LAROTRECTINIB (Vitrakvi)

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/)

Larotrectinib for the treatment of adults and children 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:

2. 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.

Site of tumour origin: (NB if sarcoma, please enter sarcoma; if unknown primary, please state as such) and Histological type: (eg for breast cancer: ductal carcinoma, lobular carcinoma, secretory carcinoma etc; eg for lung cancer: squamous NSCLC, non-squamous NSCLC etc; eg for sarcoma: fibrosarcoma, osteosarcoma, gastrointestinal stromal tumour etc).

3. Has disease that is locally advanced (for which systemic therapy has been indicated or surgical resection is likely to result in severe morbidity) or metastatic or would require surgical resection likely to result in severe morbidity.

4. 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. 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 larotrectinib in NTRK gene fusion positive patients, data will be specifically analysed as to systemic therapies before and after larotrectinib in order to test whether larotrectinib has been used after all NHS-funded systemic therapies have been used.

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

5. HAS a documented NTRK gene fusion in the tumour and this has been determined with appropriate nucleic acid-based assay(s), in NTRK, in NTRK2 or in NTRK3

6. Has not previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor.

7. Larotrectinib will be used as monotherapy.

8. 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 larotrectinib.

9. A PET/CT/MR scan of index assessable/measureable disease has been done prior to commencing larotrectinib 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).

10. 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 larotrectinib, does not have brain metastases, does have brain metastases and has not received any cerebral surgery and/or radiotherapy and is symptomatically stable, 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 larotrectinib

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

12. Fully aware of the likely toxicities of larotrectinib as listed in its SPC.

13. A formal medical review as to whether treatment with larotrectinib 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.

14. 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).

15. Larotrectinib is to be otherwise used as set out in its Summary of Product Characteristics

Larotrectinib 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:

2. A RECIST radiological assessment has been made of the index disease at 10 weeks after the start of larotrectinib 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 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 larotrectinib 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 larotrectinib:
- does not have any metastatic intracerebral disease or
- has a primary brain tumour and the response assessment has been done 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
4. The current clinical decision to continue or discontinue treatment with larotrectinib:
- will continue treatment with larotrectinib ie has so far achieved a complete response or a partial response or has stable disease or
- will discontinue or has discontinued treatment with larotrectinib on account of progressive disease or
- will discontinue or has discontinued treatment with larotrectinib on account of unacceptable toxicity
Note: RECIST-documented responses to larotrectinib in some patients can occur later than at 10 weeks and so a patient with stable disease would be expected to continue larotrectinib 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. Larotrectinib is to be otherwise used as set out in its Summary of Product Characteristics

REGIMEN

LAROTRECTINIB 100mg oral twice daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days for up to 12 weeks.
To continue beyond 12 weeks an assessment and separate Blueteq form needs to be completed, treatment may then continue until disease progression.

ADMINISTRATION

Available as 25mg and 100mg capsules, 20mg/ml oral solution.
Grapefruit and grapefruit juice should be avoided while on larotrectinib.

ANTI-EMETICS

Low emetic risk

CONCURRENT MEDICATION REQUIRED

Larotrectinib	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

MAIN TOXICITES AND ADVERSE REACTIONS

Larotrectinib	Anaemia, neutropenia and leukopenia, dizziness, myalgia, fatigue, ALT or AST increased

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Larotrectinib	Co-administration of Larotrectinib with strong or moderate CYP3A and P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided. Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of Larotrectinib with strong CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations.

DOSE MODIFICATIONS

Larotrectinib

First dose modification	75mg twice daily
Second dose modification	50mg twice daily
Third dose modification	100mg once daily

Larotrectinib should be permanently discontinued in patients who are unable to tolerate 100mg od.

Non-haematological

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:
- 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.

Hepatotoxicity
Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations.
ALT and AST increase were reported in patients receiving larotrectinib. The majority of ALT and AST increases occurred in the first 3 months of treatment.

Patients with grade 2 ALT and/or AST increases, should be followed with serial laboratory evaluations every one to two weeks after the observation of grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.
Withhold or permanently discontinue Larotrectinib based on the severity. If withheld, the Larotrectinib dose should be modified when resumed.

Hepatic impairment
The starting dose of Larotrectinib should be reduced to 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).

Renal impairment
No dose adjustment is required for patients with renal impairment.

REFERENCES
1. Hong, D et al; Lancet Oncology 2020; 21 (4) : 531-540 NICE TA630