IVOSIDENIB (Tibsovo)

INDICATION (ICD10) C22

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (IVO1)

1. Ivosidenib monotherapy for unresectable locally advanced or metastatic cholangiocarcinoma which has an isocitrate dehydrogenase-1 (IDH1) R132 mutation in patients with disease progression during or after previous systemic therapy. Has no known brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting treatment with ivosidenib. PS 0 or 1. (TA948)

REGIMEN

IVOSIDENIB 500mg orally daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Until disease progression. A first formal medical review as to whether treatment should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

ADMINISTRATION

Available as 250mg tablets
Swallowed whole with water, avoid food for 2 hours before and 1 hour after. Avoid grapefruit.

ANTI-EMETICS

Minimal emetic risk

CONCURRENT MEDICATION REQUIRED

Ivosidenib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC and U&E, Ca^{++} and PO_4^{3+}, weekly for 1st month, ever 2 weeks for 2nd month then every cycle
LFTs weekly for 1st month, ever 2 weeks for 2nd month then every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Creatinine every cycle
Baseline weight and every cycle
ECG prior to initiation QTc <450msec, then weekly for 3 weeks, then monthly if QTc remains ≤480msec.

MAIN TOXICITES AND ADVERSE REACTIONS

Ivosidenib	Differentiation syndrome Hepatic and renal impairment Leukocytosis QTc prolongation

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Ivosidenib	Concomitant use with strong or moderate CYP3A4 inhibitors is not recommended. If they cannot be avoided the dose of ivosidenib should be reduced to 250mg daily. CYP3A4 inducers

DOSE MODIFICATIONS
Non-haematological
Ivosidenib

Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of 3 days and taper only after symptom resolution. Premature discontinuation may result in symptom recurrence. • Initiate haemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt ivosidenib if severe signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume treatment at 500mg ivosidenib once daily when signs/symptoms are moderate or lower and upon improvement in clinical condition.
Leukocytosis (white blood cell count > 25 x 10^9/L or an absolute increase in total white blood cell count > 15 x 10^9/L from baseline	• Initiate treatment with hydroxycarbamide according to institutional standards of care and leukapheresis as clinically indicated. • Taper hydroxycarbamide only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence. • Interrupt ivosidenib if leukocytosis has not improved after initiation of hydroxycarbamide. • Resume treatment at 500mg ivosidenib once daily when leukocytosis has resolved.
QTc interval prolongation >480 to 500msec (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 ≤480msec. • Resume treatment at 500mg ivosidenib once daily after the QTc interval returns to ≤480msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to ≤480msec.
QTc interval prolongation >500msec (grade 3)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval prolonging effects. • Interrupt ivosedinib and monitor ECG every 24h until QTc interval returns to within 30msec of baseline or ≤480msec. • In case of QTc interval prolongation >550msec, in addition to the interruption of ivosidenib already scheduled, consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values <500msec. • Resume treatment at 250mg ivosidenib once daily after QTc interval returns to within 30msec of baseline or ≤ to 480msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to within 30msec of baseline or ≤480msec. • If alternative aetiology for QTc interval prolongation is identified, dose may be increased to 500mg 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 500mg daily (grade 3 toxicity) or 250mg daily (grade 4 toxicity). • If grade 3 toxicity recurs (a second time), reduce ivosidenib dose to 250mg daily until the toxicity resolves, then resume 500mg daily. • If grade 3 toxicity recurs (a third time), or grade 4 toxicity recurs, discontinue ivosidenib.

Hepatic impairment

Ivosidenib

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,

Renal impairment

Ivosidenib

No dose adjustment is required in patients with mild (eGFR ≥60 to <90mL/min/1.73m^2) or moderate (eGFR ≥30 to <60mL/min/1.73m^2) renal impairment.

A recommended dose has not been determined for patients with severe renal impairment (eGFR <30mL/min/1.73m^2). Ivosidenib should be used with caution in patients with severe renal impairment and this patient population should be closely monitored.

REFERENCES

1. SPC