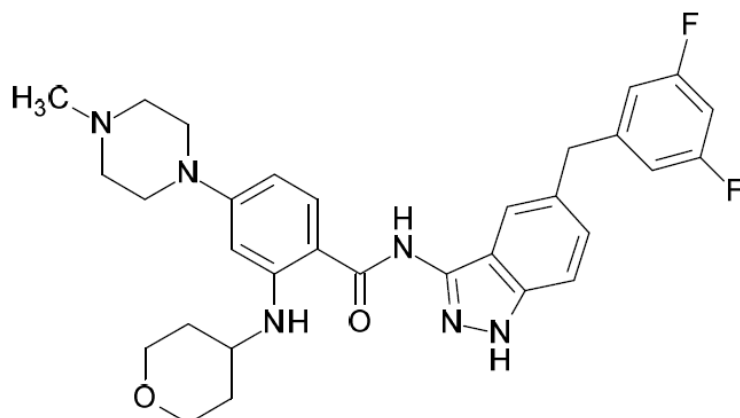
Chemical name:

*N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide

Molecular formula: C<sub>31</sub>H<sub>34</sub>F<sub>2</sub>N<sub>6</sub>O<sub>2</sub>

Molecular mass: 560.64 g/mol

Molecular structure:





Physico-chemical properties: Entrectinib is a white to off-white or pale pink powder or powder with lumps. Entrectinib shows a pH-dependent solubility in aqueous media. Entrectinib exhibits polymorphism. Form A was initially selected for development and for use in clinical studies. Form C has since been developed for use in the commercial product. Form C is the thermodynamically stable form.

Synthesis: Entrectinib drug substance is prepared from two starting materials in four synthesis steps (Steps 1–4) followed by final recrystallization of the drug substance. The synthesis of the drug substance has been adequately described and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

Specification: The active substance specifications include tests for appearance, identification (IR, HPLC, XRPD), water content, residue on ignition, residual solvents (GC), assay (HPLC) and impurities (HPLC). The specifications conform to the requirements outlined in ICH guideline Q6A and are considered appropriate in order to ensure a consistent drug substance quality.

Stability: The packaged entrectinib is placed in a suitable drum. Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type as described above.

## 4.2 Drug Product

Description and composition:

Entrectinib hard capsule, 100 mg, is a size 2, 2-piece capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body.

Entrectinib hard capsule, 200 mg, is a size 0, 2-piece capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body.

Capsule contents are tartaric acid, lactose, hypromellose, crospovidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Capsule shell is consisting of hypromellose, titanium dioxide (E171), yellow iron oxide (E172 – 100 mg hard capsule) and sunset yellow FCF (E110 – 200 mg hard capsule).

The printing ink consists of shellac, propylene glycol and indigo carmine aluminium lake (E132).

Pharmaceutical development: To attenuate the pH-dependent solubility of entrectinib, tartaric acid is added to the formulation. The commercial formulation is an immediate-release hard capsule and is manufactured with standard excipients using conventional equipment and manufacturing processes.

Manufacture: The manufacturing process is described with a sufficient level of detail. In order to achieve a consistent quality of the hard capsules, appropriate in-process controls are applied.

Satisfactory manufacturing process validation has been performed.

Specification: Adequate specifications at release and at shelf-life have been described, including the following parameters: appearance, identity of entrectinib (HPLC, UV), degradation products (HPLC), microbial quality, assay of entrectinib (HPLC), dissolution (HPLC), uniformity of dosage units (Ph Eur. mass/weight variation) and water content. Analytical methods have been described in detail and have been validated according to ICH requirements.

Container-Closure System: The primary packaging for entrectinib hard capsules consists of HDPE bottles containing 30 hard capsules with a child-resistant, tamper-evident closure and silica gel desiccant integrated in the cap.

Stability: Drug product stability studies were conducted with six primary stability batches for each dosage strength according to the recommendations of the relevant ICH guidelines. Based on these

studies, a shelf-life of 24 months was established for entrectinib hard capsules. The storage recommendation is “Do not store above 30°C”.

### **4.3 Quality Conclusions**

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

## 5 Nonclinical Aspects

The applicant provided a comprehensive nonclinical study package based on the requirements outlined in ICH S9. Pivotal studies for safety assessment of entrectinib were conducted in compliance with GLP.

### *Pharmacology*

In biochemical assays, entrectinib inhibited the activity of tropomyosin receptor kinase A (TRKA), TRKB, TRKC, receptor tyrosine kinase ROS1, and anaplastic lymphoma kinase (ALK), with  $IC_{50}$  values in the low nanomolar range ( $\leq 19$  nM). Both entrectinib and its major human metabolite M5 demonstrated potent *in vitro* antiproliferative activity ( $IC_{50} < 1$   $\mu$ M) against human cancer cell lines of various histological origins and with NTRK, ROS1 or ALK gene fusions or amplifications as oncogenic drivers. Entrectinib also inhibited the proliferation of mouse Ba/F3 cells that showed IL-3-independent growth due to the expression of different NTRK fusion genes or the ETV6-ROS1 fusion. The *in vitro* antiproliferative activity of entrectinib correlated well with the *in vivo* anti-tumour activity in different mouse xenograft models with tumour cells bearing activating NTRK or ROS1 gene fusions. Most of the *in vivo* studies were conducted with tumours implanted subcutaneously. In addition, studies with intracranial implants of tumour cells bearing NTRK1 gene fusions also demonstrated the efficacy of entrectinib. Mice generally tolerated doses up to 60 mg/kg/day, a dose with significant anti-tumour activity, without any major effects on body weight or mortality.

The mechanism of action of entrectinib was shown both *in vitro* and in tumour tissue *ex vivo*. Treatment with entrectinib led to inhibition of phosphorylation of TRK protein kinases, ROS1, and downstream effector molecules. This blockage of signal transduction was associated with cell cycle arrest and apoptosis. The effects observed in tumour tissue correlated with plasma concentration vs. time profiles of entrectinib and metabolite M5.

In a selectivity screening assay with a panel of 293 kinases, entrectinib at 100 nM (approx. 3-fold the clinical  $C_{max,free}$ ) inhibited 25 kinases other than its primary targets by  $>40\%$ . Entrectinib and metabolite M5 at 10  $\mu$ M also exhibited significant ( $>50\%$ ) inhibition of a number of receptors, ion channels, and enzymes in radioligand binding screening assays. The results of these secondary pharmacodynamics studies indicate that effects due to off-target interactions of entrectinib and/or M5 are possible. Such interactions may be the reason for some of the adverse effects observed in the nonclinical and clinical studies.

Based on results of *in vitro* and *in vivo* safety pharmacology and toxicology studies, entrectinib has a potential for QT prolongation. Clinical studies also identified observed QT prolongation as an important risk. At clinically relevant exposures, entrectinib did not cause any relevant effects on respiratory parameters in rats. Various central nervous system (CNS) effects were observed in the toxicology studies, as in the clinical studies (see *Toxicology*).

### *Pharmacokinetics*

The pharmacokinetics (PK) of entrectinib was characterised in mice, rats, and dogs. Following single oral (gavage) administration of 10 mg/kg, absorption was relatively fast ( $T_{max}$  2-3 hours), and plasma elimination occurred with terminal half-lives ( $t_{1/2}$ ) of 3-4 hours in rodents and approx. 15 hours in dogs. Longer  $t_{1/2}$  values for rats (10-60 hours) were reported in studies with higher doses ( $\geq 100$  mg/kg/day) and repeated dose administration. The volume of distribution data indicated extravascular distribution. The PK parameters in rats and dogs are comparable with those in humans. Entrectinib exposure was generally about 2-fold higher in female rats compared to male rats; in dogs, there was no sex-related effect on exposure. Accumulation with repeated dosing was low in rats. In dogs, some accumulation occurred (to 5.4-fold). In juvenile rats, systemic exposure at postnatal day (PND) 97 was about 2- to 3-fold lower than on PND 7 following oral administration of entrectinib.

The plasma protein binding of entrectinib and metabolite M5 was high ( $>99\%$ ) across species (mouse, rat, dog, and human). Based on results from *in vivo* and *in vitro* studies, there is substantial distribution of entrectinib into red blood cells (RBC) in rats, dogs, and humans (blood/plasma AUC

ratios up to 2.7 in both preclinical species). This may be related to the observed decreases in RBC counts (see *Toxicology*).

Studies with oral administration of [<sup>14</sup>C]-labelled entrectinib to albino and pigmented rats showed wide tissue distribution, with C<sub>max</sub> generally around 3 to 8 hours. There was reversible association with melanin-containing tissues, such as pigmented skin and uveal tract. Entrectinib and metabolite M5 distribute to brain in both rats and dogs (brain/plasma concentrations for entrectinib 0.5-0.6 in rats and 1.4-2.1 in dogs).

Metabolism of entrectinib *in vitro* in hepatocytes revealed no major species-specific differences in metabolite formation, and there was no human-specific metabolite. *In vivo* in rats and dogs, the main circulating metabolites were M12 (glucuronide) and M5 (demethylation product), respectively. The pharmacologically active metabolite M5 was only a minor plasma metabolite in rats (<1% of AUC), but was present at about 27% of AUC in dogs. Metabolites M5 and M12 are major plasma metabolites in humans and considered adequately characterised by the toxicology studies with entrectinib in dogs and rats. The third major human metabolite, M11, is a glucuronide and as such deemed less active. Further characterisation of this metabolite is deemed not necessary and is also not required according to ICH S9. *In vitro*, CYP3A4 and UGT1A4 were identified as main enzymes for metabolism of entrectinib in humans.

Excretion of [<sup>14</sup>C]-entrectinib-related radioactivity following oral administration was similar in rats and dogs. Most of the radioactivity was recovered in faeces (≥ 85%), as in humans (83%).

### *Toxicology*

Toxicology studies with entrectinib were conducted in rats and dogs up to a treatment duration of 13 weeks. Since the data on PK profile, metabolism, and excretion in these species are comparable to the data for humans, the species selection is deemed adequate. The protein sequences of TRK isoforms, ROS1, and ALK are conserved across species. Animals were treated via the oral route, which is the clinical administration route.

Entrectinib induced similar effects in rats and dogs. Most relevant in-life findings were decreases in body weight gain or body weight loss, CNS findings (e.g. incoordination), skin lesions (dose-limiting toxicity in rats), gastrointestinal effects in dogs, decreased RBC mass, and increases in AST, ALT, and/or bilirubin. Histological changes were mostly observed in skin, spleen, liver, rectum (dogs only), and salivary gland (rats only). Extramedullary haematopoiesis and congestion in spleen correlate with the finding of decreased RBC and might be related to the distribution of entrectinib into these cells. Most of the adverse findings in the toxicology studies were observed at clinically relevant systemic exposures. The lack of safety margins is acceptable given the proposed indication. The findings in the general toxicity studies correlate with findings in the clinical trials, such as CNS and gastrointestinal side effects, skin rash, anaemia, increased transaminases, and dysphagia.

Entrectinib was tested negative for genotoxicity in the bacterial reverse mutation assay. In the *in vitro* micronucleus assay in human peripheral blood lymphocytes, entrectinib induced a significant increase in the percentage of micronucleated cells via an aneugenic mechanism. *In vivo* in rats treated with up to 2000 mg/kg/day for 3 days, there were no statistically significant increases in DNA damage in liver cells (comet assay) or the numbers of micronucleated polychromatic erythrocytes in bone marrow. The entrectinib and metabolite M5 plasma exposures (AUC) were approx. 3.8-fold and 1.3-fold the clinical exposure. The risk for genotoxic effects in patients is therefore considered low. As a precautionary measure, female patients and male patients with female partners of child-bearing potential should use contraceptive measures. This is described adequately in the information for healthcare professionals.

Carcinogenicity studies with entrectinib were not conducted and are not required (ICH S9).

Dedicated studies to assess potential effects of entrectinib on fertility were not conducted, in accordance with ICH S9. Based on the results of the repeat-dose toxicity studies, significant effects on fertility/reproductive function are considered unlikely.

Administration of 200 mg/kg/day of entrectinib to pregnant rats led to various external, visceral, and skeletal malformations. Plasma exposure of the animals was approx. 1.4-fold the clinical exposure at

the maximum recommended human dose (MRHD; 600 mg). At  $\geq 50$  mg/kg/day, decreased foetal weights and increased incidences of skeletal variations were observed. Due to the lack of safety margins for developmental toxicity, entrectinib should not be used during pregnancy, and women of child-bearing potential should use adequate contraception. Transfer of entrectinib and/or metabolites to milk was not studied but is considered likely. Breast-feeding should be discontinued during treatment with entrectinib. The recommendations in the information for healthcare professionals with regard to use during pregnancy and lactation are considered appropriate.

Juvenile toxicity of entrectinib was assessed in a 13-week study in rats with treatment up to 16 mg/kg/day from PND 7 to PND 97, corresponding to neonatal to young adult stage. The 16 mg/kg/day dose was not tolerated (mortality and clinical signs of systemic toxicity); exposure at this dose level was about 0.3-fold the clinical exposure at MHRD. Entrectinib-related findings at all dose levels ( $\geq 4$  mg/kg/day) included clinical signs (e.g. piloerection and ptosis), decreased food consumption and weight gain, delayed sexual maturation, as well as clinical and anatomical pathology changes similar to those observed in adult animals. Additional findings at  $\geq 8$  mg/kg/day were convulsions, decreased grip strength, and effects on learning and memory (water maze test). Animals at 16 mg/kg/day also had decreased femur lengths. Given the lack of a safety margin to the clinical exposure and also taking into account the physiological role of TRK proteins, there is a risk of effects on development and cognitive function due to the use of entrectinib by paediatric patients. Cognitive disorders are classified as an important identified risk, and there is an adequate warning note in the information for healthcare professionals.

Entrectinib demonstrated phototoxic potential in the *in vitro* neutral red uptake assay in mouse 3T3 fibroblasts. In an *in vivo* phototoxicity study in pigmented female rats with 3-day oral administration of up to 200 mg/kg/day, there were no findings indicative of a phototoxic effect on skin or eye. However, there were corneal findings in entrectinib-treated animals with and without UV radiation. Such effects were not observed in the general toxicity studies but they correlate well with reports of blurred vision in the clinical trials.

All impurities are controlled at or below the respective ICH Q3A/Q3B qualification thresholds. There are no new excipients.

The description and evaluation of the findings in the nonclinical studies in the RMP are considered adequate.

Based on the ERA, a significant risk to the environment by the placing of entrectinib on the market is considered unlikely.

### *Nonclinical Conclusions*

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Rozlytrek with the new active substance entrectinib in the proposed indication. The pharmacological properties, as well as the pharmacokinetic and toxicity profiles of entrectinib and its major human metabolite M5, were adequately characterised in preclinical species. All nonclinical data that are relevant for safety are included in the information for healthcare professionals. The findings in the toxicology studies correlated with findings in clinical studies.

## **6 Clinical and Clinical Pharmacology Aspects**

### **6.1 Clinical Pharmacology**

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on a previous regulatory decision by FDA. The available assessment reports and approved product information from the FDA were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology aspects, see section 8.1 of this report.

### **6.2 Dose Finding and Dose Recommendation**

Dose finding in adult patients was evaluated based on results of the phase 1 studies ALKA and STARTRK-1. No dose limiting toxicity (DLT) occurred in ALKA. In STARTRK-1, three patients experienced one DLT each at a flat dose of 800 mg. Therefore, 600 mg once daily was chosen as the recommended phase 2 dose (RP2D) and maximum tolerated dose of entrectinib.

Dose finding in paediatric patients was evaluated based on the results of STARTRK-NG, where 4 of 15 patients evaluable for DLTs experienced a DLT (1/7 at dose level 550 mg/m<sup>2</sup>/d and 3/3 at dose level 750 mg/m<sup>2</sup>/d) of G2 creatinine increase, G2 dysgeusia and G3 pulmonary oedema. Therefore, 550 mg/m<sup>2</sup> (F1 formulation) was declared the RP2D. Based on a population approach, the paediatric dose of the formulation to be marketed, F06, was predicted to be 300 mg/m<sup>2</sup>/d.

### **6.3 Efficacy**

Efficacy data from three ongoing phase 1/2 studies in adult patients (STARTRK-1, STARTRK-2, ALKA) have been pooled to analyze patients with NTRK-positive solid tumours and ROS1-positive NSCLC, respectively. STARTRK-1 was a single-arm, open-label, non-randomized multicentre phase 1 study of entrectinib in adult patients with locally advanced or metastatic solid tumours confirmed to be positive for NTRK1/2/3, ROS1, or ALK molecular alterations. STARTRK-2 was a single-arm, open-label, non-randomized multicentre phase 2 basket study with the same target population as STARTRK-1. ALKA was a phase 1 dose escalation study of entrectinib in adult patients with advanced/metastatic solid tumours.

Efficacy data for paediatric patients derived from study STARTRK-NG, a phase 1/1b, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in children and adolescents with recurrent or refractory solid tumours and primary CNS tumours, with or without TRK, ROS1, or ALK fusions.

#### NTRK-positive solid tumours

The integrated analysis set included data for n=74 adult patients with NTRK1/2/3 fusion-positive solid tumours presenting results with a data cut-off of 31 October 2018. Overall, 94.6% of patients were tested with DNA/RNA next generation sequencing (NGS), and 78% were centrally confirmed to be NTRK fusion-positive.

The primary objectives of the integrated analysis were the objective response rate (ORR) and duration of response (DOR). Relevant secondary objectives were progression-free survival (PFS), overall survival (OS), and intracranial ORR (IC-ORR) in patients with central nervous system (CNS) metastases at baseline

The most frequently represented solid tumour types were sarcoma (n=16, 21.6%), NSCLC (n=13, 17.6%), MASC (n=13, 17.6%), colorectal cancer (CRC) (n=7, 9.5%), thyroid cancer (n=7, 9.5%), and breast cancer (n=6, 8.1%). Most of the patients had NTRK1 (n=30) or NTRK3 (n=42) gene arrangements.

Overall ORR (including all tumour entities) was 63.5% (47/74) (95%CI 51.5, 74.4). Depending on the tumour entity, the ORR ranged from 0-100%. The corresponding ORR for each tumour type is listed in the attached information for healthcare professionals, "Clinical Efficacy" section.

The median DOR was 12.9 months (95% CI 9.3, not estimable) in the n=47 responders. Response duration was variable depending on tumour entity (for further information please refer to the information for healthcare professionals, “Clinical Efficacy” section). Intracranial ORR was 62.5% (95%CI 24.5, 91.5), in patients with measurable CNS metastases at baseline (n=8). Survival data were not mature at the time of data cut-off.

In patients with primary CNS tumours, 1/7 patients showed tumour response with partial remission (PR) as best overall response and a DOR of 2.8 months.

#### Paediatric patients with NTRK fusion-positive solid tumours

Study STARTRK-NG included n=29 patients (including patients with recurrent or refractory solid tumours and primary CNS tumours, with or without TRK, ROS1, or ALK fusions). NTRK1/2/3 gene fusions were detected in n=7 patients with infantile fibrosarcomas (n=2), epithelioid glioblastoma, high grade glioma, anaplastic ganglioglioma, CNS primary ganglioneuroblastoma, and metastatic melanoma (n=1 each). Patients were aged 4 months to 9 years. These patients were not treated with the approved and commercially available drug formulation.

The approval of entrectinib in patients aged 12 years or older is based on the extrapolation of adult patient data and on pharmacokinetic data in patients  $\geq$  12 years enrolled in STARTRK-NG. In patients younger than 12 years, the extrapolation approach was limited due to uncertainties in comparable exposure levels compared to adult patients. Moreover, the approved drug formulation is considered inadequate for younger patients due to the size of the capsule and the potential swallowing or aspiration issues.

#### ROS1-positive NSCLC

The integrated analysis set included data for n=94 adult patients deriving from studies ALKA, STARTRK-1, and STARTRK-2 with ROS1-positive, ROS1 inhibitor-naïve NSCLC. The primary objectives of this integrated analysis were ORR, DOR and best overall response (BOR) based on a blinded independent central review (BICR) assessment using RECISTv1.1. Secondary endpoints included PFS and IC-ORR.

The overall ORR was 73.4% (69/94) (95% CI: 63.3, 82.0). The duration of response in the n=69 responders was 16.5 months (95% CI: 14.6, 28.6). Median PFS was 16.8 months (95% CI: 12, 21.4). Overall survival data were not mature at the time of data cut-off.

Overall, n=27 patients were included in the contributing studies who received prior crizotinib treatment. These patients were not included in the integrated analysis set. Separate analysis of this subset of patients showed a reduced ORR of 14.8% (4/27) (95% CI: 4.19, 33.73), all achieving a partial remission.

IC-ORR in the overall analysis set of patients with measurable disease was 77.8% (14/18).

## **6.4 Safety**

The integrated safety population consists of n=504 patients with solid tumours and was composed of NTRK fusion-positive patients (n =113), ROS1-positive NSCLC patients (n=210), other adults (n=152), and paediatric patients (n=29). The median exposure to entrectinib was 5.5 months at the data cut-off point of 31 October 2018.

Overall, 99.0% of patients experienced at least one adverse event (AE) of any grade, which was comparable across all safety analysis groups. The most frequently reported events were from the system organ class (SOC) of nervous system disorders (82.5%), followed by gastrointestinal disorders (81.5%), and general disorders and administration site conditions (73.4%). The most frequently reported AEs by preferred terms (PT) ( $\geq$  20%) were fatigue (44.6%), constipation (42.9%), dysgeusia (42.3%), dizziness (36.1%), diarrhoea (33.5%), nausea (32.1%), anaemia (28.2%), peripheral oedema (27.8%), dyspnoea (27.0%), weight increased (26.4%), blood creatinine increased (25.4%), vomiting (23.2%), cough (21.4%), and pyrexia (20.0%).

Grade 3-5 AEs were experienced by 61.1% of patients. The most frequently reported ( $\geq 2\%$  of patients) events by PT were anaemia (9.7%), weight increased (7.3%), dyspnoea (5.4%), fatigue (4.8%), pneumonia (3.8%), AST increased (3.6%), ALT increased (3.4%), syncope (3.0%), pulmonary embolism, pleural effusion and neutrophil count decreased (2.8% each), urinary tract infection and diarrhoea (2.6% each), hypoxia (2.4%) and hypophosphataemia (2.2%).

In total, 39.9% patients experienced at least one serious adverse event (SAE). The most frequently reported ( $\geq 2\%$  of patients) events by PT were dyspnoea (4.6%), pneumonia (4.0%), pleural effusion (3.0%), and pulmonary embolism (2.0%).

Overall, a total of 123 deaths were reported (24.4%). The most common reason for death was progression of the underlying disease, which accounted for 73.2% of all deaths. A total of 42/504 (4.8%) grade 5 events occurred, none of the events were assessed by the investigator to be related to entrectinib, and no pattern was seen with respect to the type of event.

#### *Paediatric patients:*

The median exposure to entrectinib was 3.0 months. All patients experienced at least one treatment emergent adverse event (TEAE). The most common adverse events by PT were anaemia (58.6%), increased aspartate aminotransferase, increased alanine aminotransferase and nausea (51.7% each), increased blood creatinine, pyrexia and increased weight (48.3% each), and cough (41.4%). Overall 55.2% experienced at least one grade  $\geq 3$  TEAE, most commonly in the SOC of Investigations (42.3%). Overall, n=10 (34.5%) had at least 1 treatment-emergent SAE.

Fractures were reported in 20.7% (6/29) patients, of them 3/6 were reported as G3. All fractures occurred in patients with minimal or no trauma.

## **6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment**

### **Final benefit risk assessment – NTRK**

NTRK oncogenic fusions are rare but recurrent events observed in various types of congenital and acquired cancers. Patients with NTRK fusion-positive tumours are treated with the current treatment standard irrespective of the presence of targetable oncogenic drivers. There is a high unmet medical need for effective treatment options in the advanced tumour stage after exhaustion of standard therapies.

The applicant has requested a tumour agnostic indication for all solid tumours that are NTRK fusion-positive.

Entrectinib presented compelling ORR results in adult patients with NTRK fusion-positive locally advanced or metastatic extracranial solid tumours enrolled in one of three open-label, single-arm clinical trials (ALKA, STARTRK-1, and STARTRK-2). Overall, ORR was 63.5% providing a clinically meaningful result and exceeding response rates of about 0.0 – 40.0% of standard treatment options in  $\geq$  second-line settings reported in the literature. Intracranial objective response in patients with CNS involvement was observed in 3/4 patients without prior or with  $\geq 2$  months of radiotherapy prior to start of entrectinib indicating intracranial efficacy. Additional data are mandatory to confirm these results.

Efficacy data were provided with a data cut-off of 31 October 2018. Since the number of patients per tumour type was scarce with respect to the rarity of the NTRK fusion type, further data in a greater patient population for each tumour type are needed to confirm the current results. With the data at hand, several tumour types did not respond to treatment with entrectinib (see attached information for healthcare professionals, “Clinical Efficacy” section).

Data of entrectinib in patients with NTRK-positive CNS tumours are limited. Only one patient presented partial remission.



Due to lack of efficacy in patients with known resistance mutations, this subset of patients was excluded from the indication. Due to low numbers of patients with first-line entrectinib, the indication was restricted to patients where no established and satisfactory treatment option is available.

There is limited clinical experience of entrectinib in paediatric patients. Entrectinib in patients aged 12 years or older was evaluated based on extrapolation of data from adult patients and pharmacokinetic data in patients aged  $\geq 12$  years enrolled in STARTRK-NG.

In patients younger than 12 years of age, uncertainty exists regarding a comparable exposure compared to adult patients, limiting an extrapolation approach. The potential long-term toxicities of entrectinib with respect to growth and development are considered even more relevant in younger children. Moreover, the approved formulation is considered inadequate for younger patients due to the size of the capsule and the potential swallowing or aspiration issues. The pharmacokinetics, safety and efficacy of entrectinib in paediatric patients younger than 12 years of age were not considered adequately established, leading to the exclusion of this subset of patients.

Overall, OS data were immature. Further data with a longer follow up are needed to confirm the clinically meaningful response rates translating into a better survival.

Based on the available data, the toxicity profile of entrectinib appears to be manageable. However, long-term safety results are limited and further long-term data are needed. Due to the short duration of exposure, the small patient numbers, and with respect to the potential neurotoxic effects of entrectinib (e.g. headache, muscular weakness or cognitive disorders) also taking into account the preclinical data, it is not possible to determine the final safety assessment in paediatric patients. Relevant warnings and precautions as well as adverse events are described in the attached information for healthcare professionals.

Due to the limited size of the efficacy database, including uncertainties due to the single-arm nature of the submitted studies, the presently available efficacy data (including immature data for OS) for entrectinib are not considered sufficient for full approval. In addition, concerns exist regarding the potential long-term toxicity in adults and paediatric patients and developmental effects of entrectinib in paediatric patients, and further data are needed. Therefore, a temporary approval was granted. In order to further confirm the currently available results, the applicant will submit updated efficacy and safety data of patients with NTRK fusion-positive tumours of studies ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG. Safety updates will specifically focus on cardiac risks and risk of fractures. The potential risk of adverse long-term effects on growth and development including neurological outcome will be investigated in a clinical trial in patients aged 12 years or older.

### **Final benefit risk assessment – ROS1**

ROS1 is a receptor tyrosine kinase that plays a key role in cell growth and differentiation, and ROS1 rearrangements constitute a small subset of advanced NSCLC patients (1–3% of lung adenocarcinomas). The prognosis of advanced NSCLC patients after prior surgery, radiotherapy and chemotherapy is poor, and targeted therapy provides an alternative for these patients: Crizotinib, the only ROS1 inhibitor approved in Switzerland to date, improved ICR-assessed ORR and median PFS in study PROFILE 1001 for pre-treated ROS1-positive NSCLC patients to 66% and 19.3 months, respectively.

Since most patients eventually develop acquired resistance, there is a need for additional ROS1 inhibitors with a tolerable safety profile and the ability to penetrate the blood brain barrier in order to also have an effect on CNS metastases, which are very common in patients with NSCLC.

Entrectinib presented compelling ORR results in  $n=94$  adult patients with ROS1 fusion-positive locally advanced or metastatic NSCLC enrolled in one of three open-label, single-arm clinical trials (ALKA, STARTRK-1, STARTRK-2). The ORR reported was clinically meaningful and durable with a relevant number of patients achieving a duration of response lasting  $\geq 12$  months (43%). ORR was comparable between patients with and without brain metastases at baseline (73.9% vs. 80%).

Overall, the results reported exceed the expected response rates of standard chemotherapy and are comparable to the response rates of targeted therapies.

Limitations are related to the small number of patients, the single-arm design of the submitted studies which were pooled, the immaturity of survival data and the potential selection bias of a patient population with long survival after several prior treatments.

The subset of patients with CNS-only progression under prior crizotinib (n=19) and overall systemic progression on prior crizotinib (n=8), which were excluded from the initial analysis, presented low ORRs of 10.5% and 12.5%, respectively.

Overall, 31/94 of patients received entrectinib as first-line therapy. ORR was 83.9% (95%CI: 66.3, 94.6) in a post-hoc analysis. The proportion of patients with locally advanced stage of disease at study screening was too small (1%) for evaluation of efficacy and safety in this subset of patients.

The toxicity profile of entrectinib appears to be manageable. However, long-term safety results are limited and further long-term data are needed. Relevant warnings and precautions as well as adverse events are described in the attached information for healthcare professionals.

Available efficacy data of entrectinib in patients with ROS1-positive, metastatic NSCLC appear to be clinically meaningful. Due to the limited size of the efficacy database, including uncertainties due to the single arm nature of the submitted studies, the presently available efficacy data (including immature data for OS) for entrectinib are not considered sufficient for full approval. In addition, further long-term data are needed.

In order to further confirm currently available results, the applicant will submit updated efficacy and safety data for patients with ROS1-positive NSCLC from studies ALKA, STARTRK-1, and STARTRK-2.

## **6.6 Approved Indication and Dosage**

See information for healthcare professionals in the Appendix.

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## 7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

**8 Appendix****8.1 Approved Information for Healthcare Professionals**

Please be aware that the following version of the information for healthcare professionals relating to Rozlytrek was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch)).

**Note:**

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

**“Rozlytrek” is temporarily authorised – see “Properties/Effects” section.**

## **Rozlytrek®**

### **Composition**

#### *Active substances*

Entrectinibum.

#### *Excipients*

Rozlytrek 100 mg: Lactosum 65 mg.

Rozlytrek 200 mg: Lactosum 130 mg, Flavum orangeatum (E110) 554.3 µg.

Capsule contents: Acidum tartaricum, Hypromellosum, Crospovidonum, Cellulosum microcristallinum, Silica colloidalis anhydrica (E551), Magnesii stearas.

Capsule shell: Hypromellosum, Titanii dioxidum (E171), Ferrum oxydatum flavum [E172(iii)] (for Rozlytrek 100 mg).

Printing colour: Lacca (E904), Propylenglycolum (E1520), Ammonii hydroxidi solutio concentrata, Indigocarmini lacca aluminica (E132).

### **Pharmaceutical form and active substance quantity per unit**

Each 100 mg hard capsule contains 100 mg entrectinib.

Each 200 mg hard capsule contains 200 mg entrectinib.

### **Indications/Uses**

#### *Solid tumors*

Rozlytrek is indicated as monotherapy for the treatment of adult and pediatric patients aged  $\geq 12$  with solid tumours:

- who have a tumour with NTRK (neurotrophic tyrosine receptor kinase) gene fusion without a known NTRK resistance mutation and
- whose tumour is metastatic or in whom surgical resection will probably cause severe morbidity and
- for whom no satisfactory therapeutic options are available or in whom progression has occurred after prior therapy.

Rozlytrek is not indicated for the treatment of lymphomas and primary CNS tumours (see “Warnings and precautions” and “Properties/Effects”).

*Non-small cell lung cancer (NSCLC)*

Rozlytrek is indicated as monotherapy for the treatment of adult patients with ROS1-positive, metastatic NSCLC (see “Properties/Effects”).

**Dosage/Administration**

**General**

*Patient Selection*

Solid Tumors

A validated assay is required for the selection of patients with NTRK fusion-positive locally advanced or metastatic solid tumors. NTRK fusion-positive status should be established prior to initiation of Rozlytrek therapy.

NSCLC

A validated assay is required for the selection of patients with ROS1-positive, locally advanced or metastatic NSCLC. ROS1-positive status should be established prior to initiation of Rozlytrek therapy.

*Recommended dosage*

Adults

The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily (see “Pharmacokinetic”).

Pediatric patients

The recommended dose of Rozlytrek for pediatric patients, 12 years of age and older, who have the ability to swallow capsules, is 300 mg/m<sup>2</sup> body surface area (BSA) orally, once daily (see Table 1) (see “Pharmacokinetics”).

Table 1: Recommended dosing for Pediatric patients

| <b>Body surface area (BSA)</b> | <b>Once daily dose</b> |
|--------------------------------|------------------------|
| 0.81-1.10 m <sup>2</sup>       | 300 mg                 |
| 1.11-1.50 m <sup>2</sup>       | 400 mg                 |
| ≥ 1.51 m <sup>2</sup>          | 600 mg                 |

*Duration of treatment*

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

*Dose adjustment following undesirable effects/interactions*

Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek, 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. Table 2 provides general dose reduction advice for adult patients. 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

| <b>Dose reduction schedule</b> | <b>Dose level</b> |
|--------------------------------|-------------------|
| Starting Dose                  | 600 mg once daily |
| First dose reduction           | 400 mg once daily |
| Second dose reduction          | 200 mg once daily |

Pediatric Patients

Table 3 provides specific dose reduction advice for pediatric patients. For pediatric patients, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability.

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

Table 3: Dose Reduction Schedule for pediatric patients

| <b>Action</b>  | <b>BSA of 0.81 m<sup>2</sup> to 1.10 m<sup>2</sup></b> | <b>BSA of 1.11 m<sup>2</sup> to 1.50 m<sup>2</sup></b><br>(once/day) | <b>BSA ≥ 1.51 m<sup>2</sup></b><br>(once/day) |
|--|--|--|---|
| Recommended dose   | 300 mg   | 400 mg   | 600 mg  |
| First dose reduction   | 200 mg   | 300 mg   | 400 mg  |
| Second dose reduction  | 100 mg   | 200 mg, for 5 days each week*  | 200 mg  |
| *5 days each week: Monday, Wednesday, Friday, Saturday, and Sunday |  |  |   |

Dose Modifications for Specific Adverse Reactions

Recommendations for Rozlytrek dose modifications for adults and pediatric patients for specific adverse reactions are provided in Table 4 (see “Warnings and Precautions” and “Undesirable Effects”).

Table 4: Recommended dose modifications for specified Adverse Drug Reactions for Adult and Pediatric Patients

| <b>Adverse Drug Reaction</b> | <b>Severity*</b>   | <b>Dose modification</b>  |
|------------------------------|--------------------|---|
| <b>Anemia or Neutropenia</b> | Grade 3 or Grade 4 | <ul style="list-style-type: none"> <li>Withhold Rozlytrek until recovery to ≤ Grade 2 or to baseline, then resume treatment at same dose level or reduced dose by 1 level, as clinically needed.</li> </ul>   |
| <b>Cognitive Disorders</b>   | Grade ≥ 2          | <ul style="list-style-type: none"> <li>Withhold Rozlytrek until recovery to ≤ Grade 1 or to baseline, then resume treatment at reduced dose by 1 level.</li> <li>If event recurs, further reduce dose by 1 level.</li> <li>For prolonged, severe, or intolerable events,</li> </ul> |

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|                                 |   |  |
|---------------------------------|---|--|
|                                 |   | discontinue as clinically appropriate.   |
| <b>Congestive Heart Failure</b> | Grade 2 or 3  | <ul style="list-style-type: none"> <li>Withhold Rozlytrek until recovered to <math>\leq</math> Grade 1</li> <li>Resume at reduced dose</li> </ul>  |
|                                 | Grade 4   | <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 or discontinue as clinically appropriate</li> </ul>   |
| <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 481 to 500 ms   | <ul style="list-style-type: none"> <li>Withhold Rozlytrek until recovered to baseline</li> <li>Resume treatment at same dose level.</li> </ul>   |
|                                 | 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 not identified.</li> </ul>   |
|                                 | Grade 4 (Torsade de pointes; serious arrhythmia; polymorphic ventricular tachycardia) | <ul style="list-style-type: none"> <li>Permanently discontinue Rozlytrek.</li> </ul>   |
| <b>Hepatotoxicity</b>           | Grade 3   | <ul style="list-style-type: none"> <li>Withhold Rozlytrek until recovery 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 Grade 1 or to baseline.</li> <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; total  | <ul style="list-style-type: none"> <li>Permanently discontinue Rozlytrek.</li> </ul>   |



|   |  |   |
|---|--|---|
|   | bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis. |   |
| <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 Grade 1</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) |  |   |

Dose Modifications for Specific Drug Interactions

*Concomitant strong or moderate CYP3A inhibitors:*

*Adults and pediatric patients of 12 years and older with a BSA greater than or equal to 1.50 m<sup>2</sup>*

The concomitant use of strong or moderate CYP3A inhibitors and Rozlytrek increases the drug substance levels of entrecinib and should be avoided. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, Rozlytrek dose should be reduced to 100 mg once daily for use with strong CYP3A inhibitors and to 200 mg once daily for use with moderate CYP3A inhibitors. After discontinuation of the concomitant strong or moderate CYP3A inhibitors for 3 to 5 elimination half-waves, Rozlytrek dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed (see “Interactions”).

*Pediatric patients of 12 years and older with a BSA of less than 1.5 m<sup>2</sup>*

The concomitant use of strong or moderate CYP3A inhibitors should be avoided. (see “Interactions”). The administration of grapefruit-containing product should be avoided during the treatment with Rozlytrek, as those contain CYP3A inhibitors.

*Concomitant CYP3A inducers:*

Co-administration of Rozlytrek with CYP3A inducers in adult and pediatric patients leads to a reduction of entrecinib levels and should be avoided (see “Interactions”).

*Patients with impaired hepatic function*

The safety and efficacy of Rozlytrek have not been studied in patients with hepatic impairment (see “Pharmacokinetics: Kinetics in specific patient groups”).

### *Patients with impaired renal function*

Based on population pharmacokinetic, no dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy of Rozlytrek have not been studied in patients with severe renal impairment.

### *Elderly patients*

No differences in safety or efficacy were observed between patients  $\geq 65$  years of age and younger patients. No dose adjustment is required in patients  $\geq 65$  years of age (see “Pharmacokinetics: Kinetics in specific patient groups”).

### *Children and adolescents*

Dosage for patients is based on body surface area ( $\text{mg}/\text{m}^2$ ) with a maximum daily dose of 600 mg (see Table 1 for pediatric dosing).

The safety and efficacy of Rozlytrek have been in paediatric and young adult patients (see “Undesirable Effects”, “Properties/Effects”). In addition, use of Rozlytrek in pediatric patients is supported by extrapolation of evidence from clinical trials in adults to pediatric  $\geq 12$  years population, based on population pharmacokinetic data demonstrating similar drug exposure in adults and pediatric patients (see “Properties/Effects: Clinical Studies”, and “Pharmacokinetics: Kinetics in specific patient groups”). The efficacy and safety in patients  $< 12$  years has not been established, currently available data are described in section “Clinical Efficacy”.

Rozlytrek was associated with a higher incidence of skeletal fractures in the pediatric patients compared to adult patients. See “Warnings and Precautions” and “Undesirable Effects, Clinical Efficacy”.

### *Genotype/genetic polymorphism*

No dose adjustment is necessary for patients of different ethnicities (see “Pharmacokinetics: Kinetics in specific patient groups”).

### *Delayed administration*

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.

### *Mode of administration*

Rozlytrek hard capsules can be taken with or without food, swallowed whole and must not be opened or dissolved.

## Contraindications

Rozlytrek is contraindicated in patients with a known hypersensitivity to entrectinib or any of the excipients.

## Warnings and precautions

### General

#### Efficacy across tumour types

The benefit of Rozlytrek has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions. Favourable effects of Rozlytrek have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations (see “Clinical Efficacy”). For these reasons, Rozlytrek should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted).

#### Resistance mutations

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).

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.

#### Congestive Heart Failure

Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek (see “Undesirable Effects”). These reactions were observed in patients with or without a history of cardiac disease and the majority resolved upon treatment with diuretics and/or dose reduction/interruption of Rozlytrek.

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. In patients with clinical signs and symptoms of CHF, including shortness of breath or edema, treatment with Rozlytrek should be interrupted and a clinically adequate treatment should be secured.

Rozlytrek treatment should be adapted according to Table 4 in “Dosage/Administration”.

#### QTc Interval Prolongation

QT interval prolongation has been observed in patients treated with Rozlytrek in clinical trials (see “Undesirable Effects”).

Use of Rozlytrek should be avoided in patients with congenital long QT syndrome and in patients taking medications that are known to prolong QT interval. Control of ECG and monitoring of electrolytes should be done before treatment start and during treatment at regular intervals.

Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described in Table 4 in “Dosage/Administration”.

### Cognitive Disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek (see “Undesirable Effects”). Patients should be monitored for signs of cognitive changes.

Based on the severity of the cognitive disorder, Rozlytrek treatment should be modified as described in Table 4 in “Dosage/Administration”.

Patients should be counseled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines if cognitive disorders occur (see “Effects on ability to drive and use machines”).

### Hepatotoxicity

Increases in ALT and AST levels have been reported in patients receiving Rozlytrek (see “Undesirable Effects”).

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Based on the severity, Rozlytrek treatment should be modified as described in Table 4 in section “Dosage/Administration”.

### Hyperuricemia

Hyperuricemia has been observed in patients treated with Rozlytrek. Serum uric acid levels should be assessed prior to initiating Rozlytrek and periodically during treatment. Patients should be monitored for sign and symptoms of hyperuricemia. Treatment with urate-lowering medications should be initiated as clinically indicated and Rozlytrek withheld for signs and symptoms of hyperuricemia. Rozlytrek dose should be modified based on severity as described in Table 4 in “Dosage/Administration”.

### Fractures

Rozlytrek increases the risk of fractures (see description of selected ADR). Patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures should be evaluated promptly. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients fractures occurred in patients with minimal or no trauma. There are no data on the effects of Rozlytrek on healing of known fractures and the risk of occurrence of future fractures. In the majority of pediatric patients treatment was continued with Rozlytrek and the fracture healed.

### Embryo-fetal toxicity

Findings in animal studies indicate that Rozlytrek may cause fetal harm when administered to a pregnant woman (see “Preclinical data”). Female patients receiving Rozlytrek should be advised of the potential harm to the fetus. Female patients of reproductive potential, must use highly reliable contraceptive methods during treatment with Rozlytrek and for at least 5 weeks following the last dose of Rozlytrek (see “Pregnancy, lactation”).

Men of female patients of reproductive potential, should be advised to use reliable contraceptive methods during treatment and for at least 3 months following the last dose of Rozlytrek (see "Pregnancy, lactation" and "Preclinical Data").

### Lactose intolerance

Rozlytrek hard capsules contain lactose. Patients with the rare hereditary galactose intolerance, a total lack of lactase or glucose-galactose malabsorption should not take this medicinal product.

### Azo dyes

This medication contains the azoic dye E110. This substance can cause allergic reactions.

## **Interactions**

### *Effect of Rozlytrek on other medicinal products*

#### CYP substrates

Based on the in vitro studies in human liver microsomes, entrectinib exhibits inhibitory potential toward CYP3A.

In vitro studies indicate that entrectinib and its major active metabolite, M5, do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations.

In vitro results indicate entrectinib has weak induction potential toward CYP3A and CYP2C8/9.

In a clinical study, co-administration of multiple doses of entrectinib and midazolam, a sensitive CYP3A substrate, increased the systemic exposure of midazolam by approximately 50% indicating a weak inhibitory effect of entrectinib on the metabolism of midazolam (Geometric mean ratio (GMR) with/without entrectinib for  $AUC_{inf}$  (90% CI) was 150% (129%, 173%)).

Therefore, no dose adjustment is required when Rozlytrek is co-administered with CYP3A substrates.

#### P-gp substrates

In vitro data suggest that entrectinib has inhibitory potential towards P-gp.

In a clinical study, co-administration of a single oral dose of entrectinib with a sensitive P-gp substrate, digoxin, increased the digoxin  $C_{max}$  by approximately 28% and overall exposure by approximately 18% (GMR with/without entrectinib for  $C_{max}$  (90% CI) was 128% (98.2%, 167%) and  $AUC_{inf}$  (90% CI) was 118% (106%, 132%)). 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.

These results indicate that entrectinib is a weak P-gp inhibitor and that no clinically significant interaction exists between digoxin, as a P-gp substrate, and entrectinib. Therefore, no dose adjustment is required when Rozlytrek is co-administered with P-gp substrates.

#### BCRP substrates

As with P-gp, a mild inhibition of BCRP was observed in in vitro studies. Given that no clinically significant interaction was observed with the P-gp substrate digoxin, an interaction with BCRP is not predicted. No dose adjustment is required when Rozlytrek is co-administered with BCRP substrates.

#### Other transporter substrates

In vitro data indicate that entrectinib has weak inhibitory potential toward organic anion-transporting polypeptide (OATP) 1B1 and multidrug and toxin extrusion protein 1 (MATE1).

### *Effect of other medicinal products on Rozlytrek*

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

#### CYP3A inducers

Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced the systemic exposure of entrectinib by 77%. GMR with/without rifampin for AUC<sub>inf</sub> (90% CI) was 23.3% (18.4%, 29.5%) and C<sub>max</sub> (90% CI) was 44.4% (35.3%, 55.9%).

Co-administration of Rozlytrek with CYP3A inducers should be avoided (see “Dosage/Administration”).

#### CYP3A inhibitors

Co-administration of a single oral dose of entrectinib with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased the systemic exposure of entrectinib by 500%. GMR with/without itraconazole for AUC<sub>inf</sub> (90% CI) was 604% (454%, 804%) and C<sub>max</sub> (90% CI) was 173% (137%, 218%).

Co-administration of strong and moderate CYP3A inhibitors (including anti-fungal agents, anti-retroviral agents) with Rozlytrek should be avoided. If concurrent use is unavoidable, dose adjustment of Rozlytrek is required as described in “Dosage/Administration”.

#### Medicinal products that increase gastric pH

The aqueous solubility of entrectinib in vitro is pH dependent. In a clinical study, administration of entrectinib with lansoprazole (a proton pump inhibitor (PPI)), resulted in a 25% decrease in entrectinib systemic exposure which is not clinically relevant. GMR with/without lansoprazole for AUC<sub>inf</sub> (90% CI) was 74.5% (64.7%, 85.9%) and C<sub>max</sub> (90% CI) was 76.5% (67.6%, 86.6%).

Therefore, no dose adjustments are required when Rozlytrek is co administered with PPIs or other drugs that raise gastric pH (e.g., H<sub>2</sub> receptor antagonists or antacids).

#### Effect of transporters on Entrectinib disposition

Based on the in vivo brain-to-plasma concentration ratio ( $\geq 0.6$ ) at steady-state in rats and dogs as well as lack of sensitivity to a P-gp inhibitor in vitro in a P-gp expressing cell assay, entrectinib is considered a poor substrate of P-gp. M5 is a substrate of P-gp.

Entrectinib is not a substrate of BCRP but M5 is a substrate of BCRP. Entrectinib and M5 are not substrates of organic anion transporting polypeptide (OATP) 1B1 or OATP1B3.

## **Pregnancy, lactation**

### *Females and Males of Reproductive Potential*

#### Pregnancy testing

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

### Contraception

Female patients of reproductive potential, must use highly reliable contraceptive methods during treatment with Rozlytrek and for at least 5 weeks following the last dose of Rozlytrek.

Based on the potential for genotoxicity, male patients with female partners of child-bearing potential must use highly reliable contraceptive methods during treatment and for at least 3 months following the last dose of Rozlytrek (see “Preclinical data”).

### *Pregnancy*

There is no available data on the use of Rozlytrek in pregnant women. Based on animal studies with entrectinib (see “Preclinical data”) and its mechanism of action, Rozlytrek may cause fetal harm when administered to a pregnant woman. Rozlytrek should not be administered during pregnancy unless it is clearly needed. Female patients receiving Rozlytrek should be advised to contact the doctor, should pregnancy occur, and of the potential harm to the fetus.

### *Lactation*

It is not known whether entrectinib or its metabolites are excreted in human breast milk. A risk for the nursing infant can not be excluded. Breast-feeding should be discontinued during treatment and at least 1 week following the last dose of Rozlytrek treatment.

### *Fertility*

Up till now no clinical experience on the effect of entrectinib on fertility is available. No fertility studies have been performed in animals to evaluate the effects of entrectinib. With the exception of dose dependent decrease of prostate weight in male dogs, no effect of entrectinib on reproductive organs was observed (see “Preclinical data”).

### **Effects on ability to drive and use machines**

Rozlytrek may influence the ability to drive and use machines. Patients should be instructed not to drive or use machines, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek (see “Warnings and Precautions” and “Undesirable effects”).

### **Undesirable effects**

#### Clinical Trials

##### *Summary of the safety profile*

For the clinical development program of Rozlytrek, a total of 504 patients have received Rozlytrek in 4 clinical trials (ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG). The safety of Rozlytrek was

evaluated as integrated analyses of these 4 clinical trials. The median duration of exposure to Rozlytrek was 5.5 months.

The safety of Rozlytrek in adult patients has been evaluated in a total of 475 patients with NTRK-fusion positive, ROS1-positive or ALK-positive solid tumors, in studies ALKA, STARTRK-1, STARTRK-2.

The safety of Rozlytrek has been evaluated in 29 pediatric and young adult patients with solid tumors: 27 patients enrolled in STARTRK-NG, and 2 patients enrolled in STARTRK-2. Of these, 1 patient was less than 1 year old, 21 patients were 2 to 11 years old, 7 patients were 12 to 17 years old.

The most common adverse reactions ( $\geq 10\%$ ) were fatigue (44.6%), constipation (42.9%), dysgeusia (42.3%), oedema peripheral (27.8%), dizziness (36.1%), diarrhoea (33.5%), nausea (32.1%), dyspnoea (27.0%), paraesthesia (19.8%), pain (24.4%), anaemia (28.2%), cognitive disorders (24.2%), increased weight (26.4%), vomiting (23.2%), cough (21.4%), increased blood creatinine (25.4%), pyrexia (20.0%), arthralgia (19.0%), myalgia (19.6%), headache (17.5%), hypotension (14.3%), peripheral sensory neuropathy (15.7%), AST increased (17.5%), ALT increased (16.1%), ataxia (15.7%), sleep disturbances (13.5%), lung infection (13.1%), urinary tract infection (12.7%), muscular weakness (12.3%), decreased appetite (11.9%), vision blurred (11.9%), rash (11.5%), neutropenia (11.3%), abdominal pain (11.1%), urinary retention (10.9) and dysphagia (10.1%). The below list summarizes the adverse drug reactions (ADRs) occurring in adult and pediatric patients treated with Rozlytrek (N=504). Adverse drug reactions from clinical trials 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  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

### **Infections and Infestations**

*Very common:* Lung infection<sup>1</sup> (13.1%; Grade  $\geq 3$ : 6.0%\*), Urinary tract infection (12.7%; Grade  $\geq 3$ : 2.6%).

### **Blood Disorders**

*Very common:* Anemia (28.2%; Grade  $\geq 3$ : 9.7%) including reduced haemoglobin, Neutropenia<sup>2</sup> (11.3%; Grade  $\geq 3$ : 4.4%).

### **Metabolism and Nutritional Disorders**

*Very common:* Weight increased (26.4%; Grade  $\geq 3$ : 7.3%), Decreased appetite (11.9%; Grade  $\geq 3$ : 0.2%).

*Common:* Dehydration, Hyperuricemia.

*Uncommon:* Tumor Lysis syndrome\*.

### **Nervous System Disorders**

*Very common:* Dysgeusia (42.3%; Grade  $\geq 3$ : 0.4%), Dizziness<sup>3</sup> (39.7%; Grade  $\geq 3$ : 1.2%), Dysaesthesia<sup>4</sup> (29.0%; Grade  $\geq 3$ : 0.2%), Cognitive Disorders<sup>5</sup> (24.2%; Grade  $\geq 3$ : 4.4%), Peripheral



Sensory Neuropathy<sup>6</sup> (15.7%; Grade ≥ 3: 1.0%), Headache (17.5%; Grade ≥ 3: 1.0%), Ataxia<sup>7</sup> (15.7%; Grade ≥ 3: 0.8%), Sleep disturbances<sup>8</sup> (13.5%; Grade ≥ 3: 0.4%).

*Common:* Syncope, Mood disorders<sup>9</sup>.

### **Eye Disorders**

*Very common:* Vision Blurred<sup>10</sup> (11.9%; Grade ≥ 3: 0.4%).

*Common:* Photophobia (4.2%; Grade ≥ 3: 0.0%), Diplopia (2.6%; Grade ≥ 3: 0.4%).

### **Cardiac Disorders**

*Common:* Congestive Heart Failure<sup>11</sup>, Electrocardiogram QT prolonged.

### **Vascular Disorders**

*Very common:* Hypotension<sup>12</sup> (16.5%; Grade ≥ 3: 2.4%).

### **Respiratory Disorders**

*Very common:* Dyspnea (27.0%; Grade ≥ 3: 5.8%\*), Cough (21.4%; Grade ≥ 3: 0.63%).

*Common:* Pleural effusion.

### **Gastrointestinal Disorders**

*Very common:* Constipation (42.9%; Grade ≥ 3: 0.4%), Diarrhea (33.5%; Grade ≥ 3: 2.6%), Nausea (32.1%; Grade ≥ 3: 0.8%), Vomiting (23.2%; Grade ≥ 3: 1.2%), Abdominal pain (11.1%; Grade ≥ 3: 0.6%), Dysphagia (10.1%; Grade ≥ 3: 0.4%).

### **Hepatobiliary Disorders**

*Very common:* AST increased (17.5%; Grade ≥ 3: 3.4%), ALT increased (16.1%; Grade ≥ 3: 3.4%).

### **Skin and Subcutaneous Tissue Disorders**

*Very common:* Rash<sup>13</sup> (11.5%; Grade ≥ 3: 1.4%).

### **Musculoskeletal Disorders**

*Very common:* Arthralgia (19.0%; Grade ≥ 3: 0.6%), Myalgia (19.6%; Grade ≥ 3: 0.6%), Muscular weakness (12.3%; Grade ≥ 3: 1.2%).

*Common:* Fractures<sup>14</sup>.

### **Renal and urinary disorders**

*Very common:* Blood creatinine increased (25.4%; Grade ≥ 3: 0.6%), Urinary retention<sup>15</sup> (10.9%; Grade ≥ 3: 0.6%).

### **General Disorders and Administration Site Conditions**

*Very common:* Fatigue<sup>16</sup> (45.0%; Grade ≥ 3: 5.0%), Edema<sup>17</sup> (37.3%; Grade ≥ 3: 1.4%), Pain<sup>18</sup> (24.4%; Grade ≥ 3: 1.6%), Pyrexia (20.0%; Grade ≥ 3: 0.8%).

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

\* Grades 3 to 5, inclusive of fatal adverse reactions (including 2 reactions of pneumonia, 2 reactions of dyspnea, and 1 reaction of tumour lysis syndrome).

<sup>1</sup> Includes the preferred terms: bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection

<sup>2</sup> Includes the preferred terms: neutropenia, neutrophil count decreased

<sup>3</sup> Includes the preferred terms: dizziness, vertigo, dizziness postural

<sup>4</sup> Includes the preferred terms: paresthesia, hyperesthesia, hypoesthesia, dysesthesia

<sup>5</sup> Includes preferred terms: cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination visual' and mental disorder.

<sup>6</sup> Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy

<sup>7</sup> Includes the preferred terms: 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> Includes the preferred terms: diplopia, vision blurred, visual impairment

<sup>11</sup> Includes the preferred terms: acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary edema

<sup>12</sup> Includes the preferred terms: hypotension, orthostatic hypotension

<sup>13</sup> Includes the preferred terms: 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> Urinary retention (urinary retention, urinary incontinence, urinary hesitation, micturition disorder, micturition urgency)

<sup>16</sup> Includes the preferred terms: fatigue, asthenia

<sup>17</sup> Includes the preferred terms: face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling

<sup>18</sup> Includes the preferred terms: back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity

### *Description of selected undesirable effects*

#### Cognitive disorders

A variety of cognitive symptoms were reported across clinical trials (see "General Warnings and Precautions"). 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%), hallucination visual (0.4%) and mental disorder (0.2%). Grade 3 events were reported in 4.4% of patients. In the pediatric population, 3.4% (1/29) pediatric patients experienced disturbance in attention of Grade 1 severity. Patients who had brain metastases at baseline had a higher frequency of these events (29.79%) compared to those without brain metastases (23.1%).

#### Hepatotoxicity

Increased AST of any grade occurred in 43.3% of patients and increased ALT of any grade occurred in 38.4%. Grade 3 – 4 increased AST or ALT occurred in 3.3% and 3.1% of patients, respectively; the incidence may be underestimated as 5% of patients had no post-treatment liver function tests. Events of increased AST or ALT leading to dose reductions occurred in 0.4% and 0.2% of patients, respectively. Dose interruptions due to adverse events of increased AST or ALT occurred in 2.4% of patients.

#### Fractures

Fractures were experienced by 5.3% (N=475) of adult patients and 20.7% (N=29) of pediatric 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 patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In 2 pediatric patients, bilateral femoral neck fractures occurred. No patients discontinued Rozlytrek due to fractures.

In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area. The median time to fracture was 3.42 months (range: 0.26 months to 18.5 months) in adults.

Rozlytrek was interrupted due to fractures in 36.0% of adult patients that experienced fractures.

In pediatric patients, all fractures occurred in patients with minimal or no trauma. The median time to fracture was 3.38 months (range: 1.77 months to 7.39 months) in pediatric patients. Rozlytrek was interrupted due to fractures in 33.3% of pediatric patients that experience fractures.

### 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 0.36 months (range: 0.03 months to 28.19 months) and the median duration was 0.66 months (range: 0.03 months to 11.99 months). 67.1% of patients recovered from ataxia. Ataxia related adverse events were observed more frequently in elderly patients (23.8%) compared to patients below 65 years of age (12.8%).

### Syncope

Syncope events were reported in 4.6% of patients. In some patients, syncope was reported with concurrent hypotension, dehydration, or QTc prolongation.

### 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.

### 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 0.76 months (range: 0.07 months to 6.01 months). 55.7% of patients recovered from peripheral neuropathy.

### Eye Disorders

Eye disorders reported across clinical trials included events of vision blurred (8.5%), diplopia (2.6%), and visual impairment (1.6%). The median time to onset for eye disorders was 1.87 months (range: 0.03 months to 21.59 months). The median duration of eye disorders was 1.02 months (range 0.03 months to 14.49 months). 61.7% of patients recovered from the eye disorder events.

### Paediatric population

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

The safety of Rozlytrek in paediatric patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harbouring an NTRK gene fusion (ALKA, STARTRK-1 and STARTRK-2), and data from 29 paediatric patients.

Adverse reactions and laboratory abnormalities of any grade occurring in at least a 10% increased proportion of paediatric patients compared to adult patients were: nausea (51.7% [15] vs. 30.9% [147]), anaemia (58.6% [17] vs. 26.3% [125]), weight increased (44.8% [13] vs. 25.3% [120]), blood creatinine increased (48.3% [14] vs. 24.0% [114]), pain (37.9% [11] vs. 23.6% [112]), cough (41.4% [12] vs. 20.2% [96]), pyrexia (48.3% [14] vs. 18.3% [87]), headache (37.9% [11] vs. 16.2% [77]), AST increased (51.7% [15] vs. 15.4% [73]), ALT increased (51.7% [15] vs. 13.9% [66]), decreased appetite (27.6% [8] vs. 10.9% [52]), abdominal pain (20.7% [6] vs. 10.5% [50]), neutropenia (37.9% [11] vs. 9.7% [46]), urinary retention (20.7% [6] vs. 10.3% [49]), mood disorders (27.6% [8] vs. 8.0% [38]), dehydration (20.7% [6] vs. 7.2% [34]), fractures (20.7% [6] vs. 5.3% [25]).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIVIS portal (Electronic Vigilance System). You can obtain information about this at [www.swissmedic.ch](http://www.swissmedic.ch).

### **Overdose**

There is no experience with overdose in clinical trials with Rozlytrek.

#### *Treatment*

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

### **Properties/Effects**

#### *ATC code*

L01XE56

#### *Mechanism of action*

Entrectinib is a potent inhibitor of 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; encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK). The major active metabolite of entrectinib, M5, showed similar in vitro potency and activity.

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation.

Entrectinib potently inhibits the TRK kinases, ROS1 and ALK, leading to inhibition of downstream signaling pathways, cell proliferation and induction of tumor cell apoptosis. Entrectinib demonstrates potent inhibition of cancer cell lines harboring NTRK, ROS1 and ALK fusion genes, irrespective of

tumor type. Entrectinib has anti-tumor potency in NTRK and ROS1 fusion-driven tumor models, driving tumor regressions across multiple tumor types, including sarcomas, head and neck carcinoma, non-small cell lung carcinoma (NSCLC), colorectal cancer (CRC), acute myeloid leukemia (AML), and gliomas.

Entrectinib is a CNS penetrant molecule that showed brain-to-plasma concentration ratios of 0.4-2.2 in multiple animal species (mice, rats and dogs). It has demonstrated potent anti-tumor activity in three TRKA-driven intracranial tumor models and one ALK-driven intracranial tumor model. These data are consistent with entrectinib dosing resulting in sufficient brain exposure achieving target pharmacological activities at steady-state and at clinically relevant systemic exposures.

### *Pharmacodynamics*

### *Clinical efficacy*

### **Temporary authorisation**

**The medicinal product Rozlytrek is being granted temporary authorisation due to the incomplete clinical data available at the time of the assessment of the application for marketing authorisation (article 9a of the Therapeutic Products Act). The temporary authorisation is contingent upon the timely fulfilment of obligations. Once these have been fulfilled, the temporary authorisation can be converted into an ordinary authorisation.**

### ***NTRK fusion-positive solid tumors***

#### Efficacy in adult patients

The efficacy of Rozlytrek in the treatment of NTRK fusion-positive solid tumors in adult patients was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) through a pre-specified integrated analysis.

Study ALKA was a Phase I single arm, open-label study in patients  $\geq 18$  years of age with solid tumors with NTRK1/2/3, ROS1, or ALK molecular alterations to determine the maximum tolerated dose. Study STARTRK-1 was a Phase I multi-center single arm, open label study in patients  $\geq 18$  years of age with solid tumors with NTRK1/2/3, ROS1, or ALK molecular alterations. The study included a dose escalation segment and a dose expansion segment. In the dose expansion segment, patients received 600 mg Rozlytrek daily in repeated 4-week cycles and the primary objective was to evaluate the recommended Phase 2 dose. Study STARTRK-2 was a multicenter, international Phase II single-arm basket study in patients with solid tumors with NTRK1/2/3, ROS1, or ALK gene rearrangements. Patients received 600 mg Rozlytrek once daily in 4-week cycles.

The primary efficacy endpoints in the integrated analyses were objective response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The relevant secondary efficacy

endpoint was intracranial (IC) ORR in patients presenting with CNS metastases at study inclusion (also evaluated by BICR using RECIST v1.1).

The efficacy evaluable analyses set comprised a total of 74 adult patients with confirmed NTRK fusion-positive solid tumors treated with Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline as assessed by investigator, and with ≥ 6 months of follow up. NTRK fusion-positive status was determined by a validated nucleic acid-based test performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 47.3% males, median age of 57 years (range: 21 to 83 years), 70.0% white Caucasian, 17.6% Asian, 5.55% Hispanic or Latino and 59.7% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (40.5%), 1 (45.9%), or 2 (13.5%). Most patients (97.3%) had metastatic disease [most common sites being lung (60.8%), lymph nodes (52.7%) and brain (25.7%)], 2.7% patients had locally advanced disease. 86.5% patients had received prior treatment for their cancer including surgery (82.4%), radiotherapy (63.5%), chemotherapy (81.1%) and 13.5% patients had no prior systemic therapies. The overall median duration of follow-up was 12.32 months. From 74 patients 47 were responders with a ORR of 63.5% (95% CI 51.5, 74.4) of which 6.8% showed a complete response and 56.8% a partial response. Out of the 47 responders 44.7% (n=21) patients had an event and showed a median duration of response of 12.9 months (95% CI 9.3, NE). At 6 months a durable response was observed in 71% (95%CI 58, 85) of the patients, at 9 months the response was observed in 65% (95% CI 51, 80) of patients, and at 12 months the response was observed in 55% (95% CI 39, 72) of patients.

Objective response rate and duration of response by tumor type in all efficacy evaluable adult patients with NTRK-fusion positive solid tumors is presented in Table 5.

Table 5: Efficacy by tumour type by Tumor Type in Adults with NTRK-fusion positive Solid Tumors

| Tumor Type                      | N=74 | ORR              |              | DOR Range (months) |
|---------------------------------|------|------------------|--------------|--------------------|
|                                 |      | Responders n (%) | 95% CI       |                    |
| Sarcoma                         | 16   | 9 (56.3)         | (29.9, 80.3) | 2.8, 15.1          |
| Non-small cell lung cancer      | 13   | 9 (69.2)         | (38.6, 90.9) | 1.4*, 25.9*        |
| Salivary (MASC)                 | 13   | 12 (92.3)        | (64.0, 99.8) | 2.8, 22.1*         |
| Breast cancer (secretory)       | 4    | 4 (100)          | (39.8, 100)  | 5.5, 20.2*         |
| Breast cancer (non-secretory)   | 2    | Miss, PR         | NA           | 4.2                |
| Thyroid cancer                  | 7    | 3 (42.9)         | (9.9, 81.6)  | 5.6, 10.9*         |
| Colorectal cancer               | 7    | 2 (28.6)         | (3.7, 71)    | 7.9*, 15.2         |
| Neuroendocrine cancers          | 4    | 2 (50.0)         | (6.8, 93.2)  | 1.9*, 9.2*         |
| Pancreatic cancer               | 3    | 2 (66.7)         | (9.4, 99.2)  | 7.1, 12.9          |
| Ovarian cancer                  | 1    | Non CR/PD        | NA           | NA                 |
| Endometrial carcinoma           | 1    | PR               | NA           | 26.0*              |
| Cholangiocarcinoma              | 1    | PR               | NA           | 9.3                |
| Gastrointestinal cancer (other) | 1    | PR               | NA           | 5.6*               |
| Neuroblastoma                   | 1    | Miss             | NA           | NA                 |

\* Censored  
 ORR: objective response rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma  
 Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

The ORR in 30/74 patients that had broad molecular characterisation before Rozlytrek treatment was 56.7% [37.4, 74.5]; the ORR in 24/30 patients who had other genomic alterations in addition to *NTRK* gene fusion was 50% [29.1, 70.9] and the ORR in 6/30 patients without other genomic alterations was 83.3% [35.9, 99.6].

### Intracranial Response

Of the 74 adult patients with *NTRK*-fusion positive solid tumors in the efficacy evaluable analysis set, 16 patients had CNS metastases at baseline as assessed by BICR, including 8 patients with measurable CNS lesions. Intracranial ORR (IC-ORR) was 62.5% (95% CI 24.5, 91.5) with one complete response (CR) and 4 partial responses (PR).

### Efficacy in paediatric patients

The efficacy of Rozlytrek in paediatric patients  $\geq 12$  years was based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harbouring a *NTRK* gene fusion (ALKA, STARTRK-1 and STARTRK-2), and efficacy and pharmacokinetic data in paediatric patients enrolled in STARTRK-NG.

### **ROS1-positive NSCLC**

The efficacy of Rozlytrek in the treatment of ROS1 positive locally advanced or metastatic NSCLC was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) described above, through a pre-specified integrated analysis.

The primary efficacy endpoint in the integrated analyses were ORR and DOR, as evaluated by BICR according to RECIST v1.1. The relevant secondary endpoints were PFS and IC-ORR in patients presenting with CNS metastases at study inclusion (also evaluated by BICR using RECIST v1.1). The efficacy evaluable analyses set comprised a total of 94 patients with histologically confirmed ROS1-positive NSCLC treated with Rozlytrek, not previously treated with a ROS1-inhibitor, presenting with measurable disease at baseline as assessed by the investigator, and with  $\geq 12$  months of follow up from the time of first response. ROS1-positive status was determined by a validated nucleic acid-based test performed at a CLIA-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 36.2% males, median age of 53 years (range: 27 to 86 years), 79.8% patients < 65 years of age, 48.9% white Caucasian, 43.6% Asian, 5.3% Black, 2.4% Hispanic or Latino and 59.6% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (37.2%), 1 (51.1%), or 2 (11.7%). Most patients (98.9%) had metastatic disease with 42.6% having brain metastases [other common sites were lung (57.4%) and lymph nodes (75.5%)], 1.1% patients had locally advanced disease, and 24.5% patients had no prior systemic therapies. The overall median duration of follow-up was 20.9 months.

The primary endpoints assessed by BICR were ORR and DOR. From 94 patients 69 were responders with a ORR of 73.4% (95% CI 63.3, 82.0) of which 11.7% showed a complete response

and 61.7% a partial response. Out of the 69 responders 52.2% (n=36) patients had an event and showed a median duration of response of 16.5 months (95% CI 14.6, 28.6). At 6 months a durable response was observed in 82% (95%CI 72, 91) of the patients and at 9 months the response was of 79% (95% CI 69, 89) of patients, and at 12 months the response was observed in 63% (95% CI 53, 73) of patients.

In the ROS1 positive NSCLC efficacy evaluable patients with  $\geq 12$  months of follow-up (N = 94), the median PFS was 16.8 months (95% CI: 12, 21.4).

Twenty seven patients were enrolled who had prior treatment with crizotinib, however, the 27 patients were excluded from the efficacy evaluable analysis set. Systemic ORR in patients who had prior treatment with crizotinib was 14.8% (95% CI 4.19, 33.73), all patients had partial responses.

### Intracranial Response

Of the 94 patients with ROS-1 positive NSCLC in the efficacy evaluable analysis set, 34 patients (36%) had CNS metastases at baseline as assessed by BICR, including 18 patients with measurable CNS lesions. Intracranial ORR was 77.8% (95% CI 52.36, 93.59) with two complete responses and 12 partial responses.

### *Pharmacokinetics*

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5), have been characterized in patients with NTRK-positive solid tumors and ROS1-positive NSCLC, and healthy subjects. The pharmacokinetic of entrectinib and M5 is linear and independent of dose and time.

Following administration of a single 600 mg dose of entrectinib, the estimated entrectinib mean ( $\pm$  SD)  $C_{max}$  was 1'990 ( $\pm$  1'050) nM and  $AUC_{0-24}$  33'900 ( $\pm$  15'800) nM\*h and for M5  $C_{max}$  was 765 ( $\pm$  598) nM and  $AUC_{0-24}$  13'300 ( $\pm$  10200) nM\*h. At steady-state the estimated entrectinib mean  $C_{max}$  was 3'490 ( $\pm$  1'600) nM and  $AUC_{0-24}$  62'800 ( $\pm$ 29'100) nM\*h and for M5  $C_{max}$  was 1'340 ( $\pm$  934) nM and  $AUC_{0-24}$  25'500 ( $\pm$ 29'100) nM\*h.

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.



### *Absorption*

Following a single 600 mg oral administration of Rozlytrek to patients with NTRK-fusion positive and ROS1 positive NSCLC under fed conditions, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration ( $T_{max}$ ) after approximately 4 - 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 7 days for entrectinib and within 14 days for M5 at 600 mg entrectinib once daily dosing.

No clinically significant effect of food on entrectinib bioavailability was observed. Following a single 600 mg oral administration of Rozlytrek to healthy subjects under fasting conditions and following a high fat, high calorie meal, the GMR under fed/fasted condition for  $AUC_{inf}$  (90%CI) was 115% (107, 124) and for  $C_{max}$  (90%CI) was 106% (98.9, 115). Entrectinib can be administered with or without food (see "Dosage/Administration").

### *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.

Population pharmacokinetic analysis estimated volume of distribution of 551 L and 81.1 L for entrectinib and M5, respectively.

### *Metabolism*

Entrectinib is metabolized 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) was the major circulating metabolite identified.

### *Elimination*

Following administration of a single dose of [ $^{14}C$ ]-labeled entrectinib administered orally to healthy subjects, the majority of radioactivity was excreted in feces (83%) with minimal excretion in urine (3.06%). In feces, 36% and 22% of the dose was excreted as unchanged entrectinib and M5, respectively, indicating hepatic clearance is the major route of elimination.

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 a CL/F of 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 and 40 hours, respectively.

### *Kinetics in specific patient groups*

#### *Hepatic impairment*

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

data is available in patients with hepatic impairment and a dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. Based on population pharmacokinetic analysis, entrectinib and M5 exposures were similar in patients with mild, moderate or severe hepatic impairment and normal hepatic function.

### *Renal impairment*

Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3% of the dose) indicating renal clearance plays a minor role in the elimination of entrectinib. Population pharmacokinetic data obtained in patients with mild and moderate impairment show that pharmacokinetics of entrectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with severe renal impairment.

### *Elderly patients*

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

### *Children and adolescents*

Non-compartmental analysis and population pharmacokinetic modeling approaches demonstrated that the pharmacokinetics of entrectinib and M5 were comparable in adults and children from 12 years of age allowing extrapolation of data in adults to pediatric patients.

Data obtained from population pharmacokinetic analyses show that a dose of 300 mg/m<sup>2</sup> of Rozlytrek once daily in pediatric patients results in a similar systemic exposure attained in adults treated with 600 mg of Rozlytrek, once daily. Population pharmacokinetic analysis data support dosing of pediatric patients with BSA  $\geq$  1.5 m<sup>2</sup> with 600 mg of Rozlytrek once daily.

### *Genetic polymorphisms*

Following a single oral dose of Rozlytrek in Japanese and Caucasian healthy volunteers, no clinically relevant differences in the exposure of Rozlytrek were observed. Based on population pharmacokinetics analysis, there was no relationship between systemic exposure of entrectinib and race/ethnicity (Asian, Japanese, white and other ethnicities). No dose adjustment is required for patients of different race/ethnicities (see "Dosage/Administration: Special dosage instructions").

### Preclinical data

#### *Safety pharmacology and toxicity with repeated administration*

In toxicity studies with entrectinib in rats and dogs effect on CNS, skin, liver and haematology parameter have been observed at clinical relevant plasma expositions. In addition in dogs gastrointestinal toxicity and prolonged QT/QTc intervals have been observed. In one study in pigmented rats cornea lesions have been observed after oral treatment with entrectinib.

#### *Genotoxicity*

Entrectinib was not mutagenic in the bacterial reverse mutation (Ames) assay. A potential for abnormal chromosome segregation (aneugenicity) has been detected under in vitro conditions in cultured human peripheral blood lymphocytes (HPBL). Entrectinib was not clastogenic or aneugen in the in vivo micronucleus assay in rats and did not induce DNA-damage in a comet assays in rats.

#### *Carcinogenicity*

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

#### *Reproductive toxicity*

In an embryo-fetal developmental study in rats, fetal malformations (including body closure defects and malformations of the vertebrae and ribs), were observed at clinical relevant plasma exposures. Lower fetal weights and reduced skeletal ossification were observed at exposures below the clinical exposure at the recommended dose.

#### Fertility

No fertility studies in animals have been performed to evaluate the effect of entrectinib. With the exception of dose dependent decreases in prostate weight in male dogs, no effects of entrectinib on reproductive organs were observed in the toxicology studies in rats and dogs at 2.4-fold and 0.6-fold the clinical exposure, respectively.

#### *Juvenile Toxicity*

In a 13-week juvenile rat toxicity study from post-natal day 7 to day 97 (approximately equivalent to neonate to 16 years of age in humans), 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, plasma exposure approximately 0.1 times the clinical exposure), deficits in neurobehavioral assessments including functional observational battery and learning and memory (at  $\geq 8$  mg/kg/day, plasma exposure approximately 0.2 times the clinical exposure) and decreased femur length (at 16 mg/kg/day, plasma exposure approximately 0.3 times the clinical exposure). The 16 mg/kg/d-dose was in addition associated with severe systemic toxicity, including mortality. Other findings in juvenile animals were similar to entrectinib-induced findings in adult rats.

#### *Additional data*

Entrectinib was observed after oral treatment of rats and dogs in the CNS. The brain-to-plasma concentration ratios was of 0.6-1.5 in rats and 1.4-2.2 in dogs.

### **Other information**

#### *Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the pack.

#### *Special precautions for storage*

Keep out of the reach of children.

Do not store above 30 °C.

#### *Instructions for handling*

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

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

### **Authorisation number**

67280 (Swissmedic).

### **Packs**

Rozlytrek 100 mg: Bottle with 30 hard capsules.

Rozlytrek 200 mg: Bottle with 90 hard capsules.

### **Marketing authorisation holder**

Roche Pharma (Switzerland) Ltd., Basel.

### **Date of revision of the text**

November 2020.