Indication	Pemigatinib monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 21 days. Continue until disease progression, unacceptable toxicity or patient choice. There should be a first formal medical review as to whether treatment with pemigatinib should continue or not before the 3rd cycle.
Monitoring Parameters pre-treatment	• FBC, U&Es (including Ca^{2+} and PO_4^{3-}) and LFTs at baseline, day 8 and day 15 of cycle 1 and at each cycle. • If a patient develops hyperphosphatemia during cycle 1 bloods should be checked at day 8 of cycle 2 onwards until phosphate is <2.26mmol/l for 2 consecutive cycles on a stable dose of phosphate binders. • Ophthalmic examination including optical coherence tomography (OCT) is required prior to initiation of therapy, every 2 months for the first 6 months of treatment and then every 3 months thereafter. • Patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment should be treated with caution at clinician's discretion. • The patient should not have untreated or symptomatic brain metastases prior to starting treatment. • **Hepatic impairment:** No dose adjustment is required in mild or moderate impairment. In severe impairment the pemigatinib dose should be reduced as follows: patients on 13.5mg reduced to 9mg; patients on 9mg reduced to 4.5mg • **Renal impairment:** No dose adjustment required in mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis. In **severe** renal impairment (<30ml/min) the pemigatinib dose should be reduced as follows: patients on 13.5mg reduced to 9mg; patients on 9mg reduced to 4.5mg. • **Management of adverse reactions and dose adjustments: (see table 1)** • For grade 3 toxicities (for serous retinal detachment and Hyperphosphataemia see table 1), stop treatment until recovery to Grade ≤ 1 or baseline. Resume at next lower dose if resolves within 2 weeks. For patients receiving 13.5mg once daily for 14 days followed by 7 day break, the first dose reduction should be 9mg once daily for 14 days followed by 7 day break and the 2nd dose reduction is to 4.5mg once a day for 14 days followed by 7 day break. Treatment should be permanently discontinued if: - Toxicity does not resolve within 2 weeks. - Recurrent Grade 3 after 2 dose reductions. - patients that are unable to tolerate 4.5mg daily, or - any Grade 4 toxicity occurs. • **Hyperphosphataemia:** Increases in phosphate levels can occur whilst taking pemigatinib. Monitor for hyperphosphatemia and withhold, reduce the dose, or permanently discontinue based on duration and severity of hyperphosphatemia (see table 1). In all patients, a low-phosphate diet should be initiated when serum phosphate level is >1.78mmol/L and adding a phosphate-lowering therapy should be considered when the level is >2.26mmol/L. The dose of phosphate-lowering

	therapy should be adjusted until serum phosphate level returns to <2.26mmol/L. Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below the normal range. • **<u>Common drug interactions (for comprehensive list refer to SPC)</u>** • Avoid concomitant use of strong CYP3A inhibitors (e.g., grapefruit/grapefruit juice, itraconazole, ketoconazole, ritonavir), if concomitant use with a strong CYP3A inhibitor cannot be avoided reduce dose by one level (13.5mg to 9mg; 9mg to 4.5mg). If concomitant use of a strong CYP3A inhibitor is discontinued, increase the dose (after 3 plasma half-lives of the CYP3A inhibitor) to the dose that was used before starting the strong inhibitor. • Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) and moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, phenobarbital, primidone) should be avoided during treatment with pemigatinib. Concomitant St John's wort is contraindicated. • Co-administration of pemigatinib with P-gp substrates (e.g., digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. Pemigatinib administration should be separated by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index. Pemigatinib induces CYP2B6. Co-administration of pemigatinib with CYP2B6 substrates (e.g., cyclophosphamide, ifosfamide, methadone, efavirenz) may decrease their exposure. • PPIs should be avoided in patients receiving pemigatinib. • Patients should not drink grapefruit juice or eat grapefruit whilst taking pemigatinib. • **Missed dose:** If a dose of pemigatinib is missed by four or more hours or vomiting occurs after taking a dose, an additional dose should not be administered, and dosing should be resumed with the next scheduled dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet**.** • Patients should be advised that pemigatinib may affect their ability to drive or operate machinery.
References	SPC accessed online 10.08.21 Blueteq form accessed online 10.08.21 CDF list 1.185 accessed online 10.08.21

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

Table 1 Recommended dose modifications for pemigatinib adverse reactions

Adverse Reaction	Severity	Dose Modification
serous retinal detachment	Asymptomatic	If asymptomatic and stable on serial examination, continue pemigatinib.
	Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤3 lines of decreased vision from baseline); limiting instrumental activities of daily living.	Withhold until resolution. If improved on subsequent examination, resume at the next lower dose level. If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status
	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200) limiting activities of daily living **OR** Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	Withhold until resolution. If improved on subsequent examination, resume at 2 dose levels lower. If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status
Hyperphosphatemia	Serum phosphate >2.26mmol/L to ≤3.23mmol/L	Initiate phosphate lowering therapy and monitor serum phosphate weekly. Withhold if levels are not <2.26mmol/L within 2 weeks of starting phosphate lowering therapy. Resume at the same dose when phosphate levels are <2.26mmol/L for first occurrence; resume at a lower dose level for subsequent recurrences.
	Serum phosphate 3.23mmol/L	Initiate phosphate lowering therapy (refer to local trust policy) and monitor serum phosphate weekly. Withhold if levels are not ≤ 3.23mmol/L within 1 week after starting phosphate lowering therapy. Resume at the next lower dose level when phosphate levels are <2.26mmol/L. Permanently discontinue for recurrence of serum phosphate >3.23mmol/L following 2 dose reductions.

Repeat every 21 days

TTO	Drug	Dose	Route	Directions
Day 1	**PEMIGATINIB**	**13.5mg* * see notes above**	PO	OD for 14 days followed by a 7 day break. Take at the same time every day. Swallow tablets whole, do not crush, chew or dissolve. Available as 4.5mg, 9mg and 13.5mg tablet
	Hypromellose	0.3%	topical	One drop each eye QDS. Dispense on cycle 1 only, then only if required.
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously. Dispense on Cycle 1 only, then only if required
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, then only if required.