# Entrectinib Therapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| As monotherapy for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors | C34 | 00702a | CDS 01/06/2022 |

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

Entrectinib is administered as a single oral daily dose until disease progression or unacceptable toxicity occurs.

| Drug | Dose | Route | Cycle |
|---|---|---|---|
| Entrectinib | 600mg once daily | PO | Continuous |
| If a planned dose is missed, patients can make up that dose unless the next dose is due within 12 hours.<br>If vomiting occurs immediately after taking a dose, patients may repeat that dose. | | | |
| The hard capsules should be swallowed whole and must not be opened or dissolved since the contents of the capsule are very bitter.<br>Entrectinib can be taken with or without food but should not be taken with grapefruit or grapefruit juice | | | |

## ELIGIBILITY:

- Indication as above
- Age >18 years
- ROS1-positive NSCLC as demonstrated by an accurate and validated test method
- Patients with CNS involvement
- ECOG 0-2
- Adequate organ function

## CAUTION:

Use with caution in patients with:

- Peripheral neuropathy grade 2 or worse

## EXCLUSIONS:

- Known hypersensitivity to entrectinib or any of its ingredients.
- Prior treatment with ROS1 inhibitor
- Prolonged QTc interval
- Interstitial lung disease, interstitial fibrosis or history of TK1-induced pneumonitis
- Pregnancy and lactation

## PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

## TESTS:

**Baseline tests:**

- Baseline confirmation that the patient's NSCLC tumour is ROS-1 positive by an accurate and validated test method.
- FBC, renal and liver profile
- Serum uric acid measurement
- ECG and electrolytes
- Left ventricular ejection fraction (LVEF) assessment in patients with known risk factors of CHF.
- Evaluation for symptoms of cognitive disorders

**Regular tests:**

- FBC, renal and liver profile
- Serum uric acid measurement
- ECG and electrolytes after one month, followed by periodic monitoring
- Cardiac assessment as clinically indicated
- Evaluation for central nervous system (CNS) symptoms or cognitive disorders
- Report and investigate as required any visual disturbances

**Disease monitoring:**

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with entrectinib, in case of specified adverse reactions (see Table 2) or based on the prescriber's assessment of the patient's safety or tolerability.
- The dose of entrectinib may be reduced up to 2 times, based on tolerability (see Table 1). Entrectinib treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

**Table 1: Dose reduction schedule for entrectinib**

| Dose reduction schedule | Dose level |
|---|---|
| Recommended dose | 600mg once daily |
| First dose reduction | 400mg once daily |
| Second dose reduction | 200mg once daily |

## Management of adverse events:

**Table 2: Recommended dose modifications for adverse reactions**

| Adverse reaction | Severity* | Dose modification |
|---|---|---|
| **Congestive heart failure** | Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3) | Withhold until recovered to ≤ Grade 1<br><br>Resume at reduced dose |
| | Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4) | Withhold until recovered to ≤ Grade 1<br><br>Resume at reduced dose or discontinue as clinically appropriate |
| **Cognitive disorders** | Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2) | Withhold until recovery to ≤ Grade 1 or to baseline<br><br>Resume at same dose or reduced dose, as clinically needed |
| | Severe changes limiting activities of daily living (Grade 3) | Withhold until recovery to ≤ Grade 1 or to baseline<br><br>Resume at reduced dose |
| | Urgent intervention indicated for event (Grade 4) | For prolonged, severe, or intolerable events, discontinue as clinically appropriate |
| **Hyperuricemia** | Symptomatic or Grade 4 | Initiate urate lowering medication<br><br>Withhold until improvement of signs or symptoms<br><br>Resume at same or reduced dose |
| **QT interval prolongation** | QTc 481 to 500 ms | Withhold until recovered to baseline |

| | | |
|---|---|---|
| | | Resume at same dose |
| | QTc greater than 500 ms | Withhold until QTc interval recovers to baseline<br><br>Resume at same dose if factors that cause QT prolongation are identified and corrected<br><br>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 |
| **Transaminase Elevations** | Grade 3 | Withhold until recovery to ≤ Grade 1 or to baseline<br><br>Resume at same dose if resolution occurs within 4 weeks<br><br>Permanently discontinue if adverse reaction does not resolve within 4 weeks<br><br>Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks |
| | Grade 4 | Withhold until recovery to ≤ Grade 1 or to baseline<br><br>Resume at reduced dose if resolution occurs within 4 weeks<br><br>Permanently discontinue if adverse reaction does not resolve within 4 weeks<br><br>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 |
| **Anaemia or Neutropenia** | Grade 3 or 4 | Withhold until recovery to ≤ Grade 2 or to baseline<br><br>Resume at the same dose or reduced dose, as clinically needed |
| **Other clinically relevant adverse reactions** | Grade 3 or 4 | Withhold until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline<br><br>Resume at the same or reduced dose, if resolution occurs within 4 weeks<br><br>Consider permanent discontinuation if adverse reaction does not resolve within |

| | | |
|---|---|---|
| | | 4 weeks<br><br>Permanently discontinue for recurrent Grade 4 events |

## Renal and Hepatic Impairment:

**Table 3: Dose modification of entrectinib in renal and hepatic impairment**

| **Renal Impairment** | | **Hepatic Impairment** | |
|---|---|---|---|
| **Mild** | No dose adjustment required | **Mild** | No dose adjustment required |
| **Moderate** | No dose adjustment required | **Moderate** | No dose adjustment required |
| **Severe** | Entrectinib has not been studied in patients with severe renal impairment | **Severe** | Entrectinib has not been studied in patients with severe hepatic impairment |

## Dose modifications for use with CYP3A inhibitors

The concomitant use of strong or moderate CYP3A inhibitors should be avoided. If co-administration 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 described in Table 4.

Table 4: Management of potential entrectinib interactions with CYP3A inhibitors

| Inhibitors | Dose[a] |
|---|---|
| Moderate CYP3A inhibitor | Reduce the entrectinib to 200mg once daily |
| Strong CYP3A inhibitor | Reduce the entrectinib to 100mg once daily |
| [a] 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. | |

## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:** Minimal to low (**Refer to local policy).**

**PREMEDICATIONS:** None

**OTHER SUPPORTIVE CARE:** None

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.*

- **Cognitive disorders:** Cognitive disorders were reported in clinical trials with entrectinib. A higher incidence was experienced in patients over the age of 65 years. Patients should be monitored for signs of cognitive changes. Based on the severity of cognitive disorders, entrectinib treatment should be modified as described in Table 2 above.
- **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 as described in Table 2 above
- **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, 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 should be evaluated and treated as clinically appropriate. Based on the severity of CHF, entrectinib treatment should be modified as described in Table 2 above.
- **QTc interval prolongation:** QTc interval prolongation has been observed in patients treated with entrectinib in clinical trials. 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. If 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 as described in Table 2 above.
- **Women of childbearing potential**. 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:

- Current drug interaction databases should be consulted for more information.
- 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. The co-administration of entrectinib with a strong or moderate CYP3A inhibitor should be avoided. 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.

## REFERENCES:


1. Drilon A, et al. Entrectinib in ROS1 fusion –positive non-small cell lung cancer: integrated analysis of three phase 1-2 trials Lancet Oncol 2020; 21(2):261-270. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7811790/
2. Entrectinib (Rozlytrek®) Summary of Product Characteristics. Accessed May 2022. Available at https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_en.pdf


| Version | Date | Amendment | Approved By |
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| 1 | 25/05/2022 | | Prof Maccon Keane |

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