Ivosidenib

Indication
Inoperable locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

Regimen details
Ivosidenib tablets 500mg taken once daily

Cycle frequency
Continuous treatment (dispense as 28-day cycles)

Number of cycles
Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient

Administration
The tablets are taken once daily at about the same time each day. Patients should not eat anything for 2 hours before and through 1 hour after taking the tablets. The tablets should be swallowed whole with water.

Patients should be advised to avoid grapefruit and grapefruit juice during treatment. Patients should also be advised not to swallow the silica gel desiccant found in the tablet bottle

Pre-medication
None

Emetogenicity
Low (supply metoclopramide with first cycle)

Additional supportive medication
Supply loperamide with first cycle

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
ECG	14 days

Note: ivosidenib is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Concomitant administration of strong CYP3A4 inducers or dabigatran
- Congenital long QT syndrome
- Familial history of sudden death or polymorphic ventricular arrhythmia
- QT/QTc interval > 500 msec, regardless of the correction method

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST) – weekly for the first month, every other week for the second month and with each medical review as clinically indicated thereafter

ECG weekly for the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains <480msec

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Hb	> 8g/dL
eGFR	≥ 30mL/min/1.73m^2 (see below)
Bilirubin	≤ ULN (see below)

Dose modifications

Renal Impairment

No dose adjustment is required in patients with mild (eGFR ≥ 60 to < 90 mL/min/1.73 m^2) or moderate (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) renal impairment. A recommended dose has not been determined for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Ivosidenib should be used with caution in patients with severe renal impairment and this patient population should be closely monitored.

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 and this patient population should be closely monitored.

OTc Interval prolongation

QTc interval prolongation > 480 to 500 msec (Grade 2)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects • Interrupt Ivosidenib until QTc interval returns to ≤ 480 msec. • Resume treatment at 500 mg ivosidenib once daily after the QTc interval returns to ≤ 480 msec. • 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. • Review and adjust concomitant medicinal products with known QTc interval prolonging effects • Interrupt Ivosidenib and monitor ECG every 24 h until QTc interval returns to within 30 msec of baseline or ≤ 480 msec. • In case of QTc interval prolongation > 550 msec, in addition to the interruption of ivosidenib already scheduled, consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec. • Resume treatment at 250 mg ivosidenib once daily after QTc interval returns to within 30 msec of baseline or ≤ to 480 msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to within 30 msec of baseline or ≤ 480 msec. • If alternative aetiology for QTc interval prolongation is identified, dose may be increased to 500 mg ivosidenib once daily.
QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4)	• Permanently discontinue treatment.

Other toxicities

Other Grade 3 or higher adverse reactions	• Interrupt Ivosidenib 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 Ivosidenib 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 ivosidenib.

Adverse effects - for full details consult product literature/ reference texts

Nausea/vomiting
Diarrhoea
Fatigue
Cough
Abdominal pain
Decreased appetite
Ascites
Asthenia
QTc interval prolongation

Significant drug interactions – for full details consult product literature/ reference texts

Strong CYP3A4 inducers

Ivosidenib is a CYP3A4 substrate. Concomitant administration of strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (Hypericum perforatum)) is expected to decrease plasma concentrations of ivosidenib and is contraindicated during treatment.

Moderate CYP3A4 inducers

Concomitant administration of moderate or strong 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 with ivosidenib. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250 mg once daily

Medicinal products known to prolong the QTc interval

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 during treatment with ivosidenib. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible.

Interactions with transporters

Ivosidenib inhibits P-gp and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp (e.g. dabigatran). Concomitant administration of dabigatran is contraindicated

Ivosidenib inhibits OAT3, organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3). Therefore, it may increase systemic exposure to OAT3 or OATP1B1/1B3 substrates. 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 with ivosidenib. Patients should be treated with caution if use of a suitable alternative is not possible. If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation

Cytochrome P450 (CYP) enzymes

Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Therefore, it may decrease systemic exposure to substrates of these enzymes. Suitable alternatives that are not CYP3A4, CYP2B6, CYP2C8 or CYP2C9 substrates with a narrow therapeutic index, or CYP2C19 substrates should be considered during treatment with ivosidenib. Patients should be monitored for loss of substrate efficacy if use of such medicinal products cannot be avoided.

• CYP3A4 substrates with a narrow therapeutic index include: alfentanil, ciclosporin, everolimus, fentanyl, pimozide,

quinidine, sirolimus, tacrolimus.
• CYP2B6 substrates with a narrow therapeutic index include: cyclophosphamide, ifosfamide, methadone.
• CYP2C8 substrates with a narrow therapeutic index include: paclitaxel, pioglitazone, repaglinide.
• CYP2C9 substrates with a narrow therapeutic index include: phenytoin, warfarin.
• CYP2C19 substrates include: omeprazole.

Itraconazole or ketoconazole should not be used concomitantly with ivosidenib due to the expected loss of antifungal efficacy.

Oral contraceptives
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

Uridine diphosphate glucuronosyltransferases (UGTs)
Ivosidenib has the potential to induce UGTs and it may, therefore, decrease systemic exposure to substrates of these enzymes (e.g. lamotrigine, raltegravir). Suitable alternatives that are not UGT substrates should be considered during treatment with ivosidenib. Patients should be monitored for loss of UGT substrate efficacy if use of such medicinal products cannot be avoided.

Additional comments
Product contains lactose

References
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THIS PROTOCOL HAS BEEN DIRECTED BY DR MITCHELL, DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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