▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – TIBSOVO® (IVOSIDENIB)

1 NAME OF THE MEDICINE

TIBSOVO

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of ivosidenib.

Excipient with known effect: contains lactose. For the full list of excipients, see *section 6.1 - List of excipients*.

3 PHARMACEUTICAL FORM

Blue, oval shaped, film-coated tablets approximately 18 mm in length, debossed with 'IVO' on one side and '250' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TIBSOVO is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation after at least one prior line of systemic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by a physician experienced in the use of anti-cancer therapies. Before taking TIBSOVO , patients must have confirmation of an IDH1 mutation using an appropriate diagnostic test, and an electrocardiogram (ECG) to assess heart rate-corrected QT (QTc) interval.

Dose

The recommended dose of ivosidenib is 500 mg orally once daily until disease progression or unacceptable toxicity.

Method of administration

TIBSOVO should be taken at about the same time each day, with or without food, but not with a high fat meal (see *section 4.5 - Interactions with other medicines and other forms of interactions* and *5.2 - Pharmacokinetic properties*). Do not split, crush or chew the tablets.

Two doses should not be taken within 12 hours. If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible within 12 hours after it was missed. Administer the following

day's dose at the usual time. If 12 hours or longer have elapsed since a dose was missed, do not administer the dose; wait until the next scheduled dose is due. If a dose of TIBSOVO is vomited, do not administer replacement tablets; wait until the next scheduled dose is due.

Monitoring

Perform an ECG at baseline, at least weekly during the first 3 weeks of therapy and at least monthly thereafter. Monitor electrolytes at baseline and throughout treatment as clinically indicated. Patients at higher risk of QT prolongation, including due to concomitant medications, may require more frequent monitoring. Promptly manage abnormalities (see Table 1 and *section 4.4 - Special warnings and precautions for use*).

Dose modification for concomitant administration of strong CYP3A4 inhibitors

If use of strong CYP3A4 inhibitors is unavoidable, reduce the ivosidenib dose to 250 mg once daily. If the strong CYP3A4 inhibitor is discontinued, increase the ivosidenib dose to 500 mg after at least 5 half-lives of the strong CYP3A4 inhibitor (see above and *sections 4.4 - Special warnings and precautions for use* and *4.5- Interactions with other medicines and other forms of interactions*).

Dose modifications for adverse reactions

Guidelines for management in case of adverse reactions are summarised in Table 1. See also *sections 4.4 - Special warnings and precautions for use, 4.5 - Interactions with other medicines and other forms of interactions* and *4.8 - Adverse effects (Undesirable effects).*

Table 1 - Recommended dose modifications for adverse reactions

Adverse reaction	**Recommended action**
QTc interval >480 to 500 msec (Grade 2)	• Review concomitant medicines and check electrolytes. • Interrupt ivosidenib treatment until QTc interval returns to ≤480 msec, then resume at 500 mg daily. Monitor ECGs at least weekly for 2 weeks following return of QTc interval to ≤480 msec.
QTc interval >500 msec (Grade 3)	• Review concomitant medicines and check electrolytes. • Interrupt ivosidenib treatment until QTc interval returns to within 30 msec of baseline or ≤480 msec, then resume treatment at 250 mg daily. • Monitor ECGs at least weekly for 2 weeks following return of QTc interval to within 30 msec of baseline or ≤480 msec.

Adverse reaction	Recommended action
	Dose re-escalation to 500 mg daily can be considered if alternative aetiology for QTc interval prolongation is identified.
QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4)	Permanently discontinue ivosidenib.
Guillain-Barré syndrome	Permanently discontinue ivosidenib.
Other Grade 3 or higher adverse reactions	• Interrupt ivosidenib treatment 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 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening.

Special populations

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). See *sections 4.4 - Special warnings and precautions for use* and *5.2 - Pharmacokinetic properties*.

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child Pugh class A or B). No studies have been conducted in patients with severe hepatic impairment (Child Pugh class C) and a recommended dose has not been determined in this population. See *sections 4.4 - Special warnings and precautions for use* and *5.2 - Pharmacokinetic properties*.

Elderly population

No dose adjustment is required in elderly patients (≥65 years old; see *sections 4.8 - Adverse effects (Undesirable effects)* and *5.2 - Pharmacokinetic properties*).

Paediatric population

No data are available. See *section 4.4 - Special warnings and precautions for use.*

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *section 6.1 - List of excipients*.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QTc interval prolongation

Ivosidenib causes prolongation of the QTc interval, and ventricular arrhythmias have been reported following treatment with ivosidenib in patients with haematological malignancies (see *sections 5.1 - Pharmacodynamic properties and 4.8 - Adverse effects (Undesirable effects)*). Perform an ECG prior to treatment initiation, at least weekly during the first 3 weeks of therapy and at least monthly thereafter, and monitor electrolytes. Manage any abnormalities promptly (see *section 4.2 - Dose and method of administration*).

Avoid concomitant administration of medicines known to prolong the QTc interval (e.g. anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals), or moderate or strong CYP3A4 inhibitors, as these may increase the risk of QTc interval prolongation (see *section 4.5 - Interactions with other medicines and other forms of interactions*). If concomitant use is unavoidable, or for patients with other risk factors (such as congenital long QTc syndrome, congestive heart failure or electrolyte abnormalities), monitor closely, with more frequent ECGs and regular monitoring of electrolytes as required. Adjust dosing if concomitant use of a strong CYP3A4 inhibitor is unavoidable (see *section 4.2 - Dose and method of administration*).

Interrupt TIBSOVO for QTc interval over 480 msec, and permanently discontinue TIBSOVO in patients with QTc interval prolongation and signs or symptoms of life-threatening arrhythmia (see *section 4.2 - Dose and method of administration*).

Guillain-Barré syndrome

Two cases of Guillain-Barré syndrome (<1%) occurred in patients with haematological malignancies receiving ivosidenib. A causal mechanism is not known, and preclinical studies did not identify the CNS as a target organ for ivosidenib toxicity. No cases of Guillain-Barré syndrome have been reported in patients with solid tumours, though peripheral neuropathy is common (see *4.8 - Adverse effects (Undesirable effects)*).

Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paraesthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

Use in renal impairment

The safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), including those requiring dialysis. Use TIBSOVO with caution and monitor closely in this population (see *sections 4.2 - Dose and method of administration* and *5.2 - Pharmacokinetic properties*).

Use in hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with severe hepatic impairment (Child Pugh class C). Use TIBSOVO with caution and monitor closely in this population (see *sections 4.2 - Dose and method of administration* and *5.2 - Pharmacokinetic properties*).

Use in the elderly

No overall differences in effectiveness or safety were observed in patients ≥65 years of age (see *4.8 - Adverse effects (Undesirable effects)*).

Paediatric use

The safety and efficacy of TIBSOVO (ivosidenib) in children and adolescents <18 years old have not been established. No data are available.

Effects on laboratory tests

See Table 4 in *section 4.8 - Adverse effects (Undesirable effects)*).

Reproductive toxicity

TIBSOVO may cause fetal harm if administered during pregnancy. Verify pregnancy status prior to starting treatment, and advise the use of barrier contraception as ivosidenib may decrease systemic concentrations of hormonal contraceptives (see *sections 4.5 - Interactions with other medicines and other forms of interactions* and *4.6 - Fertility, pregnancy and lactation*).

Interactions

Clinically significant interactions are predicted with ivosidenib. Give advice regarding potential for food interactions and review concomitant medications (see *QT interval prolongation* and *Reproductive toxicity,* above, and *sections 4.5 - Interactions with other medicines and other forms of interactions* and *5.2 - Pharmacokinetic properties*).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Summary of interactions

Co-administration of ivosidenib with certain medicines and foods is likely to lead to clinically significant interactions. Categories of substances that interact (or may interact) with ivosidenib are summarised in Table 2, though the included examples are not an exhaustive list.

Table 2 -Summary of substances with clinically relevant ivosidenib interactions

Category	Some examples	Expected/possible outcome
Strong CYP3A4 inducers [2]	carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort (*Hypericum perforatum*)	decreased ivosidenib exposure
Moderate CYP3A4 inhibitors [1]	aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice, isavuconazole, verapamil	increased ivosidenib exposure
Strong CYP3A4 inhibitors [1, 3]	clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole	greatly increased ivosidenib exposure
CYP3A4 substrates with a narrow therapeutic index	alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus	decreased CYP3A4 substrate exposure
CYP3A4 substrates with significant clinical consequences of inefficacy [4]	itraconazole, ketoconazole, , voriconazole, hormonal contraceptives	decreased substrate exposure
CYP2B6 substrates with a narrow therapeutic index	cyclophosphamide, ifosfamide, methadone	decreased CYP2B6 substrate exposure
CYP2C8 substrates with a narrow therapeutic index	paclitaxel, pioglitazone, repaglinide	decreased CYP2C8 substrate exposure
CYP2C9 substrates with a narrow therapeutic index	phenytoin, warfarin	decreased CYP2C9 substrate exposure
CYP2C19 substrates	omeprazole, voriconazole	decreased CYP2C19 substrate exposure
UGT substrates	lamotrigine, raltegravir, posaconazole	decreased UGT substrate exposure
Sensitive P-gp substrates [5]	dabigatran	altered P-gp substrate exposure
OAT3 substrates	benzylpenicillin, furosemide	increased OAT3 substrate exposure
Medicines that prolong the QT interval [1]	anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals	additive or synergistic effect on QT prolongation
High-fat food at time of ivosidenib dose	bacon, butter, milk and eggs (about 1,000 calories and 58 g of fat)[6]	increased ivosidenib exposure

OAT3 = organic anion transporter 3. P-gp = P glycoprotein. UGT = uridine diphosphate glucuronosyltransferases.

1 See *section 4.4 - Special warnings and precautions for use* regarding QTc interval prolongation.

2 Avoid co-administration of strong CYP3A4 inducers due to risk of decreased ivosidenib efficacy.

3 See *section 4.2 - Dose and method of administration.*

4 In patients receiving ivosidenib, do not rely on efficacy of antifungals that are CYP3A4 substrates or efficacy of hormonal contraceptives. See also *section 4.6 - Fertility, pregnancy and lactation.*

5 Avoid co-administration of dabigatran with ivosidenib due to risk of dabigatran toxicity.

6 See *section 5.2 – Pharmacokinetic properties*

Effect of other medicines on ivosidenib

Strong CYP3A4 inducers

Ivosidenib is a CYP3A4 substrate. Physiologically-based pharmacokinetic (PBPK) modelling predicted a 33% decrease in ivosidenib steady-state AUC (AUCss) when given at the recommended dose in the presence of

co-administered 600 mg rifampin once daily for 15 days. Avoid co-administration of strong CYP3A4 inducers (see Table 2).

Moderate or strong CYP3A4 inhibitors

Co-administration of a single dose of 250 mg ivosidenib with a strong CYP3A4 inhibitor (200 mg itraconazole daily for 18 days) increased the ivosidenib AUC by 2.7-fold (with no change in C_{max}) in healthy volunteers. PBPK modelling predicted an increase in ivosidenib AUCss in the presence of a co-administered strong (ketoconazole: 3.2-fold) or moderate (fluconazole: 1.9-fold) CYP3A4 inhibitor. Avoid co-administration of moderate or strong CYP3A4 inhibitors (see Table 2): consider alternative therapies. If co-administration is unavoidable, treat with caution and monitored closely for QTc interval prolongation (see *section 4.4 - Special warnings and precautions for use*). If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce the ivosidenib dose (*see section 4.2 - Dose and method of administration*).

Interactions with transporters

Ivosidenib is a P-glycoprotein (P-gp) substrate. However, data from study in healthy subjects suggest that the potential for clinically relevant interactions with ivosidenib and P-gp inhibitors is low.

Effect of ivosidenib on other medicines

Enzyme induction

Ivosidenib induces CYP3A4 (including its own metabolism), CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19 and UGT (see *section 5.2 - Pharmacokinetic properties)*. Therefore, it may decrease systemic exposure to substrates of these enzymes. This is of particular relevance for substrates with a narrow therapeutic index or with significant clinical consequence of inefficacy (such as hormonal contraceptives and antifungals: see Table 2). Consider suitable alternatives, recommend barrier contraception (see *section 4.6 - Fertility, pregnancy and lactation*), and if concomitant use can't be avoided, monitor for loss of substrate efficacy.

Interactions with transporters

Ivosidenib inhibits P-gp and OAT3, and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp, and may increase systemic exposure to OAT3 substrates (see Table 2). Consider suitable alternatives, and if concomitant use can't be avoided, monitor for loss of substrate efficacy or P-gp substrate toxicity. Avoid co-administration of dabigatran due to risk of dabigatran toxicity (haemorrhage).

Other interactions

Medicines known to prolong the QTc interval

Co-administration of other medicines known to prolong the QTc interval (see Table 2) may increase the risk of QTc interval prolongation. Avoid co-administration of medicines known to prolong the QTc interval (see Table 2): consider alternative therapies. If co-administration is unavoidable, treat with caution and monitored closely for QTc interval prolongation (see *section 4.4 - Special warnings and precautions for use*).

Food interactions

Administration of ivosidenib with a high fat meal should be avoided, as it has a significant effect on the absorption of ivosidenib and leads to increased exposure (see *sections 4.2 Dose and method of administration* and *5.2 - Pharmacokinetic properties*).

Grapefruit and grapefruit juice moderately inhibit CYP3A4 (see *Moderate or strong CYP3A4 inhibitors*, above).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effect of ivosidenib on fertility. No specific fertility studies have been conducted in animals, but undesirable effects on reproductive organs were observed in a 28-day repeat-dose toxicity study in rats. Uterine atrophy was observed in females at non-tolerated dose levels approximately 1.7-fold the clinical exposure (based on AUC) and was reversible after a 14 days recovery period. Testicular degeneration was observed in males at non-tolerated dose levels approximately 1.2-fold the clinical exposure (based on AUC) and reversibility of this finding has not been assessed. The clinical relevance of these effects is unknown.

Use in pregnancy

Pregnancy Category D

There are no human data, but based on animal data, TIBSOVO may cause fetal harm if administered during pregnancy. Reproductive toxicity (embryo-fetal mortality and growth alteration) was seen in animal studies, starting at 2-fold the steady-state clinical exposure (based on AUC) at the recommended human dose (see *Preclinical data* below).

Advise patients of the risk to the fetus if TIBSOVO is used during pregnancy. Assess pregnancy status prior to starting treatment with TIBSOVO. Advise patients to use effective contraception during treatment with TIBSOVO and for at least 1 month after the last dose.

As ivosidenib may decrease systemic concentrations of hormonal contraceptives, concomitant use of an alternative contraceptive method such as barrier contraceptives is recommended (see *sections 4.4 - Special warnings and precautions for use* and *4.5- Interactions with other medicines and other forms of interactions*).

Preclinical data

In embryofetal development studies in rats, lower fetal body weights, delayed skeletal ossification and development variation of major blood vessels occurred in the absence of maternal toxicity. In rabbits, maternal toxicity, spontaneous abortions, decreased fetal body weights, increased post implantation loss, delayed skeletal ossification and visceral development variation (small spleen) were observed. In rats and rabbits, the no adverse effect levels for embryofetal development were 0.4-fold and 1.4-fold the clinical exposure (based on AUC), respectively. Animal studies indicate that ivosidenib crosses the placenta and is found in fetal plasma. It is not known whether ivosidenib or its metabolites are excreted in milk.

Use in lactation

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on a breastfed child, or the effects on milk production. Due to the potential risk to a breastfed child, breastfeeding should be discontinued during treatment with ivosidenib and for at least 1 month after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ivosidenib has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients taking ivosidenib (see *section 4.8 - Adverse effects (Undesirable effects)*) and should be considered when assessing a patient's ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Previously treated, locally advanced or metastatic cholangiocarcinoma

Summary of the safety profile

The safety profile of TIBSOVO was studied in 123 patients with previously treated, locally advanced or metastatic cholangiocarcinoma in Study AG120-C-005. Patients received at least one dose of either TIBSOVO 500 mg daily (n=123) or placebo (n=59). The median (range) and mean (standard deviation, SD) duration of treatment with TIBSOVO were 2.8 (0.1 to 45.1) months and 6.7 (8.2) months, respectively.

The most common adverse events and laboratory abnormalities in patients who received TIBSOVO in Study AG120-C-005 are presented in Table 3 and Table 4 below.

Serious adverse events occurred in 35% of patients receiving TIBSOVO. Serious adverse events that occurred in ≥2% of patients in the TIBSOVO arm were pneumonia, ascites, hyperbilirubinaemia, and jaundice cholestatic. Fatal adverse events occurred in 4.9% of patients receiving TIBSOVO, including sepsis (1.6%) and pneumonia, intestinal obstruction, pulmonary embolism, and hepatic encephalopathy (each 0.8%).

TIBSOVO was permanently discontinued in 7% of patients. The most common adverse event leading to permanent discontinuation was acute kidney injury (1.6%).

Dose interruptions due to adverse events occurred in 30% of patients treated with TIBSOVO. The most common (>2%) adverse events leading to dose interruption were hyperbilirubinaemia, alanine aminotransferase increased, aspartate aminotransferase increased, ascites, and fatigue.

Dose reductions of TIBSOVO due to an adverse event occurred in 4% of patients. Adverse events leading to dose reduction were electrocardiogram QT prolonged (3.3%) and neuropathy peripheral (0.8%).

Table 3 - Adverse events reported in at least 10% of patients with locally advanced or metastatic cholangiocarcinoma receiving ivosidenib in clinical Study AG120-C-005

Body System / Adverse Event	TIBSOVO (500 mg daily) N=123		Placebo N=59	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions				
Fatigue[1]	53 (43)	4 (3)	18 (31)	3 (5)
Gastrointestinal disorders				
Nausea	52 (42)	3 (2)	17 (29)	1 (2)
Diarrhoea	43 (35)	0	10 (17)	0
Abdominal pain[2]	43 (35)	3 (2)	13 (22)	2 (3)
Ascites	28 (23)	11 (9)	9 (15)	4 (7)
Vomiting[3]	28 (23)	3 (2)	12 (20)	0
Respiratory, thoracic, and mediastinal disorders				
Cough[4]	33 (27)	0	5 (9)	0
Metabolism and nutrition disorders				
Decreased appetite	30 (24)	2 (2)	11 (19)	0
Blood and lymphatic system disorders				
Anaemia	23 (19)	9 (7)	3 (5)	0
Skin and subcutaneous tissue disorders				
Rash[5]	19 (15)	1 (1)	4 (7)	0
Nervous system disorders				
Headache	16 (13)	0	4 (7)	0
Neuropathy peripheral[6]	13 (11)	0	0	0
Investigations				
Electrocardiogram QT prolonged	12 (10)	2 (2)	2 (3)	0

1 Grouped term includes asthenia and fatigue.

2 Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort, abdominal tenderness, and gastrointestinal pain.

3 Grouped term includes vomiting and retching.

4 Grouped term includes cough and productive cough.

5 Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalised, drug eruption, and drug hypersensitivity.

6 Grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paraesthesia.

Table 4 - Selected laboratory abnormalities occurring in at least 10% of patients with locally advanced or metastatic cholangiocarcinoma receiving ivosidenib in clinical Study AG120-C-005#

Parameter	TIBSOVO (500 mg daily)		Placebo	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
AST increased	41 (34)	5 (4)	14 (24)	1 (2)
Bilirubin increased	36 (30)	15 (13)	11 (19)	2 (3)
Haemoglobin decreased	48 (40)	9 (8)	14 (25)	0

Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

Description of selected adverse reactions

QTc interval prolongation

Prolongation of the electrocardiogram QTc interval is a known risk associated with ivosidenib treatment and may occur at any time during treatment (see *sections 4.2 - Dose and method of administration*, 4.4 - Special warnings and pre*cautions for use,* and *4.5 - Interactions with other medicines and other forms of interactions).*

In Study AG120-C-005, in the 123 patients with locally advanced or metastatic cholangiocarcinoma treated with ivosidenib monotherapy, QTc prolongation was reported in 10%; 2% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 2% of patients had a QTc interval > 500 msec and 5% had QTc interval prolongation >60 msec from baseline. No patient discontinued treatment due to QTc prolongation, and dose reduction to manage signs/symptoms was required in (3% of patients. The median time to onset after treatment initiation was 28 days (range: 1 day to 698 days [23 months].

Special populations

Elderly

Of 123 patients with cholangiocarcinoma treated with TIBSOVO in Study AG120-C-005, 36% were ≥65 years of age and 11% were ≥75 years of age. No overall difference in safety was observed between patients ≥65 years old and younger patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of overdose, toxicity may manifest as QT prolongation or ventricular arrhythmia, or exacerbation of other adverse reactions (see *section 4.4 - Special warnings and precautions for use* and *4.8 - Adverse effects (Undesirable effects)*). Patients should be closely monitored and provided with appropriate supportive care (see *sections 4.2 - Dose and method of administration*). There is no specific antidote for ivosidenib overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents ATC code: L01XX62

Mechanism of action

Ivosidenib is a small molecule inhibitor of R132-mutated isocitrate dehydrogenase 1 (IDH1) enzymes. Through a gain of neomorphic function, the mutant IDH1 converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG). As 2-HG competitively inhibits α-KG-dependent enzymes, including histone and DNA demethylases, its accumulation leads to widespread epigenetic dysregulation.

Ivosidenib inhibited selected IDH1 mutants (R132C, R132L, R132G, R132H and R132S) at much lower concentrations than wild-type IDH1 in vitro.

Cholangiocarcinoma

In a patient-derived xenograft intra-hepatic cholangiocarcinoma mouse model with IDH1 R132C, ivosidenib reduced 2-HG levels.

Pharmacodynamic effects

Multiple doses of ivosidenib 500 mg daily decreased plasma concentrations of 2-HG in patients with cholangiocarcinoma with mutated IDH1 to levels approximating those observed in healthy subjects. In tumour biopsy of patients with cholangiocarcinoma, the mean (coefficient of variation) reduction in 2-HG concentrations was 82% (32%).

Concentration-dependent prolongation of the QTc interval was observed following administration of ivosidenib at the recommended dose in patients with haematological malignancies and solid tumours. The mean maximal prolongation in both settings was 17 msec, with an upper confidence interval of 20 msec. Co-administration of moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline. See *sections 4.2 - Dose and method of administration* and *4.4 - Special warnings and precautions for use*.

Clinical efficacy

Previously treated, locally advanced or metastatic cholangiocarcinoma

The efficacy of TIBSOVO (ivosidenib) was evaluated in a randomised (2:1), multicentre, double-blind, placebo- controlled, phase 3 clinical trial (Study AG120-C-005, also known as 'ClarIDHy') of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation whose disease had progressed following at least 1 but not more than 2 prior treatment regimens, including at least 1 gemcitabine- or 5-FU-containing regimen. Patients with certain IDH1 mutations (R132C, R132CL, R132G, R132H or R132S) were selected using a central diagnostic next generation sequencing assay (the Oncomine Focus Assay).

Patients were randomised to receive either TIBSOVO 500 mg orally once daily or matched placebo until disease progression or development of unacceptable toxicity. Randomisation was stratified by number of prior therapies (1 or 2). Eligible patients who were randomised to placebo were allowed to cross over to

receive TIBSOVO (ivosidenib) after documented radiographic disease progression as assessed by the Investigator.

Tumour imaging assessments were performed every 6 weeks for the first 8 assessments and every 8 weeks thereafter. The primary efficacy outcome was progression-free survival (PFS) assessed by an independent review committed (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 62 years (range: 33 to 83). Most patients were female (63%), 57% were Caucasian, all patients had an ECOG performance status of 0 (37%) or 1 (62%), and 47% had received two prior lines of systemic therapy. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. Across both arms, 70% of patients had an R132C mutation, 15% had an R132L mutation, 12% had an R132G mutation, 1.6% had an R132S mutation, and 1.1% had an R132H mutation. No patients with R132H-mutant IDH1 were randomised to ivosidenib.

The study demonstrated a statistically significant improvement in PFS. The efficacy results for Study AG120-C-005 are summarised in Table 5 and Figure 1.

Table 5 - Efficacy results in patients with locally advanced or metastatic cholangiocarcinoma

	Ivosidenib (500 mg daily)	**Placebo**
Progression-free survival (PFS) by IRC	**N=124**	**N=61**
Events, n (%) Progressive Disease Death	76 (61) 64 (52) 12 (10)	50 (82) 44 (72) 6 (10)
Median PFS, months (95% CI)	2.7 (1.6, 4.2)	1.4 (1.4, 1.6)
Hazard ratio (95 % CI)[1]	0.37 (0.25, 0.54)	
P-value[2]	<0.0001	
Objective response rate, n (%)	3 (2.4)	0
Overall survival[3]	**N=126**	**N=61**
Deaths, n (%)	100 (79)	50 (82)
Median OS (months, 95 % CI)	10.3 (7.8, 12.4)	7.5 (4.8, 11.1)
Hazard ratio (95 % CI)[1] **P-value[2]**	ITT: Ivosidenib vs. placebo 0.79 (0.56, 1.12) 0.093	

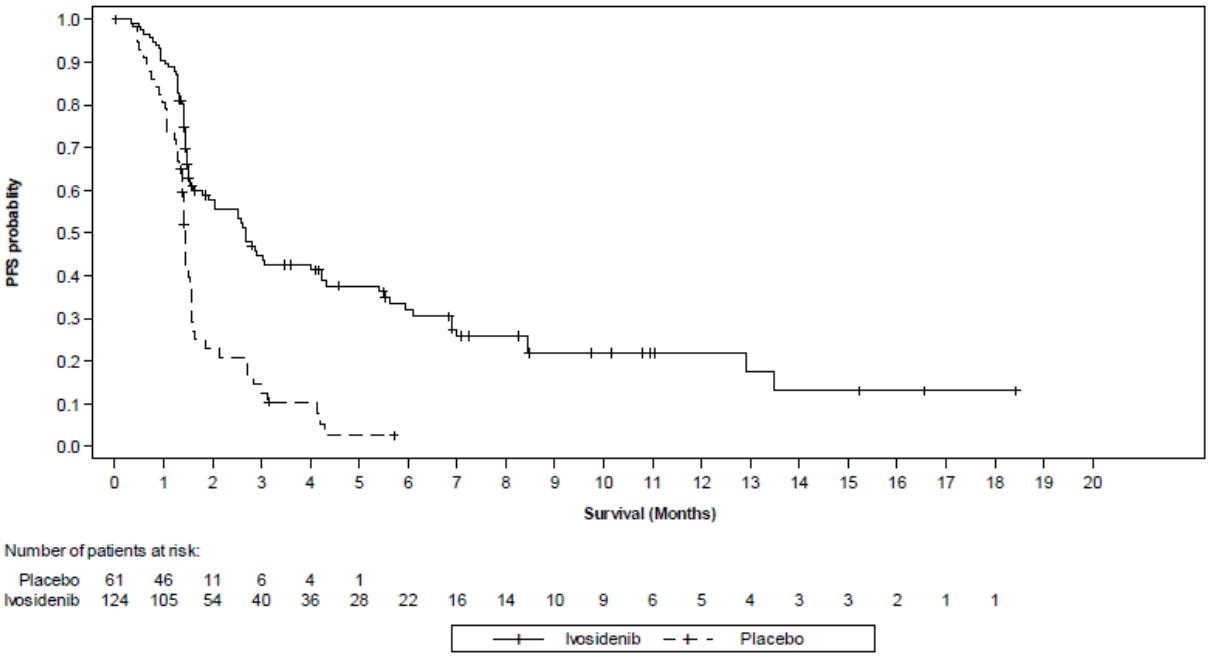
IRC: Independent Radiology Center; CI: Confidence Interval; NE = not estimable.

1 Hazard ratio is calculated from stratified Cox regression model. Stratified by number of prior lines of therapy.

2 P-value is calculated from the one-sided stratified log-rank test without adjusting for crossover. Stratified by number of prior lines of therapy.

3 OS results reflect the final analysis of OS (based on 150 deaths) which occurred 16 months after the final analysis of PFS, and was conducted based on the Intent-to-Treat (ITT) principle without adjusting for crossover. Of the patients randomised to placebo (and counted in the placebo arm in this OS analysis), 70% had crossed over to receive TIBSOVO after radiographic disease progression.

Figure 1 - Kaplan Meier Plot of Progression-Free Survival per IRC



5.2 PHARMACOKINETIC PROPERTIES

A summary of ivosidenib pharmacokinetic (PK) parameters following administration of ivosidenib 500mg as a single or daily dose (for steady state) is provided in Table 6 The AUC and C_{max} of ivosidenib increase in a less than dose proportional manner from 200 mg to 1,200 mg once daily (0.4 to 2.4 times the recommended dose). Steady-state PK is reached within 14 days with daily dosing.

Table 6 - Summary of plasma PK parameters of ivosidenib[a] after administration in clinical studies

PK parameter		Cholangiocarcinoma population
Mean (CV) single dose C_{max}		4060 (45%) ng/mL
Mean (CV) steady-state C_{max}		4799 (33%) ng/mL
Mean (CV) steady-state AUC		86382 (34%) ng/mL
Accumulation ratio: C_{max}		1.2
Accumulation ratio: AUC		1.5
Absorption		
Median T_{max} (range)		2.1 (0.5, 4.1) hr
Effect of food: [b]	on Cmax on AUC	1.98-fold (90% CI: 1.79, 2.19) 1.24-fold (90% CI: 1.16, 1.33)
Distribution		
In vitro protein binding		92 to 96%
Mean (CV) Vd at steady state		2.97 (26%) L/kg

PK parameter		Cholangiocarcinoma population
Elimination		
Mean (CV) CL at steady state		6.1 (31%) L/hr
Mean (CV) T½ at steady state		129 (102%) hr
Excretion: [c]	urinary	17% (10% as unchanged ivosidenib)
	faecal	77% (67% as unchanged ivosidenib)

CI = confidence interval; CL = apparent clearance; CV = geometric coefficient of variation; T½ = terminal half life; Vd = apparent volume of distribution.

[a] 500 mg either as a single dose or after multiple daily doses (for steady state), unless otherwise specified

[b] Following administration of a single dose in healthy subjects with a high-fat meal (approximately 900 to 1000 calories in total: 500 to 600 fat calories, 250 carbohydrate calories and 150 protein calories)

[c] Data from a single radio-labelled ivosidenib dose in healthy subjects

Metabolism

Ivosidenib was the predominant component (>92 %) of total radioactivity in plasma from healthy subjects. It is primarily metabolised by CYP3A4 with minor contributions by N-dealkylation and hydrolytic pathways.

Special populations

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on age (18 to 89 years), sex, race, body weight (38 to 150 kg), ECOG performance status, mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2), and mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), including patients requiring dialysis, and in patients with severe hepatic impairment (Child Pugh class C) are unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ivosidenib was not mutagenic in a bacterial reverse mutation assay or clastogenic *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with ivosidenib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose acetate succinate
- Colloidal anhydrous silica

- Magnesium stearate
- Sodium lauryl sulfate
- Hypromellose
- Titanium dioxide
- Lactose monohydrate
- Triacetin
- Indigo carmine aluminium lake

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a dry place below 30°C. Keep the bottle tightly closed to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

White, high density polyethylene (HDPE) bottle with polypropylene (PP) child resistant closure and polyethylene (PE) faced induction heat seal liner. Each bottle contains 60 film-coated tablets and a silica gel desiccant in a HDPE canister. The bottles are packaged in a cardboard box; each box contains 1 bottle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

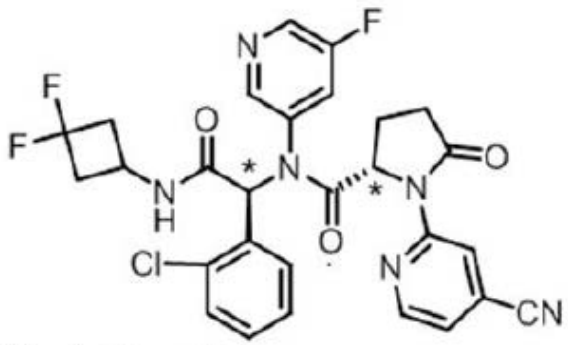
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The active component of TIBSOVO is ivosidenib which is a white to light yellow solid and has the chemical name: Glycinamide, 1-(4-cyano-2-pyridinyl)-5-oxo-L-prolyl-2-(2-chlorophenyl)-N-(3,3-difluorocyclobutyl)-N2-(5-fluoro-3-pyridinyl)-, (2S)- and molecular formula: $C_{28}H_{22}ClF_3N_6O_3$ (MW = 583.0). Ivosidenib is practically insoluble in aqueous solutions and is variably soluble in various organic solvents.

Chemical structure

The chemical structure of ivosidenib free form drug substance:



*Denotes stereocenter.

CAS number

1448347-49-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au
Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

9 DATE OF FIRST APPROVAL

05 April 2023

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information