Entrectinib (Rozlytrek®) for the treatment of patients whose solid tumours have a NTRK gene fusion, or patients with ROS1-positive advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]	Indication [2]
Entrectinib is a potent inhibitor of tropomyosin receptor kinase (TRK) A, B, and C, which has been shown to have anti-tumour activity against NTRK gene fusion-positive solid tumours, including CNS activity due to its ability to penetrate the blood-brain barrier.	Entrectinib is indicated for the treatment of patients whose solid tumours have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, or patients with ROS1-positive advanced NSCLC.

Current treatment

Solid tumours [3]:

- There are multiple treatment options currently available for the generic treatment of solid tumours including surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapies (e.g. monoclonal antibodies) and targeted cancer drugs (e.g. cancer growth blockers)
- The treatment provided will vary according to type of cancer, how big the cancer is, if it has spread and according to the patients' general health
- Regarding specific treatment for NTRK positive solid tumours, there are currently no licensed TRK inhibitors licensed for the treatment of TRK fusion positive cancers.

NSCLC [4]:

- Chemotherapy:
  - Pemetrexed-platin doublet treatment – shows special activity in ROS1 positive patients
- Targeted therapies:
  - Crizotinib – recommended by NICE for the treatment of advanced ROS1-positive NSCLC.

Regulatory status

EMA [2]

Approval status for this indication: On 28 May 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Rozlytrek®.

Date of issue of marketing authorisation valid throughout the European Union: **31/07/2020.**

The full indication is:

- Rozlytrek® as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours expressing a NTRK gene fusion,
  - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
  - who have not received a prior NTRK inhibitor
  - who have no satisfactory treatment options.
- Rozlytrek® as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced NSCLC not previously treated with ROS1 inhibitors.

Other indications: none

- ✓ **Medicine under additional monitoring**
- ✓ **Conditional approval (further evidence awaited)**

FDA [5]

Approval status for this indication: approved (08/2019)

Rozlytrek® is indicated for the treatment of:

- Adult patients with metastatic NSCLC whose tumors are ROS1-positive
- Adult and paediatric patients 12 years of age and older with solid tumors that:
  - have a 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.

Other indications: none

Costs

90 Rozlytrek® hard capsules 200 mg = € 7,579.00 (ex-factory price) [6].

The recommended dose for adults is 600 mg Entrectinib once daily [7].

Special warnings and precautions for use [7]

- Efficacy across tumour types:
  - The benefit of entrectinib has been established in single-arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions.
  - Favourable effects of Rozlytrek have been shown based on overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations.
  - For these reasons, entrectinib should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted).
- Cognitive disorders:
  - Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with entrectinib.
  - Patients over the age of 65 years experienced a higher incidence of these events than younger patients.
  - Patients should be monitored for signs of cognitive changes. Based on the severity of cognitive disorders, entrectinib treatment should be modified (see product information).
  - Patients should be counselled on the potential for cognitive changes with entrectinib treatment.
  - Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders.
- Fractures:
  - Fractures have been reported in 21.9% (7/32) paediatric patients treated with entrectinib in clinical trials. Bone fractures were reported in patients less than 12 years of age and were localised in the lower extremity (with a predilection for hip, femur and tibia).
  - Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly.
- Hyperuricemia:
  - Hyperuricemia has been observed in patients treated with entrectinib.
  - Serum uric acid levels should be assessed prior to initiating entrectinib and periodically during treatment.
  - Patients should be monitored for signs and symptoms of hyperuricemia.
  - Treatment with urate-lowering medicinal products should be initiated as clinically indicated and entrectinib withheld for signs and symptoms of hyperuricemia.
  - Entrectinib dose should be modified based on severity (see product information).
- Congestive heart failure (CHF):
  - CHF has been reported across clinical trials with Entrectinib. These reactions were observed in patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or entrectinib dose reduction/interruption.
  - For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of entrectinib treatment.
  - Patients receiving entrectinib should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate.
  - Based on the severity of CHF, entrectinib treatment should be modified (see product information).
- QTc interval prolongation:
  - QTc interval prolongation has been observed in patients treated with entrectinib in clinical trials.
  - Use of entrectinib should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval.
  - Entrectinib should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, CHF, unstable angina, and bradyarrhythmias . If in the opinion of the treating physician, the potential benefits of entrectinib in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.
  - Assessment of ECG and electrolytes at baseline and after 1 month of treatment with entrectinib are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout entrectinib treatment, are also recommended.
  - Based on the severity of QTc prolongation, entrectinib treatment should be modified (see product information).
- Women of childbearing potential:

- Entrectinib may cause foetal harm when administered to a pregnant woman.
- Women of childbearing potential must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of entrectinib.
- Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with entrectinib and for 3 months after the last dose.

❖ Drug interactions:
- Co-administration of entrectinib with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations, which could increase the frequency or severity of adverse reactions.
- In adult and paediatric patients 12 years and older, co-administration of entrectinib with a strong or moderate CYP3A inhibitor should be avoided.
- For adult patients, if co-administration is unavoidable, the entrectinib dose should be reduced.
- During treatment with entrectinib, the consumption of grapefruit and grapefruit products should be avoided.
- Co-administration of entrectinib with a strong or moderate CYP3A or P-gp inducer decreases entrectinib plasma concentrations, which may reduce efficacy of entrectinib, and should be avoided.

❖ Lactose intolerance:
- Entrectinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

❖ Sunset yellow FCF (E110):
- Rozlytrek® 200 mg hard capsules contain sunset yellow FCF (E110), which may cause allergic reactions.

Study characteristics [1, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	Co-primary PEs	Characteristics	Biomarker	Funding	Publication(s)
NCT02097810 (STARTRK-1) and NCT02568267 (STARTRK-2) and EudraCT 2012–000148–88 (ALKA-372-001)	54 [1][1], 53 [8]	entrectinib orally at a dose of at least 600 mg once per day in a capsule	-	Proportion of patients with an objective response + duration of response	integrated analysis of three open-label phase 1–2 trials	NTRK fusion positive	Ignyta/ F Hoffmann-La Roche	Link Link

Efficacy [1]

Objective response: n=31/54 (57%; 95% CI 43.2-70.8)
Complete response: n=4/54 (7%)
Partial response: n=27/54 (50%)
Stable disease: n=9/54 (17%)
Median duration of response: 10 months (95% CI 7.1 to not estimable)

Safety[2] [1]

Grade ≥3 AEs: most common treatment-related AEs in both safety populations were
- increased weight: n=7/68 (10%) in the NTRK fusion-positive safety population and n=18/355 (5%) in the overall safety-evaluable population) and
- anaemia in n=8/68 (12%) and n=16/355 (5%), respectively

Treatment-related SAEs: reported in n=7/68 (10%) patients in the *NTRK* fusion-positive and in n=30/355 (9%) in the overall safety population
Treatment-related deaths: none
Discontinuation[3]: 3/68 (4%) in the NTRK fusion-positive population and 14/355 (4%) in the overall safety population

Efficacy [8]

Objective response (in the efficacy-evaluable population): n=41/53 (77%; 95% CI 64–88)
Complete response: n=3/53 (6%)
Partial response: n=38/53 (72%)
Stable disease: n=1/53 (2%)
Median duration of response (in the overall integrated efficacy-evaluable population): 24.6 months (95% CI 11.4–34.8).

Safety [8]

AEs: 59% of treatment-related AEs were grade 1 or 2
Grade 3 treatment-related AEs: n=41/134 (31%)
Grade 4 treatment-related AEs: n=5/134 (4%)
Serious treatment-related AEs: n=15/134 (11%)
Deaths due to AEs: none

[1] Ten tumour types were treated (with at least 19 distinct histologies represented)
[2] The safety analysis included two safety populations: the NTRK fusion-positive safety-evaluable population (68 patients from STARTRK-1, STARTRK-2, and ALKA-372-001 who received at least one dose of entrectinib) and the overall safety-evaluable population (355 patients), which included patients from the phase 1 STARTRK-NG study with any tumour type and gene rearrangement who received at least one dose of entrectinib.
[3] discontinuation due to treatment-related AE(s)

Median PFS: 19.0 months (95% CI 12.2–36.6) **Median OS:** not estimable (95% CI 15.1 to not estimable) At the time of data cutoff, n=9/53 (17%) of patients had died; n=45/53 (85%; 95% CI 74–95) of patients were alive at **12 months** and n=43/53 (82%; 70–93) were alive at **18 months.**	**Discontinuation**[4]: n=7/134 (5%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	19 months	(95% CI 12.2–36.6)	PFS ≥6 months	3	-	-	-	3
Adapted	-	-	-	-	-	-	-	-	-	-	-

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	no (open-label)	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, CHF=congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CNS=central nervous system, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HR=hazard ratio, LVEF= left ventricular ejection fraction, n=number, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, NTRK=neurotrophic tyrosine receptor kinase, SAE=serious adverse event, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life

References:

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8. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. Lancet Oncol 2020; 21: 261–70 Published Online December 11, 2019.

[4] Due to treatment-related AES
[5] Two of the trials are currently ongoing
[6] No final analysis data available (ongoing trials), industry-funded