Taiwan Food and Drug Administration

Assessment Report

Trade Name：羅思克 100 毫克 / 200 毫克膠囊
Rozlytrek 100 mg / 200 mg hard capsules

Active Ingredient：Entrectinib

License Number：衛部藥輸字第 027864/ 027865 號

Applicant：羅氏大藥廠股份有限公司

Approval Date：2020/05/21

Indication：
1. ROS1 陽性之非小細胞肺癌: 適用於治療 ROS1 陽性之局部晚期或轉移性非小細胞肺癌的成人病人。

2. NTRK 基因融合陽性之實體腫瘤: 適用於治療 NTRK 基因融合陽性之實體腫瘤的成人病人，並應符合以下條件：

- **具 NTRK 基因融合且無已知的後天阻抗性突變 (acquired resistance mutation)**
- **為轉移性實體腫瘤，或手術切除極可能造成嚴重病狀 (severe morbidity)**
- **於治療後發生疾病惡化，或沒有合適的替代治療選項**

本適應症係依據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

1. **Background Information**

Trade Name	**羅思克 100 毫克 / 200 毫克膠囊** Rozlytrek 100 mg / 200 mg hard capsules
Active Ingredient(s)	Entrectinib
Applicant	羅氏大藥廠股份有限公司
Dosage Form & Strengths	膠囊 100 mg, 200 mg
Indication	**1. ROS1 陽性之非小細胞肺癌:** **適用於治療 ROS1 陽性之局部晚期或轉移性非小細胞肺癌的成人病人。** **2. NTRK 基因融合陽性之實體腫瘤:** **適用於治療 NTRK 基因融合陽性之實體腫瘤的成人病人，並應符合以下條件：** - **具 NTRK 基因融合且無已知的後天阻抗性突變 (acquired resistance mutation)** - **為轉移性實體腫瘤，或手術切除極可能造成嚴重病狀 (severe morbidity)** - **於治療後發生疾病惡化，或沒有合適的替代治療選項** **本適應症係依據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。** ROZLYTREK is a kinase inhibitor indicated for the treatment of: 1. **ROS1-Positive Non-Small Cell Lung Cancer**: Adult patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. **2. NTRK Gene Fusion-Positive Solid Tumors:** Adult patients with solid tumors that: - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, - are metastatic or where surgical resection is likely to result in severe morbidity, and

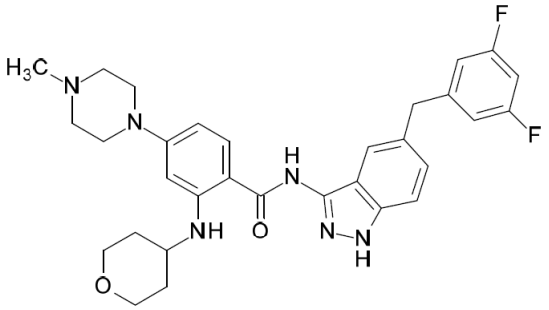
	- have progressed following treatment or have no satisfactory alternative therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Posology	請詳見仿單。
Pharmacological Category **ATC Code**	L01XE56

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, entrectinib, is chemically designated as N-{5-[(3,5-difluorophenyl)methyl]-1H-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino] benzamide:



It is white to off-white or pale pink powder or powder with lumps. The molecular formula and the molecular weight are $C_{31}H_{34}F_2N_6O_2$ and 560.64 Daltons, respectively. It is non-hygroscopic.

Adequate information of characterization of the drug substance has been provided. The molecular structure of entrectinib has been confirmed by elemental analysis, UV, IR, NMR, MS and single crystal x-ray crystallography.

The specification of the drug substance includes tests for description, identity, water, residual solvents, residue on ignition, elemental impurities, organic impurities, particle size distribution and assay.

2.1.2 Drug Product

Rozlytrek® capsules for oral use are supplied as printed hard-shell capsules containing 100 mg (yellow opaque HPMC capsule) or 200 mg of entrectinib (orange opaque HPMC capsule). The excipients used in the drug product formulation comply with the compendial monographs.

The specification of the drug product includes description, identification, content per capsule of entrectinib, degradation products, uniformity of dosage units, water content, dissolution and microbial limits. Analytical methods were described well and validated.

Stability studies of Rozlytrek® hard capsules under long term condition (30℃/65% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Entrectinib is a drug for the treatment of advanced or metastatic solid tumors with NTRK fusion-positive or ROS1-positive. The *in vitro* radiometric kinase assays demonstrated the selectivity of entrectinib was limited to TRKA, TRKB, TRKC, ROS1, and ALK. Entrectinib presented an anti-proliferative effect on the cell lines driven by *NTRK*, *ROS1,* and *ALK* gene fusions. There was a high correlation in the IC_{50} values between entrectinib and the M5 metabolite. In the *in vivo* xenograft model, oral administration of entrectinib inhibited tumor growth in the tumor harboring *NTRK1*, *NTRK3,* and *ROS1* gene fusions. The source of cell lines included colorectal cancer, non-small cell lung cancer, acute myeloid leukemia, head and neck cancer, sarcoma, and glioma.

For the safety pharmacology, single oral administration of entrectinib at 100 mg/kg in rats or 120 mg/kg in dogs did not cause any effects on CNS and cardiovascular system. However, repeated oral administrations at 120 mg/kg in dogs caused some adverse effects on CNS (tremor, hyperactivity, staggering and incoordination of limbs) and cardiovascular system (increase QT and QTcF interval).

2.2.2 Toxicological Studies

Pivotal nonclinical toxicity studies were 4-week and 13-week repeated-dose studies in rats and dogs, respectively. The primary target organs were skin (ulcer, acanthosis, hyperkeratosis, dermal fibrosis, and inflammation) and spleen (increase extramedullary hematopoiesis and spleen weight). The embryo-fetal development and juvenile toxicity studies suggested that entrectinib might delay the growth rate. The target organs in juvenile animals were the same as in adult animals. Entrectinib presented aneugenicity in the *in vitro* micronucleus assay but not in the *in vivo* micronucleus assay. Entrectinib presented no phototoxicity *in vivo*. The

genotoxicity of the impurities in the early development batches have been evaluated and present negative results.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK). Entrectinib also inhibits JAK2 and TNK2. The major active metabolite of entrectinib, M5, showed similar *in vitro* activity against TRK, ROS1, and ALK. Entrectinib is indicated for the treatment of adult patients with NTRK fusion-positive metastatic solid tumors, and patients with ROS1-positive, locally advanced or metastatic NSCLC. The recommended dose is 600 mg orally once daily for adults until disease progression or unacceptable toxicity.

The pharmacokinetics of entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for entrectinib and two weeks for M5 following daily administration. The geometric mean (CV%) steady-state C_{max} of entrectinib and M5 at the dose of 600 mg once daily was 3130 (80%) nM and 1250 (90%) nM, respectively, and the corresponding AUC_{ss} was 48000 (77%) nM*h and 24000 (97%) nM*h. The mean accumulation ratio after repeat dosing was 1.55 (49%) for entrectinib and 2.84 (93%) for M5. There was no significant food effect on entrectinib exposure.

Entrectinib and its active major metabolite M5 are both > 99% bound to human plasma proteins *in vitro*. The estimated apparent volume of distribution (V/F) was 551 L and 81.1 L for entrectinib and M5, respectively.

Entrectinib is metabolized primarily by CYP3A4 (~76%). The active metabolite M5 (formed by CYP3A4) is the only major active circulating metabolite identified. M5 has similar pharmacological potency to entrectinib *in vitro* and circulating M5 exposures at steady-state in patients were 40% of the corresponding entrectinib exposure. Following oral administration of a single oral dose of [^{14}C]-labeled entrectinib, 83% of radioactivity was excreted in feces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

2.3.2 Interaction Studies

The results of drug-drug interaction studies showed that strong CYP3A inhibitor (itraconazole) increased entrectinib $AUC_{0\text{-}INF}$ by 6-fold and C_{max} by 1.7-fold. And the moderate CYP3A inhibitor is predicted to increase entrectinib $AUC_{0\text{-}Tau}$ by 3-fold and C_{max} by 2.9-fold. While the strong CYP3A inducer reduced entrectinib $AUC_{0\text{-}INF}$ by 77% and C_{max}

by 56%. And the moderate CYP3A inducer is predicted to reduce entrectinib $AUC_{0\text{-}Tau}$ by 56% and C_{max} by 43%. When entrectinib was co-administrated with proton pump inhibitor (PPI), lansoprazole, the AUC and C_{max} of entrectinib was reduced by 25% and 23%, respectively. Coadministration of entrectinib with oral midazolam (a sensitive CYP3A substrate) and digoxin (a sensitive P-gp substrate) increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21%, and increased digoxin AUC by 18% and C_{max} by 28%.

2.3.3 Special Populations

Based on the population PK analysis, no clinically significant differences in the pharmacokinetics of entrectinib were observed based on age (18 years to 86 years), sex, race (White, Asian and Black), body weight (32 to 130 kg), mild to moderate renal impairment (CL_{cr} 30 to < 90 mL/min) and mild hepatic impairment (total bilirubin ≤ 1.5 times ULN). The impact of moderate to severe hepatic impairment or severe renal impairment on the pharmacokinetics of entrectinib is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The clinical data to support the efficacy of the claimed indications were based on the primary integrated analysis from the 3 adult studies (STARTRK-2, ALKA, and STARTRK-1).

The integrated efficacy analyses in ROS1-positive NSCLC patients were performed on 53 efficacy-evaluable subjects. The results showed entectinib treatment yielded an BICR assessment ORR of 77.4% (95% CI: 63.8, 87.7), achieving the pre-specified goal (lower limit >50%).

The integrated efficacy analyses in NTRK-positive adults were performed on 54 efficacy-evaluable subjects. The results showed entectinib treatment yielded a BICR assessment ORR of 57.4% (95% CI: 43.2, 70.87), also achieving the pre-specified goal (lower limit >30%).

For pediatric population, the pediatric trial STARTRK-NG is ongoing. Only preliminary results of 7 pediatric subjects (4.5 m/o to 6 y/o) were provided and the dosage used was not the proposed 300 mg/m^2 for pediatric patients. Therefore, the clinical evidence of indication and posology for pediatric population was limited and needed further supporting data from pharmacokinetic analysis. However, there were several deficiencies regarding pediatric PK evaluation. In summary, the submitted data could not support the efficacy and safety of pediatric population.

2.4.2 Safety Results

Major adverse events include constipation, dysgeusia, fatigue, dizziness, paresthesia, headache, muscular weakness, diarrhea, nausea, dyspnea, peripheral edema, anemia, infections, increased creatinine, neutropenia, blurred vision, cognitive impairment, photophobia, elevated liver enzymes, increased weight, heart failure, pneumonitis, hyperuricemia, QTc prolongation and electrolytes abnormalities.

2.5 Bridging Study Evaluation

The effect of race on the PK of entrectinib was assessed in healthy Japanese and Caucasian subjects, who received doses of 400 mg while fasted, and 600 mg in the both of fasted and fed state. The study result showed that average entrectinib peak exposures were 13%-14% higher in Japanese subjects (C_{max} ratios: 1.14, 1.13, and 1.13 for 400 mg fasted, 600 mg fasted, and 600 mg fed dosing, respectively). While the entrectinib total exposures were comparable between Japanese and Caucasian subjects (AUC_{inf} ratios: 1.00, 0.98, and 0.96 for 400 mg fasted, 600 mg fasted, and 600 mg fed dosing, respectively). M5 exposure was also similar between Japanese and Caucasian groups under both fed and fasted conditions. In summary, there was no significant ethnic difference from PK perspective.

The East Asian population consisted of 12.5% in NTRK fusion positive solid tumor efficacy evaluable set, 40.3% in ROS1 positive NSCLC efficacy evaluable setand 26.5% in safety evaluable set for both indications. Generally, the efficacy and safety profile were comparable between East Asian and Global population.

Overall, considering the characteristics of precision medicine of entrectinib and based on available data, bridging study was waived. Complete study reports (along with subgroup analyses of East Asian) of STARTRK-1, STARTRK-2 and BFAST should be submitted once available.

2.6 Conclusion

Overall, the submitted NDA package of entrectinib for CMC, PT, PK and Clinical section were adequate. The efficacy of claimed indications was demonstrated and safety profile is acceptable.

Based on the evaluation of provided evidence and applying the consistent review principles, accelerated approval was granted for the treatment of adult patients with NTRK gene fusion-positive metastatic solid tumors; and regular approval was granted for the treatment of adult patients with ROS1-positive, locally advanced or metastatic NSCLC.

The approval of pediatric indication for NTRK fusion-positive solid tumors was not recommended due to lack of sufficient PK and clinical data.

3. Post-Marketing Requirements

(1) Complete study reports (along with subgroup analyses of East Asian) of STARTRK-1, STARTRK-2 and BFAST should be submitted once available.

(2) The indication "NTRK fusion-positive metastatic solid tumors" is approved under accelerated approval, the following results should be submitted to confirm the clinical benefit.

1) Submit the final report from the first 54 patients with *NTRK*-fusion solid tumors enrolled across the ALKA, STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267] studies to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to entrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

2) Submit the final report from ongoing and proposed trials conducted to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion and without a known acquired resistance mutation; are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

   A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for each of the following tumor types: pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, and melanoma.

   A minimum of 40 patients with cancers other than pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, melanoma, soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer will also be studied. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.