Ivosidenib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated with at least one prior line of systemic therapy	C22,C24	00901a	ODMS 01/10/2025

* This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ivosidenib is administered orally once a day, treatment should be taken continuously until disease progression or unacceptable toxicity occurs.

Drug	Dose	Route and Method of administration	Cycle
Ivosidenib	500mg once daily	PO, without food	Continuous
Treatment doses should be taken at approximately 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.			
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. The tablets should be taken as usual the following day. If a dose is vomited, replacement tablets should not be taken. The tablets should be taken as usual the following day. Ivosidenib is commonly available as 250 mg tablet.			

ELIGIBILITY:

- Indication as above
- IDH1 R132 mutation confirmed by a validated test method
- ECOG 0 - 2
- Adequate haematological, hepatic, and renal function

CAUTIONS:

- Patients who are at significant risk of developing QT interval prolongation
    - In the presence of an abnormal QT, the benefit/risk of initiating ivosidenib should be evaluated. Where QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment should remain exceptional and be accompanied by close monitoring
    - Patients with low albumin levels
    - Underweight patients
    - Patients receiving concomitant medicinal products known to prolong the QT interval , or moderate or strong CYP3A4 inhibitors that may increase the risk of QTc interval prolongation
- Severe renal impairment
- Hepatic impairment

EXCLUSIONS:

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

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG

Regular tests:

- FBC, once weekly for cycle 1, once every other week for cycle 2, then prior to each cycle as clinically indicated
- Renal and liver profile
- ECG weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec
- Any QTc abnormalities ≥ 480 msec should be managed promptly

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250mg once daily. If the moderate or strong CYP3A4 inhibitor is discontinued, the dose of ivosidenib should be increased to 500 mg after at least 5 half-lives of the CYP3A4 inhibitor
- Management adverse reactions may require dose interruption and/or dose reduction as outlined in Tables 1 and 2

Renal and Hepatic Impairment:

Table 1: Dose modification of ivosidenib in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
CrCl (mL/min)	**Dose**		**Dose**
≥30	No dose adjustment is needed	Child-Pugh A/B	No dose adjustment is needed
<30	No need for dose adjustment is expected	Child-Pugh C	Not recommended
Haemodialysis	No need for dose adjustment is expected		
Recommendations as per Giraud et al 2023			

Management of adverse events:

Table 3: Dose Modification of ivosidenib for Adverse Events

Adverse reactions	Recommended action
QTc interval prolongation > 480 to 500 msec	• 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 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

Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Ivosidenib Minimal to Low (**Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Treatment with anti-diarrhoeal agents, such as loperamide as required.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **QTc interval prolongation:** QTc interval prolongation has been reported following treatment with ivosidenib. An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec. 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 hypokalaemia and magnesium, must be performed. Patients should be informed of the risk of QT prolongation, its signs and be advised to contact their physician immediately if these occur. 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 with ivosidenib. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with

ivosidenib. Treatment with ivosidenib should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Alert Card:
https://assets.hpra.ie/products/Human/39161/2ddd3447-19b2-46ae-b3c1-ef541f3251d9.pdf

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3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
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Version	Date	Amendment	Approved By
1	25/09/2025		Prof Maccon Keane

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