Indication	Is indicated as monotherapy for the treatment of adult patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion and have 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. NB The patient must not have previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor or have a leukaemia or a lymphoma or myeloma.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until progressive disease or unacceptable toxicity or patients' choice or potentially curative surgery can be performed. A formal medical review must take place by the start of the second cycle to establish if treatment should continue or not.
Monitoring Parameters pre-treatment	• FBCs and U&Es baseline and before each cycle. • LFTs including ALT and AST baseline and monthly for the first 3 months and then as clinically indicated thereafter. More frequent monitoring may be required in patients who experience raised transaminases. • Proceed with treatment if PLTS>/=50 and Neuts>/=1. • Confirm the patient either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting larotrectinib. • A PET/CT/MR scan of index assessable/measureable disease and also of the brain must be done prior to commencing larotrectinib and is be repeated 10 weeks after the start of treatment or sooner if clinically indicated. • **Hepatic Impairment:** no dose adjustment to starting dose in mild (Child-Pugh A) hepatic impairment, in moderate to severe (Child-Pugh B to Child-Pugh C) hepatic impairment the dose should be reduced by 50%. • **Renal Impairment:** no recommended dose adjustment. • **Dose modification and adverse reactions:** o Dosing interruption or dose reduction may be required based on individual safety and tolerability. First dose reduction: 75 mg taken orally twice daily. Second dose reduction: 50 mg taken orally twice daily. Third dose reduction: 100mg taken orally once daily. o For all Grade 2 adverse reactions, dose reduction is not always required, but increase monitoring to ensure no worsening toxicity, dose reduction is at the clinician's discretion. Patients observed to have Grade 2 ALT and/or AST increases (>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal), should have weekly or fortnightly bloods until toxicity has resolved to establish whether a dose interruption or reduction is required. o For Grade 3 or 4 adverse (e.g. for haematological toxicity PLTS <50 and Neuts <1) reactions interrupt larotrectinib until toxicity resolves or improves to baseline or Grade 1. Resume at the next dose modification if resolution occurs within 4 weeks. o Larotrectinib should be permanently discontinued if an adverse reaction does not resolve within 4 weeks or if the patient cannot tolerate after 3 dose modifications. • **<u>Common drug interactions</u>: (for comprehensive list refer to BNF/SPC)** o Co-administration with strong CYP3A4, 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. If concomitant use with a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin) is necessary the

	dose of larotrectinib should **be reduced by 50%.** If the strong CYP3A4 inhibitor is discontinued, larotrectinib should be resumed at the dose used prior to the initiation of the strong CYP3A4inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A4 inhibitor. ○ Co-administration with strong or moderate CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, St John's Wort) and strong or moderate P-gp inducers should be avoided. ○ Caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) dose modification of the CYP3A substrate may be required. • **Adverse reactions** ○ Neurologic reactions: including dizziness, gait disturbance and paraesthesia have been reported. Withholding, reducing, or discontinuing treatment should be considered depending on severity of symptoms. • **Missed dose**: If a dose is missed, the dose should be omitted and the next dose taken at the next scheduled time. If vomiting occurs after dosing, patients should not take another dose. • Dizziness and fatigue have been reported in patients taking larotrectinib, patients should be advised not to drive and or operate machinery until they have established if they are safe to do so. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	SPC accessed online 04/05/20 CDF list v1.162 accessed online BNF accessed online 05/05/20

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days.

TTO	Drug	Dose	Route	Directions
	LAROTRECTINIB oral solution 20mg/ml	**100mg**	PO	BD Should not be taken with grapefruit or grapefruit juice. Store in a refrigerator. Once open after 30 days return any remaining solution to the hospital pharmacy. Available as 100ml bottle. Reduced dose with strong CYP3A4 inhibitors, see drug interactions.
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously. Dispense on cycle 1 then only if required.