Entrectinib Monotherapy – Adult

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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 Subject to a Managed Access Protocol – details available here
For the treatment of adult patient with solid tumours expressing a neurotrophic tyrosine receptor kinase (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	Multiple	00702b	CDS 01/10/2024 Subject to a Managed Access Protocol – details available here

* This is for post 2012 indications only

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
The hard capsules should be swallowed whole and must not be opened or dissolved since the contents of the capsule are very bitter. Entrectinib can be taken with or without food but should not be taken with grapefruit or grapefruit juice.			
If a planned dose 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, patients may repeat that dose.			

ELIGIBILITY:

- Indications as above
- Age >18 years
- ECOG 0-2
- Adequate organ function
- **NSCLC indication**
  - Subject to a managed access protocol, see here for details on how to apply and register

- ROS1-positive NSCLC as demonstrated by an accurate and validated test method
- Patients with CNS involvement

- **NTRK gene fusion indication**
  - Subject to a managed access protocol, see here for details on how to apply and register
  - Patients with metastatic or locally-advanced unresectable solid tumour
    - with an NTRK gene fusion without a known acquired resistance mutation confirmed using validated test method (Reference NCCP NTRK Gene Fusion Testing Guidance available here) AND
    - that has progressed or was nonresponsive to available therapies, are unfit for standard chemotherapy or for which no standard or available curative therapy exists and surgery would lead to substantial morbidity

CAUTION:

- Peripheral neuropathy grade 2 or worse

EXCLUSIONS:

- Known hypersensitivity to entrectinib or any of the excipients.
- Prolonged QTc interval
- Interstitial lung disease, interstitial fibrosis or history of TK1-induced pneumonitis
- Pregnancy and lactation
- **NSCLC indication**
  - Prior treatment with ROS1 inhibitor
- **NTRK gene fusion indication**
  - Prior treatment with an NTRK inhibitor

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- 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
- Brain scan at discretion of prescribing consultant

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 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 Resume at reduced dose or discontinue as clinically appropriate
Cognitive disorders	Intolerable, but moderate changes interfering with activities of daily living	Withhold until recovery to ≤ Grade 1 or to baseline Resume at same dose or reduced dose, as

	(Intolerable Grade 2)	clinically needed
	Severe changes limiting activities of daily living (Grade 3)	Withhold until recovery to ≤ Grade 1 or to baseline 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 Withhold until improvement of signs or symptoms 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 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
Transaminase Elevations	Grade 3	Withhold until recovery 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 until recovery 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	Permanently discontinue

	total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	
Anaemia or Neutropenia	Grade 3 or 4	Withhold until recovery to ≤ Grade 2 or to baseline 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 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
* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0		

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 is recommended
Moderate	No dose adjustment required	**Moderate**	No dose adjustment is recommended
Severe	Entrectinib has not been studied in patients with severe renal impairment	**Severe**	No dose adjustment is recommended. Patients with severe hepatic impairment should be carefully monitored for hepatic function and adverse reactions.
Renal and hepatic recommendations as per SPC			

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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked Available on NCCP website

Minimal to low (**Refer to local policy).**

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link Available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link Available on NCCP website

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.

- **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 entrectinib 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 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.
- **Fractures:** Fractures have been reported in paediatric patients treated with entrectinib in clinical trials. Bone fractures mostly occurred in paediatric patients less than 12 years of age and were localised in the lower extremity. In both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area. 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 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**: Entectinib 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. 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.
- 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.
- Current drug interaction databases should be consulted for more information.

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. Doebele R et al. Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials Lancet Oncol. 2020 Feb; 21(2): 271–282. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7461630/
3. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Entrectinib (Rozlytrek®) Summary of Product Characteristics. Accessed November 2023. Available at https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	25/05/2022		Prof Maccon Keane
2	01/10/2024	Regimen reviewed. New indication added. Reimbursement status updated for indications 702a and 702b.	Prof Ray McDermott

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.