ENTRECTINIB (Rozlytrek)

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

Entrectinib for the treatment of patients aged 12 and over who have solid tumours (including primary cerebral tumours) that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options where the following criteria have been met:

2. Is aged 12 years or older. Entrectinib is only licensed in those aged 12 and above. If the patient is aged under 12 years, larotrectinib is licensed in this age group and can be accessed via form LAR1a.

3. Has a proven histological diagnosis of a malignant solid tumour (ie a carcinoma or a sarcoma or melanoma or a brain or spinal cord tumour) and does NOT have a leukaemia or a lymphoma or myeloma.

4. Has disease that is locally advanced or metastatic or would require surgical resection likely to result in severe morbidity.

5. Has no satisfactory systemic therapy options. A satisfactory systemic treatment option is defined as one which is funded by NHS England for the disease and indication in question. I confirm that the patient has already been treated with all the systemic therapy options funded by NHS England for the disease in question. As part of the evidence that NICE and NHS England wish to see at the NICE re-appraisal of entrectinib in NTRK gene fusion positive patients, data will be specifically analysed as to systemic therapies before and after entrectinib in order to test whether entrectinib has been used after all NHS-funded systemic therapies have been used.

- 1 line of systemic therapy for locally advanced/metastatic disease or
- 2 lines of systemic therapy for locally advanced/metastatic disease or
- 3 or more lines of systemic therapy for locally advanced/metastatic disease.

6. HAS a documented NTRK gene fusion in the tumour and this has been determined with appropriate nucleic acid-based assay(s).

- in NTRK1 or in NTRK2 or in NTRK3

7. The patient has not previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor.

8. Entrectinib will be used as monotherapy.

9. ECOG performance status (PS) of 0 or 1 or 2.

Note: a patient with a performance status of 3 or more is not eligible for entrectinib.

10. A PET/CT/MR scan of index assessable/measureable disease has been done prior to commencing entrectinib and that this will be repeated 10 weeks after the start of treatment (if not indicated before 10 weeks on account of assessing risk of disease progression).

11. Has had a recent CT or MR scan of the brain and either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting entrectinib.

- the patient does not have brain metastases or
- the patient does have brain metastases and has not received any cerebral surgery and/or radiotherapy and is symptomatically stable or
- the patient does have brain metastases and has received previous cerebral surgery and/or radiotherapy and is symptomatically stable.

Note: repeat imaging of the brain is required at week 10 after commencing entrectinib.

12. Entrectinib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or potentially curative surgery takes place.

13. The prescribing clinician is fully aware of the likely toxicities of entrectinib as listed in its SPC and aware that a significant rate of bone fractures has been reported in patients treated with entrectinib.

14. A formal medical review as to whether treatment with entrectinib should continue or not (on basis of being fit to continue treatment) will be scheduled to occur by the start of the second cycle (month) of treatment.
15. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
16. Entrectinib is to be otherwise used as set out in its Summary of Product Characteristics

Entrectinib response assessment and treatment continuation form in the treatment of patients who have solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options where the following criteria have been met:
2. A RECIST radiological assessment has been made of the index disease at 10 weeks after the start of entrectinib and I have indicated the outcome of this RECIST assessment below. This response assessment should exclude metastatic disease in the brain/CNS.
If the patient has a primary brain tumour indicate the response status.
- complete response of disease or
- partial response of disease or
- stable disease or
- progressive disease
Indicate how many weeks there were between date of start of entrectinib and date of above PET/CT/MR response assessment scan
3. A RECIST radiological assessment has been made of any metastatic intra-cerebral or CNS disease at 10 weeks after the start of entrectinib and have indicated the outcome of this RECIST assessment. If the patient does not have any metastatic intra-cerebral disease, indicate If the patient has a primary cerebral tumour,
- the patient does not have any metastatic intracerebral disease or
- the patient has a primary brain tumour and the response assessment has been done in the above section of this form or
- complete response in the brain/CNS or
- partial response in the brain/CNS or
- stable disease in the brain/CNS or
- progressive disease in the brain/CNS
Indicate how many weeks there were between date of start of entrectinib and date of above CT/MR response assessment scan:
4. The current clinical decision to continue or discontinue treatment with entrectinib is as set out:
- will continue treatment with entrectinib ie has so far achieved a complete response or a partial response or has stable disease or
- will discontinue or discontinued treatment with entrectinib on account of progressive disease or
- will discontinue or has discontinued treatment with entrectinib on account of unacceptable toxicity
Note: RECIST-documented partial/complete responses to entrectinib in some patients can occur later than at 10 weeks and so a patient with stable disease would be expected to continue entrectinib as long as the clinical assessment is that the patient is/may be benefitting. This 10 week treatment period is to assess the early response rate.
5. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
6. Entrectinib is to be otherwise used as set out in its Summary of Product Characteristics

REGIMEN
ENTRECTINIB 600mg oral once daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES
Every 28 days continuously until disease progression.

ADMINISTRATION
Available as 100mg and 200mg capsules.
Grapefruit and grapefruit juice should be avoided while on entrectinib.

ANTI-EMETICS
Low emetic risk

CONCURRENT MEDICATION REQUIRED

Entrectinib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS
Not applicable

INVESTIGATIONS
Blood results required before SACT administration
FBC, U&E every cycle
LFTs every cycle for 3 cycles then periodically, more frequently in those with elevated ALT or AST
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine every cycle
Baseline weight and every cycle
PET/CT/MRI baseline, then 10 weeks after starting treatment
Baseline ECG (QT interval >450msec avoid treatment), and after 1 month treatment, repeat as clinically indicated

MAIN TOXICITES AND ADVERSE REACTIONS

Entrectinib	Lung infection, Anaemia, neutropenia, dizziness, sensory neuropathy, blurred vision, hypotension, dysphagia, nausea, vomiting, myalgia, arthralgia, muscular weakness, raised blood creatinine, pain, pyreixia, fatigue, oedema

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Entrectinib	The concomitant use of strong or moderate CYP3A inhibitors, should be avoided. If coadministration is unavoidable, the use of strong or moderate CYP3A inhibitors with entrectinib should be limited to 14 days and the entrectinib dose should be reduced as follows: • 100mg once daily for use with strong CYP3A inhibitors • 200mg once daily for use with moderate CYP3A inhibitors. After discontinuation of the concomitant strong or moderate CYP3A inhibitors, the entrectinib dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash-out period may be required for CYP3A4 inhibitors with a long half-life Phenytoin and carbazepine are CYP3A inducers.

DOSE MODIFICATIONS
Entrectinib

First dose reduction	400mg once daily
Second dose reduction	200mg once daily

Entrectinib should be permanently discontinued in patients who are unable to tolerate 200mg od.

Non-haematological

Anaemia or neutropenia

Grade 3 or 4	• Withhold entrectinib until recovery to less than or equal to grade 2 or to baseline • Resume at the same dose or reduced dose, as clinically needed

Cognitive disorders

Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	• Withhold entrectinib until recovery to less than or equal to grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
Severe changes limiting activities of daily living (Grade 3)	• Withhold entrectinib until recovery to less than or equal to grade 1 or to baseline • Resume at reduced dose
Urgent intervention indicated for event (Grade 4)	• For prolonged, severe, or intolerable events, discontinue entrectinib as clinically appropriate

Congestive heart disease

Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3	• Withhold entrectinib until recovered to less than or equal to grade 1 • Resume at reduced dose
Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold entrectinib until recovered to less than or equal to grade 1 • Resume at reduced dose or discontinue as clinically appropriate

Hyperuricemia

Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold entrectinib until improvement of signs or symptoms • Resume entrectinib at same or reduced dose
Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold entrectinib until improvement of signs or symptoms • Resume entrectinib at same or reduced dose

QT interval prolongation

QTc 481 to 500ms	• Withhold entrectinib until recovered to baseline • Resume treatment at same dose
QTc greater than 500ms	• Withhold entrectinib until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are not identified
Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue entrectinib

Transaminase elevations

Grade 3	• Withhold entrectinib until recovery to less than or equal to grade 1 or to baseline • Resume at same dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Resume at a reduced dose for recurrent grade 3 events that resolve within 4 weeks
Grade 4	• Withhold entrectinib until recovery to less than or equal to grade 1 or to baseline • Resume at reduced dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent grade 4 events
ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue entrectinib

Other clinically relevant adverse reactions

Grade 3 or 4	• Withhold entrectinib until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Entrectinib has not been studied in patients with severe hepatic impairment.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Entrectinib has not been studied in patients with severe renal impairment.

REFERENCES
1. Doebele, R et al; Lancet Oncology 2020; 21 (2): 271–282 (NTRK)
2. Drilon, A et al; Lancet Oncology 202 ; 21 (2): 261-270 (ROS1)