Larotrectinib Monotherapy - Adult

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursed status*
For the treatment of adult patients with solid tumours that display 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 no satisfactory treatment options	Multiple	00758a	CDS 01/05/2023 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.

Treatment with larotrectinib should be continued until disease progression or unacceptable toxicity occurs.

Drug	Dose	Route	Cycle
Larotrectinib	100mg twice daily	PO	Continuous
Larotrectinib is available as a capsule or oral solution with equivalent oral bioavailability and may be used interchangeably. The capsule should be swallowed whole with a glass of water. Due to the bitter taste, the capsule should not be opened, chewed or crushed. The capsules can be taken with or without food but should not be taken with grapefruit or grapefruit juice.			
If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.			

ELIGIBILITY:

- Indication as above
  - Subject to a managed access protocol, see here for details on how to apply and register
- 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
- ECOG 0-2
- Adequate haematologic, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to larotrectinib or to any of the excipients
- Clinically significant active cardiovascular disease
- Patients with symptomatic brain metastases
- Active uncontrolled systemic bacterial, viral or fungal infection
- Pregnancy or lactation
- Co-administration with strong or moderate CYP3A4/P-gp inducers
- Prior treatment with an NTRK inhibitor
- Major surgery within 2 weeks prior to cycle 1, day 1

CAUTION IN USE:

- If co-administration with a strong CYP3A4 inhibitor is necessary, the larotrectinib dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, larotrectinib should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Brain scan at discretion of prescribing consultant

Regular tests:

- FBC, renal and liver profile monthly for first three months, then periodically during treatment

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.
- For all Grade 2 adverse reactions,
  - continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.
- For Grade 3 or 4 adverse reactions not referring to liver function test abnormalities,
  - Larotrectinib should be withheld until the adverse reaction resolves or improves to baseline or Grade 1.
  - Resume at the next dose modification if resolution occurs within 4 weeks.
  - Larotrectinib should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.
- Refer to Table 1 below for recommended dose modifications for larotrectinib for adverse reactions.
- Refer to Table 3 below for recommended dose modifications in case of liver function test abnormalities during treatment with larotrectinib.
- Larotrectinib should be permanently discontinued in patients who are unable to tolerate larotrectinib after three dose modifications.

Table 1: Recommended dose modifications for larotrectinib for adverse reactions

Dose Reduction Level	Dose
First	75 mg twice daily
Second	50 mg twice daily
Third	100 mg once daily

Renal and Hepatic Impairment:

Table 2: Dose modifications for larotrectinib[a] in renal and hepatic impairment

Renal impairment	Hepatic impairment
No dose adjustment is required for patients with renal impairment	The starting dose of larotrectinib should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).
[a] Larotrectinib (renal and hepatic from SPC)	

Management of adverse events:

Table 3: Recommended dose modifications and management for larotrectinib for liver function test abnormalities

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST (>3x ULN and ≤5x ULN)	Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5x ULN and ≤20x ULN) or Grade 4 ALT and/or AST (>20x ULN), with bilirubin <2x ULN	• Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. • Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk.

	• Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3x ULN with bilirubin ≥2x ULN	• Withhold treatment and monitor liver function frequently until resolution or return to baseline. • Consider permanent treatment discontinuation. • Treatment should only be resumed in patients where the benefit outweighs the risk. • If resumed, start at the next lower dose. Monitor liver function frequently upon restart. • Permanently discontinue treatment if adverse reaction recurs after resuming treatment.
ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = upper limit of normal	

SUPPORTIVE CARE:

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

PREMEDICATIONS: No specific recommendations

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Larotrectinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Efficacy across tumour types:** The benefit of larotrectinib has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions. Favourable effects of larotrectinib have been shown on the basis of 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 genetic alterations. For these reasons, larotrectinib should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).
- **Neurologic reactions:** Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib. For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing larotrectinib dosing should be considered, depending on the severity and persistence of these symptoms.
- **Hepatotoxicity:** Abnormalities of liver function tests including increased ALT, AST, alkaline phosphatase (ALP) and bilirubin have been observed in patients receiving larotrectinib**. :** The majority of ALT and AST increases occurred in the first 3 months of treatment. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported in adult patients. In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue larotrectinib based on the severity. Liver function including ALT, AST, ALP and bilirubin should be monitored before the first dose, then every 2 weeks during the first month of treatment, then monthly for the next 6 months of treatment, then periodically during treatment. In patients who develop transaminase elevations, more frequent testing is needed.

- **Co-administration with CYP3A4/P-gp inducers:** Avoid co-administration of strong or moderate CYP3A4/P-gp inducers with larotrectinib due to a risk of decreased exposure.
- **Co-administration with CYP3A4/P-gp/BCRP inhibitors:** Co-administration of larotrectinib with strong or moderate CYP3A inhibitors, P-gp and BCRP inhibitors may increase larotrectinib plasma concentrations. Avoid co-administration of strong CYP3A4/P-gp inhibitors with larotrectinib due to a risk of increased exposure. If co-administration with a strong CYP3A4 inhibitor is necessary, the larotrectinib dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, larotrectinib should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor.
- **Contraception in female and male:** Women of childbearing potential must use highly effective contraception while taking larotrectinib and for at least one month after stopping treatment. It is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.
  Males of reproductive potential with a non-pregnant woman partner of child bearing potential should be advised to use highly effective contraception during treatment with larotrectinib and for at least one month after the final dose.
- **Effects on ability to drive or use machines:** Larotrectinib has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly Grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain larotrectinib therapy does not affect them adversely.

DRUG INTERACTIONS:

Consult current drug interaction databases and relevant SmPC.

REFERENCES:

1. Drilon A, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018; 378:731-739. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1714448
2. 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.pd
3. Larotrectinib (Vitrakvi®) Summary of Product Characteristics. Last updated: 22/09/2023. Accessed Dec 2023. Available at https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	19/08/2022		Prof Ray McDermott
2	28/04/2023	Updated reimbursement status and included links to MAP	NCCP
3	15/04/2024	Regimen reviewed. - Amended dose modifications for liver function tests abnormalities, including addition of Table 3 (as per SPC update). - Amended adverse effects as per SPC update (hepatotoxicity and co-administration with CYP3A4/P-gp/BCRP inhibitors).	Prof Ray McDermott

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.