Ivosidenib (Cholangiocarcinoma)

Indication
Locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments.

(NICE TA948)

ICD-10 codes
Codes prefixed with C22

Regimen details

Drug	Dose	Route
Ivosidenib	500mg OD	Oral

Cycle frequency
Continuous

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Ivosidenib is available as 250mg film-coated tablets. Tablets should be swallowed whole with water at about the same time each day. Patients should not eat anything for 2 hours before and 1 hour after taking the tablets.

If a dose is missed or not taken at the usual time, the tablets should be taken as soon as possible within 12 hours after the missed dose. Two doses should not be taken within 12 hours. If a dose is vomited, replacement tablets should not be taken. The tablets should be taken as usual the following day.

Grapefruit and grapefruit juice should be **avoided** whilst taking ivosidenib.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential – refer to local policy.

Additional supportive medication
Loperamide as required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
ECG (for QTc interval)	Baseline

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
ECG (for QTc interval)	At least weekly for 3 weeks then monthly

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
AST/ALT	< 5 x ULN
Bilirubin	< 2 x ULN
QTc interval	≤ 480 msec

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L or platelets < 100 x 10^9/L discuss with prescriber.

- **Renal impairment**

No dose adjustment is required in patients with mild or moderate renal impairment (CrCl ≥ 30mL/min). In patients with severe renal impairment (CrCl < 30mL/min) ivosidenib should be used with caution and with close monitoring for toxicity.

- **Hepatic impairment**

No dose adjustment is required in mild hepatic impairment (Child Pugh Class A). In patients with moderate or severe hepatic impairment (Child Pugh Class B or C) ivosidenib should be used with caution and with close monitoring for toxicity.

- **Other toxicities**

QT prolongation

Toxicity	Action/dose adjustment
QTc interval prolongation > 480-500 msec	- Interrupt ivosidenib until QTc interval returns to ≤ 480 msec - Monitor and supplement electrolyte levels as clinically indicated - Review and adjust any concomitant medicinal products with known QTc interval-prolonging effects - Resume ivosidenib at 500mg daily once QTc ≤ 480 msec - Monitor with weekly ECGs for at least 3 weeks and then as clinically indicated
QTc interval prolongation > 500 msec	- Interrupt ivosidenib and monitor ECG every 24 hrs until QTc interval returns to within 30 msec of baseline or ≤ 480 msec - If QTc interval prolongation > 550 msec consider continuous ECG monitoring until QTc interval < 500 msec. - Monitor and supplement electrolyte levels as clinically indicated - Review and adjust any concomitant medicinal products with known QTc interval-prolonging effects - Resume ivosidenib at 250mg daily once QTc interval returns to within 30 msec of baseline or ≤ 480 msec - Monitor with weekly ECGs for at least 3 weeks and then as clinically indicated - If alternative aetiology for QTc interval prolongation Is identified, re-escalation of the dose is permitted at consultant discretion
QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia	Permanently discontinue treatment.

Any other adverse event:

Toxicity	Definition	Action/Dose adjustment
Grade 3 adverse reaction	Severe	**1st occurrence**: Interrupt ivosidenib until toxicity resolves to ≤ Grade 1 or baseline then resume dosing at same dose (500mg daily) **2nd occurrence:** Interrupt ivosidenib until toxicity resolves to ≤ Grade 1 or baseline then resume dosing at 250mg daily **3rd occurrence:** discontinue ivosidenib
Grade 4 adverse reaction	Life-threatening	**1st occurrence:** Interrupt ivosidenib until toxicity resolves to ≤ Grade 1 or baseline then resume dosing at 250mg daily **2nd occurrence:** discontinue ivosidenib

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

- **Serious side effects**

Myelosuppression
QT prolongation

- **Frequently occurring side effects**

Peripheral neuropathy
Headache
Decreased appetite
Diarrhoea
Nausea, vomiting
Abdominal pain
Jaundice
Deranged LFTs
Rash
Fatigue

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

Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort): avoid concomitant treatment as will decrease plasma levels of ivosidenib.
Moderate or strong CYP3A4 inhibitors (e.g. clarithromycin, azole antifungals, ritonavir, aprepitant, ciclosporin, diltiazem, erythromycin, diltiazem, verapamil): increased plasma levels of ivosidenib increasing risk of toxicities including QT prolongation. If concomitant administration is unavoidable ivosidenib should be reduced to 250mg once daily.
Medicinal products known to prolong QT interval: increased risk of QT prolongation, if concomitant use is unavoidable use with caution and close monitoring for toxicity.
P-gp substrates (e.g. dabigatran): ivosidenib inhibits and has the potential to induce P-gp and may alter systemic exposure to active substances that are predominantly transported via P-gp. Concomitant administration of ivosidenib and dabigatran is contraindicated.
OAT3, OATP1B1 and OATP1B3 substrates (e.g. benzylpenicillin, furosemide, atorvastatin, pravastatin, rosuvastatin): ivosidenib inhibits these transporters and may increase exposure of the substrate so co-administration should be avoided were possible or monitored closely if there is no alternative option.
CYP3A4 substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus): ivosidenib is an enzyme inducer therefore risk of loss of efficacy.
CYP2B6 substrates with a narrow therapeutic index (e.g. cyclophosphamide, ifosfamide, methadone): ivosidenib is an enzyme inducer therefore risk of loss of efficacy.
CYP2C8 substrates with a narrow therapeutic index (e.g. paclitaxel, pioglitazone, repaglinide): ivosidenib is an enzyme inducer therefore risk of loss of efficacy.
CYP2C9 substrates with a narrow therapeutic index (e.g. phenytoin, warfarin): ivosidenib is an enzyme inducer therefore risk of loss of efficacy.
CYP2C19 substrates (e.g. omeprazole): ivosidenib is an enzyme inducer therefore risk of loss of efficacy.
Itraconazole, ketoconazole: loss of antifungal efficacy due to CYP induction by ivosidenib
Uridine diphosphate glucuronosyltransferase (UGT) substrates (e.g. lamotrigine, raltegravir): Ivosidenib induces UGTs therefore decreasing exposure to these substrates. If concomitant administration cannot be avoided, monitor for loss of UGT substrate efficacy.
Oral contraceptives: ivosidenib may decrease systemic concentrations of hormonal contraceptives, use of a barrier method of contraception is recommended.

Additional comments

Nil

References

- National Institute for Health and Clinical Excellence (TA948) accessed 2nd July 2024 via www.nice.org.uk
- Summary of Product Characteristics Ivosidenib (Servier) accessed 2nd July 2024 via www.medicines.org.uk
- Abou-Alfa, G.K. et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncology 21(6):796-807.

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