Indication	For the treatment of locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation in adults after 1 or more systemic treatments.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continuous until disease progression or unacceptable toxicity or patient choice to stop treatment. A formal medical review as to whether treatment with ivosidenib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • An **ECG** must be performed prior to treatment initiation, QTc should be <450 msec, in the presence of an abnormal QT, consultant should thoroughly reassess the benefit/risk of initiating ivosidenib. If QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with ivosidenib should remain exceptional and be accompanied by close monitoring. • **ECG** must be performed at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains </= 480 msec and when clinically indicated. QTc interval abnormalities should be managed promptly (see management of adverse reactions and dose adjustments below). • FBCs, U&Es and LFTs should be assessed prior to initiation, at least once weekly for the first month of treatment, once every other week for the second month, and at each cycle. • Inform clinician if Hb is less than 8g/dl. • **Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Ivosidenib should be used with caution in patients with moderate and severe hepatic impairment with close monitoring. • **Renal impairment:** No dose adjustment is required if CrCl >/=30ml/min. No recommended dose for patients with severe renal impairment (CrCL <30ml/min), ivosidenib should be used with caution with close monitoring. • **Management of adverse reactions and dose adjustments:** • **Cardiac Contraindications:** o Congenital long QT syndrome. o Familial history of sudden death or polymorphic ventricular arrhythmia. o QT/QTc interval > 500 msec, regardless of the correction method. • **Cardiac monitoring:** o QTc interval prolongation has been reported following treatment with ivosidenib. Any abnormalities should be managed promptly. In case of suggestive symptomatology, an ECG should be performed as clinically indicated. In case of severe vomiting and/or diarrhoea, an assessment of serum electrolytes abnormalities, especially potassium and magnesium, must be performed. o Patients should be informed of the risk of QT prolongation, the associated signs and symptoms (palpitation, dizziness, syncope or even cardiac arrest) and be advised to contact the oncology team immediately if any symptoms are experienced.

	○ Patients with congestive heart failure or electrolyte abnormalities should be closely monitored, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib. ○ Treatment should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia. ○ Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated. ***The recommended dose of ivosidenib should be reduced to 250mg once daily if use of moderate or strong CYP3A4 inhibitors cannot be avoided.** If the moderate or strong CYP3A4 inhibitor is discontinued, the dose of ivosidenib should be increased to 500mg after at least 5 half-lives of the CYP3A4 inhibitor. • **Recommended dose modification for QTc prolongation:** ○ **QTc interval prolongation > 480 to 500 msec (Grade 2)** Monitor and supplement electrolyte levels as clinically indicated, interrupt treatment until QTc interval returns to </=480 msec, then restart ivosidenib at 500 mg once daily. Review and adjust concomitant medicinal products with known QTc interval-prolonging effects. Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to </= 480 msec. ○ **QTc interval prolongation > 500 msec (Grade 3)** Monitor and supplement electrolyte levels as clinically indicated, interrupt treatment and monitor ECG every 24 h until QTc interval returns to within 30 msec of baseline or </= 480 msec. If QTc interval prolongation > 550 msec, treatment should be interrupted and consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec. Resume ivosidenib at 250mg once daily after QTc interval returns to within 30 msec of baseline or </= 480 msec and monitor ECGs at least weekly for 3 weeks and as clinically indicated. If alternative aetiology for QTc interval prolongation is identified, dose may be increased to 500 mg ivosidenib once daily. Review and adjust concomitant medicinal products with known QTc interval prolonging effects. ○ **QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4)** Permanently discontinue treatment. • **Other Grade 3 or higher adverse reactions:** ○ Interrupt until toxicity resolves to Grade 1 or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity). ○ If Grade 3 toxicity recurs (a second time), reduce dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily. ○ If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • Concomitant administration of medicinal products known to prolong the QTc interval, (e.g. anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals) may increase the risk of QTc interval prolongation and should be avoided whenever possible. If use of a suitable alternative is not possible, patients should be treated with caution and closely monitored for QTc interval prolongation. An ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated.

	• Concomitant administration of moderate (e.g. aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice) or strong (e.g. clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole) CYP3A4 inhibitors increases plasma concentrations of ivosidenib. This may increase the risk of QTc interval prolongation and suitable alternatives that are not moderate or strong CYP3A4 inhibitors should be considered whenever possible during treatment (* see dose adjustment in cardiac monitoring section above). • Concomitant administration of strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort) is expected to decrease plasma concentrations of ivosidenib and is **contraindicated** during treatment. • Ivosidenib inhibits P-gp and has the potential to induce P-gp. Concomitant administration of dabigatran is **contraindicated**. • Concomitant administration of OAT3 substrates (e.g. benzylpenicillin, furosemide) or sensitive OATP1B1/1B3 substrates (e.g. atorvastatin, pravastatin, rosuvastatin) should be avoided whenever possible during treatment. Patients should be treated with caution if use of a suitable alternative is not possible. • Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Therefore, it may decrease systemic exposure to substrates of these enzymes (such as itraconazole or ketoconazole). Suitable alternatives that are not CYP3A4, CYP2B6, CYP2C8 or CYP2C9 substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, methadone, pioglitazone, repaglinide, phenytoin, warfarin), or CYP2C19 substrates (e.g. omeprazole) should be considered during treatment. Patients should be monitored for loss of substrate efficacy if use of such medicinal products cannot be avoided. • Ivosidenib has the potential to induce UGTs and it may, therefore, decrease systemic exposure to substrates of these enzymes (e.g. lamotrigine, raltegravir). • Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended for at least 1 month after the last dose. • **Missed dose:** If a dose is missed or not taken at the usual time, the dose should be taken as soon as possible within 12 hours after the missed dose. If longer than 12 hours the dose should be omitted and the dose taken at the next scheduled time, two doses should not be taken within 12 hours. If a dose is vomited, replacement tablets should not be taken. • **Driving:** Ivosidenib may cause fatigue and dizziness, patients who experience these symptoms should use caution when driving or operating machines. • **Oral Guidelines:** For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	SPC accessed online 30.11.2023 BlueTeq form accessed online 14.12.2023

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

Repeat every 28 days: continuous treatment.

TTO	Drug	Dose	Route	Directions
Day 1	**IVOSIDENIB**	500mg	PO	OD Patients should not eat anything for 2 hours before and until 1 hour after taking the tablets. Swallow whole with water. Avoid grapefruit/grapefruit juice. Available as 250mg tablets
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously. Dispense on Cycle 1 then only if specified.