▼ 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)

WARNING: DIFFERENTIATION SYNDROME AND QTc INTERVAL PROLONGATION

Differentiation syndrome (DS), which can be fatal if not treated, can occur in patients with AML treated with TIBSOVO. This can occur a few days, or many months after starting treatment. Symptoms may include leukocytosis, pyrexia, hypoxia, hypotension, dyspnoea, fluid overload, pleural/pericardial effusion, pneumonitis, rash, and creatinine increase. If DS is suspected, initiate corticosteroid therapy and haemodynamic monitoring for at least three days; and until symptoms resolve. Additionally, in all indications, TIBSOVO can cause dose-dependent prolongation of the heart rate-corrected QT (QTc) interval. QTc interval prolongation can cause fatal ventricular arrhythmias. Avoid co-administration of strong CYP3A4 inhibitors (which increase TIBSOVO levels). Assess and minimise other risk factors, monitor ECGs and interrupt treatment if necessary. See *section 4.4 Special warnings and precautions for use* and *section 4.8-Adverse effects.*

1 NAME OF THE MEDICINE

Ivosidenib

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

Cholangiocarcinoma

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.

Acute myeloid leukaemia

TIBSOVO is indicated for the treatment of acute myeloid leukaemia (AML) that carries an IDH1 R132 mutation:

- as monotherapy, or in combination with azacitidine, in newly diagnosed patients who are not eligible to receive intensive induction chemotherapy; or

- as monotherapy in patients whose AML is relapsed and/or refractory to prior 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. Patients with AML without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment or at relapse.

Dose

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

When TIBSOVO is used in combination with azacitidine to treat patients with newly diagnosed AML, the recommended dose of azacitidine is 75 mg/m^2 of body surface area, intravenously or subcutaneously, once daily on Days 1-7 (or on Days 1-5, then on Days 8 and 9) of each 28-day cycle. Refer to the full product information for azacitidine for additional dosing information.

Continue treatment for AML (whether monotherapy or in combination with azacitidine) for a minimum of six months to allow time for clinical response.

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

QTc interval prolongation
Perform an ECG at baseline, at least weekly during the first three weeks of therapy and at least monthly thereafter. Monitor electrolytes at baseline and throughout treatment as clinically indicated. Patients at higher risk of QTc interval 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*).

Differentiation syndrome in AML
Assess full blood count and blood chemistry prior to initiating treatment, and then as clinically indicated: including at least weekly for the first month, at least fortnightly for the second month, and at least monthly thereafter. 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 TIBSOVO dose to 250 mg once daily. If the strong CYP3A4 inhibitor is discontinued, increase the TIBSOVO 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
Differentiation syndrome in AML	• If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of three days and taper only after symptom resolution. Premature discontinuation may result in symptom recurrence and initiate haemodynamic monitoring until symptom resolution and for a minimum of three days. • Interrupt TIBSOVO if Grade 3 or higher signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume TIBSOVO at 500 mg daily when signs and symptoms improve to Grade 2 or lower.
Non-infectious 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 (hydroxyurea) according to institutional standards of care and leukapheresis as clinically indicated. • Taper hydroxycarbamide only after leukocytosis improves or resolves. • Interrupt TIBSOVO if leukocytosis has not improved with hydroxycarbamide. • Resume TIBSOVO at 500 mg daily when leukocytosis has resolved.
QTc interval >480 to 500 msec (Grade 2)	• Review concomitant medicines and check electrolytes. • Interrupt TIBSOVO treatment until QTc interval returns to ≤480 msec, then resume at 500 mg daily. • Monitor ECGs at least weekly for two weeks following return of QTc interval to ≤480 msec.

Adverse reaction	Recommended action
QTc interval >500 msec (Grade 3)	• Review concomitant medicines and check electrolytes. • Interrupt TIBSOVO 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 two weeks following return of QTc interval to within 30 msec of baseline or ≤480 msec. • 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 TIBSOVO
Guillain-Barré syndrome	• Permanently discontinue TIBSOVO
Other Grade 3 or higher adverse events	*In the setting of AML treatment in combination with azacitidine, or treatment of CCA:* • Interrupt TIBOSVO 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 TIBSOVO 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 TIBSOVO *In the setting of AML treatment as monotherapy:* • Interrupt TIBSOVO until toxicity resolves to Grade 2 or lower. • Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1 or lower. • If Grade 3 or higher toxicity recurs, discontinue TIBSOVO.
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 m2) or moderate (eGFR ≥30 to <60 mL/min/1.73 m2) renal impairment. A recommended dose has not been determined for patients with severe renal impairment (eGFR <30 mL/min/1.73 m2). 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

Differentiation syndrome in patients with acute myeloid leukaemia (AML)

TIBSOVO treatment can cause Differentiation syndrome in patients with AML (see *section 4.8 - Adverse effects (Undesirable effects)*), in keeping with its mechanism of action. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal.

Symptoms of differentiation syndrome in patients treated with TIBSOVO in pivotal studies included non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased. The timing of onset of differentiation syndrome follows that of AML response to treatment: it can occur within a day or after many months of treatment.

If differentiation syndrome is suspected, commence systemic corticosteroids (dexamethasone 10 mg IV every 12 hours or an equivalent dose of an alternative oral or IV corticosteroid) and initiate haemodynamic monitoring. If non-infectious leukocytosis is also observed, initiate treatment with hydroxycarbamide or leukapheresis as clinically indicated.

Continue corticosteroids for a minimum of three days, and taper corticosteroids and hydroxycarbamide only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxycarbamide treatment.

If severe (Grade 3 or higher) signs/symptoms persist for more than 48 hours after the initiation of systemic corticosteroids, interrupt TIBSOVO until signs/symptoms are no longer severe (see *section 4.2 Dose and method of administration*).

QTc interval prolongation

TIBSOVO causes prolongation of the QTc interval, and ventricular arrhythmias have been reported following treatment with TIBSOVO 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

Guillain-Barré syndrome has occurred uncommonly in patients with haematological malignancies treated with TIBSOVO. 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 TIBSOVO 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 TIBSOVO 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 *section 4.8 - Adverse effects (Undesirable effects)*).

Paediatric use

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

Effects on laboratory tests

See

Table ***4***, Table ***6***, ***Table 8*** and Table ***10*** 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 TIBSOVO. Give advice regarding potential for food interactions and review concomitant medications (see *QTc 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 TIBSOVO 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

Category	Some examples	Expected/possible outcome
OAT3 substrates	benzylpenicillin, furosemide	increased OAT3 substrate exposure
Medicines that prolong the QTc interval [1]	anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals	additive or synergistic effect on QTc 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 TIBSOVO

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 TIBSOVO 250 mg 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 TIBSOVO 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 importance 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 TIBSOVO 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-day 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 (embryofetal 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 TIBSOVO and for at least one month after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TIBSOVO does not have sedating properties and does not specifically change the ability to drive and use machines. However, any adverse effects of TIBSOVO which a patient experiences (which could include fatigue, dizziness and QTc interval prolongation – see *section 4.8 – Adverse effects (Undesirable effects)*) should be considered when assessing ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Safety profile in cholangiocarcinoma

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.

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 QTc interval prolongation (3.3%) and neuropathy peripheral (0.8%).

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***, respectively.

Table 3 – Adverse events reported in at least 10% of patients with locally advanced or metastatic cholangiocarcinoma receiving TIBSOVO 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 QTc interval prolongation	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 TIBSOVO in clinical Study AG120-C-005[#]

	TIBSOVO (500 mg daily) N=123		Placebo N=59	
Parameter	**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.

Safety profile in acute myeloid leukaemia (AML)

Summary of the safety profile in AML across studies

TIBSOVO 500 mg daily has been studied in combination with azacitidine in newly diagnosed AML (study AG120-C-009 [N=71]) and as monotherapy in patients with newly diagnosed or with relapsed/refractory AML (study AG120-C-001 [N=213]). These studies are described further in section 5.1 – Pharmacodynamic properties. In patients with AML across both of these studies, the most common adverse events including laboratory abnormalities (≥25% in either trial) were leukocytes decreased, diarrhoea, haemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, oedema, potassium decreased, nausea, vomiting, phosphatase decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnoea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QTc interval prolongation, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia.

Safety profile in the treatment of newly diagnosed AML (TIBSOVO in combination with azacitidine)

In the randomised, phase 3 Study AG120-C-009, patients with newly diagnosed AML received azacitidine in combination with either TIBSOVO (500 mg daily, n=72) or matching placebo (n=74). The median duration of treatment with TIBSOVO was 7.8 months (range 0.1 to 40.0 months). Forty patients (55.6%) were exposed to TIBSOVO for at least six months and twenty-nine patients (40.3%) were exposed for at least one year.

The most common adverse events and laboratory abnormalities reported in patients who received TIBSOVO and azacitidine are shown in Table 5 and Table ***6*** respectively.

The most common (≥5%) serious adverse event to TIBSOVO was differentiation syndrome (8%). There were eleven fatal adverse events in patients who received TIBSOVO (15%) – Most common (≥2%) included pneumonia (3%) and haemorrhage intracranial (3%).

The frequency of discontinuation of TIBSOVO due to adverse events was 29%. Adverse event leading to discontinuation of TIBSOVO in ≥ 2% of patients was pulmonary embolism (3%).

The frequency of dose interruption of TIBSOVO due to adverse events was 67%. The most common (≥5%) adverse events leading to dose interruption of TIBSOVO were neutropenia (24%), febrile neutropenia (13%), pneumonia (13%), thrombocytopenia (7%) and electrocardiogram QTc interval prolongation (7%).

The frequency of dose reduction of TIBSOVO due to adverse events was 22%. The most common (≥5%) adverse events leading to dose reduction were electrocardiogram QTc interval prolongation (10%) and neutropenia (8%).

Table 5- Adverse events that occurred in at least 10% of patients with AML who received TIBSOVO + azacitidine, with at least 5% higher incidence than in the comparator arm, in Study AG120-C-009

	TIBSOVO + azacitidine N=72		Placebo + azacitidine N=74	
Body system Adverse events	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Blood and lymphatic system disorders				
Differentiation syndrome[1]	11 (15)	7 (10)	6 (8)	6 (8)
Neutropenia[2*]	28 (39)	28 (39)	21 (28)	21 (28)
Thrombocytopenia[3*]	27 (38)	24 (33)	21 (28)	21 (28)
Leukopenia[4*]	9 (13)	8 (11)	5 (7)	5 (7)
Leukocytosis[5]	9 (13)	0	2 (3)	1 (1)
Gastrointestinal disorders				
Nausea	32 (44)	2 (3)	29 (39)	3 (4)
Vomiting[6]	29 (40)	0	20 (27)	1 (1)
Investigations				
Electrocardiogram QTc interval prolongation	15 (21)	7 (10)	5 (7)	2 (3)
Musculoskeletal and connective tissue disorders				
Arthralgia[7]	25 (35)	3 (4)	9 (12)	3 (4)
Nervous system disorders				
Headache	8 (11)	0	2 (3)	0
Dizziness	8 (11)	1 (1)	4 (5)	0
Psychiatric disorders				
Insomnia	14 (19)	1 (1)	9 (12)	0
Vascular disorders				
Haematoma[8]	12 (17)	0	3 (4)	0

[*] Laboratory results indicated rates of neutropenia, thrombocytopenia and leukopenia (including high grade events) were similar or higher in the placebo arm (see Table 6). These events are probably not caused by TIBSOVO and have not included when describing 'reactions' for this trial.

[1] Differentiation syndrome can be associated with other commonly reported events such as peripheral oedema, leukocytosis, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonia, pericardial effusion, rash, fluid overload, tumour lysis syndrome, and creatinine increased.

[2] Group term includes neutropenia and neutrophil count decreased. Rate and severity of laboratory-confirmed neutropenia was higher in the placebo arm.

[3] Group term includes thrombocytopenia and platelet count decreased.

[4] Group term includes leukopenia, white blood cell count decreased, and lymphocyte count decreased

[5] Grouped term includes leukocytosis and white blood cell count increased.

[6] Grouped term includes vomiting and retching.

[7] Grouped term includes pain in extremity, arthralgia, back pain, musculoskeletal stiffness, cancer pain, and neck pain.

[8] Grouped term includes haematoma, eye haematoma, catheter site haematoma, oral mucosa haematoma, spontaneous haematoma, application site haematoma, injection site haematoma, periorbital haematoma.

Table 6- Selected laboratory abnormalities that were new or worse in at least 10% of patients who received TIBSOVO + azacitidine in Study AG120-C-009

	TIBSOVO + azacitidine N=72		Placebo + azacitidine N=74	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Chemistry parameters				
Glucose increased	41 (57)	9 (13)	35 (47)	8 (11)
Phosphate decreased	30 (42)	7 (10)	27 (36)	9 (12)
Magnesium decreased	29 (40)	1 (1)	22 (30)	0
Aspartate aminotransferase increased	26 (36)	0	18 (24)	0
Potassium increased	19 (26)	3 (4)	10 (14)	1 (1)
Calcium increased	10 (14)	1 (1)	5 (7)	2 (3)
Haematology parameter				
Leukocytes decreased	46 (64)	41 (57)	48 (65)	44 (59)
Platelets decreased	42 (58)	32 (44)	53 (72)	42 (57)
Haemoglobin decreased	41 (57)	34 (47)	52 (70)	44 (59)
Neutrophils decreased	19 (26)	18 (25)	25 (34)	23 (31)
Lymphocytes increased	17 (24)	1 (1)	8 (11)	1 (1)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.
[2] The denominator used to calculate percentages is the number of treated subjects who can be evaluated for CTCAE criteria for each parameter in each arm.

Safety profile in the treatment of newly diagnosed AML (TIBSOVO monotherapy)

The safety profile of single-agent TIBSOVO at a dose of 500 mg daily was studied in 28 adults with newly diagnosed AML in a single-arm, open-label, multicenter clinical trial (Study AG120-C-001).

The median duration of exposure to TIBSOVO amongst this group was 4.3 months (range 0.3 to 40.9 months). Ten patients (36%) were exposed to TIBSOVO for at least six months and six patients (21%) were exposed for at least one year.

Common (≥5%) serious adverse events included differentiation syndrome (18%), electrocardiogram QTc interval prolongation (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).

Common (≥10%) adverse events leading to dose interruption included electrocardiogram QTc interval prolongation (14%) and differentiation syndrome (11%). Two (7%) patients required a dose reduction due to electrocardiogram QTc interval prolongation. One patient each required permanent discontinuation due to diarrhoea and PRES.

The most common adverse events and changes in selected post-baseline laboratory values reported in Study AG120-C-001 amongst these patients with newly diagnosed AML are shown in Table 7 and Table 8, respectively.

Table 7 – Most common (≥10% incidence) and most common severe ((≥5% incidence of Grade ≥3) adverse events in patients with newly diagnosed AML who received TIBSOVO as monotherapy at a dose of 500 mg daily in Study AG120-C-001

	TIBSOVO (500 mg daily) N=28	
Body System Adverse Event	**All Grades** **n (%)**	**Grade ≥ 3** **n (%)**
Gastrointestinal disorders		
Diarrhoea	17 (61)	2 (7)
Nausea	10 (36)	2 (7)
Abdominal pain[1]	8 (29)	1 (4)
Constipation	6 (21)	1 (4)
Vomiting	6 (21)	1 (4)
Mucositis[2]	6 (21)	0
Dyspepsia	3 (11)	0
General disorders and administration site conditions		
Fatigue[3]	14 (50)	4 (14)
Oedema[4]	12 (43)	0
Metabolism and nutrition disorders		
Decreased appetite	11 (39)	1 (4)
Blood system and lymphatic system disorders		
Leukocytosis[5]	10 (36)	2 (7)
Differentiation syndrome[6]	7 (25)	3 (11)
Musculoskeletal and connective tissue disorders		
Arthralgia[7]	9 (32)	1 (4)
Myalgia[8]	7 (25)	1 (4)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea[9]	8 (29)	1 (4)
Cough[10]	4 (14)	0
Investigations		
Electrocardiogram QTc interval prolongation	6 (21)	3 (11)
Weight decreased	3 (11)	0
Nervous system disorders		
Dizziness	6 (21)	0
Neuropathy[11]	4 (14)	0
Headache	3 (11)	0
Skin and subcutaneous tissue disorders		
Pruritis	4 (14)	1 (4)
Rash[12]	4 (14)	1 (4)

1 Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
2 Grouped term includes aphthous ulcer, oesophageal pain, oesophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
3 Grouped term includes asthenia and fatigue.
4 Grouped term includes oedema, face oedema, fluid overload, fluid retention, hypervolaemia, peripheral oedema, and swelling face.
5 Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
6 Differentiation syndrome can be associated with other commonly reported events such as peripheral oedema, leukocytosis, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonia, pericardial effusion, rash, fluid overload, tumour lysis syndrome, and creatinine increased.
7 Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.

8 Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
9 Grouped term includes dyspnoea, dyspnoea exertional, hypoxia, and respiratory failure.
10 Grouped term includes cough, productive cough, and upper airway cough syndrome.
11 Grouped term includes burning sensation, lumbosacral plexopathy, neuropathy peripheral, paresthesia, and peripheral motor neuropathy.
12 Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.

Table 8 – Most common (≥10% incidence) and most common severe (≥5% incidence of Grade ≥3) new or worsening laboratory abnormalities in patients with newly diagnosed AML who received TIBSOVO as monotherapy at a dose of 500 mg daily in Study AG120-C-001[1]

	TIBSOVO (500 mg daily) N=28	
Parameter	**All Grades n (%)**	**Grade ≥3 n (%)**
Haemoglobin decreased	15 (54)	12 (43)
Alkaline phosphatase increased	13 (46)	0
Potassium decreased	12 (43)	3 (11)
Sodium decreased	11 (39)	1 (4)
Uric acid increased	8 (29)	1 (4)
Aspartate aminotransferase increased	8 (29)	1 (4)
Creatinine increased	8 (29)	0
Magnesium decreased	7 (25)	0
Calcium decreased	7 (25)	1 (4)
Phosphate decreased	6 (21)	2 (7)
Alanine aminotransferase increased	4 (14)	1 (4)

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

Safety profile in the treatment of relapsed or refractory AML (TIBSOVO monotherapy)

The safety profile of single-agent TIBSOVO was studied in 179 adults with relapsed or refractory AML who received TIBSOVO 500 mg daily in Study AG120-C-001 *(*see *section 5.1 – Pharmacodynamic properties)*.

The median duration of exposure to TIBSOVO was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to TIBSOVO for at least six months and 16 patients (9%) were exposed for at least 1 year.

Serious Treatment emergent adverse events (TEAEs) (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QTc interval prolongation (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

The most common adverse events leading to dose interruption were electrocardiogram QTc interval prolongation (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnoea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse events leading to a dose reduction included electrocardiogram QTc interval prolongation (1%), diarrhoea (1%), nausea (1%), decreased haemoglobin (1%), and increased transaminases (1%). Adverse events leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

The most common adverse events and changes in selected post-baseline laboratory values reported in this group of patients with relapsed or refractory AML are shown in Table 9 and Table 10, respectively.

Table 9- Most common (≥10% incidence) and most common severe (≥5% incidence of Grade ≥3) adverse events reported in patients with relapsed or refractory AML who received TIBSOVO as monotherapy at a dose of 500 mg daily in study AG120-C-001

	TIBSOVO (500 mg daily) N=179	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**
General disorders and administration site conditions		
Fatigue[1]	69 (39)	6 (3)
Oedema[2]	57 (32)	2 (1)
Pyrexia	41 (23)	2 (1)
Chest pain[3]	29 (16)	5 (3)
Blood system and lymphatic system disorders		
Leukocytosis[4]	68 (38)	15 (8)
Differentiation syndrome[5]	34 (19)	23 (13)
Musculoskeletal and connective tissue disorders		
Arthralgia[6]	64 (36)	8 (4)
Myalgia[7]	33 (18)	1 (1)
Gastrointestinal disorders		
Diarrhoea	60 (34)	4 (2)
Nausea	56 (31)	1 (1)
Mucositis[8]	51 (28)	6 (3)
Constipation	35 (20)	1 (1)
Vomiting[9]	32 (18)	2 (1)
Abdominal pain[10]	29 (16)	2 (1)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea[11]	59 (33)	16 (9)
Cough[12]	40 (22)	1 (<1)
Pleural effusion	23 (13)	5 (3)
Investigations		
Electrocardiogram QTc interval prolongation	46 (26)	18 (10)
Skin and subcutaneous tissue disorders		
Rash[13]	46 (26)	4 (2)
Metabolism and nutrition disorders		
Decreased appetite	33 (18)	3 (2)
Tumour lysis syndrome	14 (8)	11 (6)
Nervous system disorders		
Headache	28 (16)	0
Neuropathy[14]	21 (12)	2 (1)
Vascular disorders		
Hypotension[15]	22 (12)	7 (4)

1 Grouped term includes asthenia and fatigue.
2 Grouped term includes peripheral oedema, oedema, fluid overload, fluid retention, and face oedema.
3 Grouped term includes angina pectoris, chest pain, chest discomfort, and non-cardiac chest pain.
4 Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.

5 Differentiation syndrome can be associated with other commonly reported events such as peripheral oedema, leukocytosis, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonia, pericardial effusion, rash, fluid overload, tumour lysis syndrome, and creatinine increased.
6 Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
7 Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
8 Grouped term includes aphthous ulcer, oesophageal pain, oesophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
9 Grouped term includes vomiting and retching.
10 Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
11 Grouped term includes dyspnoea, respiratory failure, hypoxia, and dyspnoea exertional.
12 Grouped term includes cough, productive cough, and upper airway cough syndrome.
13 Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.
14 Grouped term includes ataxia, burning sensation, gait disturbance, Guillain-Barré syndrome, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, peripheral motor neuropathy, and sensory disturbance.
15 Grouped term includes hypotension and orthostatic hypotension.

Table 10– Most common (≥10% incidence) and most common severe (≥5% incidence of Grade ≥3) new or worsening laboratory abnormalities reported in patients with relapsed or refractory AML who received TIBSOVO as monotherapy at a dose of 500 mg daily in Study AG120-C-001 [1]

	TIBSOVO (500 mg daily) N=179	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Haemoglobin decreased	108 (60)	83 (46)
Sodium decreased	69 (39)	8 (4)
Magnesium decreased	68 (38)	0
Uric acid increased	57 (32)	11 (6)
Potassium decreased	55 (31)	11 (6)
Alkaline phosphatase increased	49 (27)	1 (1)
Aspartate aminotransferase increased	49 (27)	1 (1)
Phosphate decreased	45 (25)	15 (8)
Creatinine increased	42 (23)	2 (1)
Alanine aminotransferase increased	26 (15)	2 (1)
Bilirubin increased	28 (16)	1 (1)

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

Description of selected adverse events

Differentiation syndrome in patients with AML

Differentiation syndrome is a known risk associated with TIBSOVO treatment in patients with AML (see *sections 4.2 – Dose and method of administration and 4.4 – Special warnings and precautions for use*).

In the monotherapy clinical trial AG120-C-001, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Of the seven patients with newly diagnosed AML who experienced differentiation syndrome, six (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as one day and up to three months after initiation with TIBSOVO and has been observed with or without concomitant leukocytosis.

In study AG120-C-009, 14% (10/71) of patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine experienced differentiation syndrome. Of these ten patients, two required dose interruptions to manage signs/symptoms and zero patients permanently discontinued TIBSOVO treatment due to differentiation syndrome. The median time to onset of differentiation syndrome after initiation of combination therapy was 20 days, with a range of three to 46 days.

QTc interval prolongation

Prolongation of the electrocardiogram QTc interval is a known risk associated with TIBSOVO 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 TIBSOVO 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: one day to 698 days [23 months].

Of the 258 patients with hematological malignancies treated with TIBSOVO monotherapy in the clinical trial AG120-C-001, 9% were found to have a QTc interval greater than 500 msec and 14% of patients had an increase from baseline QTc greater than 60 msec [see *section 4.8 – Adverse effects (Undesirable effects*)). One patient developed ventricular fibrillation attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥450 msec (unless the QTc ≥450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

In Study AG120-C-009, in the 71 patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine, electrocardiogram QT prolonged was reported in 20%; 10% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 14% of patients treated with TIBSOVO in combination with azacitidine, who had at least one post-baseline ECG assessment, were found to have a QTc interval >500 msec, 22% had an increase from baseline QTc >60 msec. One patient discontinued TIBSOVO treatment due to electrocardiogram QT prolongation. Dose interruption and reduction were required in 6% and 9% of patients, respectively. The median time to onset of QT prolongation in patients treated with TIBSOVO was 29 days. Electrocardiogram QT prolongation occurred as early as 1 day and up to 5 months after treatment initiation.

Guillain-Barré syndrome

Two cases of Guillain-Barré syndrome (<1%) occurred in patients with haematological malignancies receiving TIBSOVO in study AG120-C-001. There were no cases in study AG120-C-009 or Study AG120-C-005.

Special populations

Elderly

Of the 72 patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine, 94% were 65 years of age or older, and 54% were 75 years or older. Of the 34 patients with newly diagnosed

AML treated with TIBSOVO monotherapy, 97% were 65 years of age or older, and 56% were 75 years or older. Of the 179 patients with relapsed or refractory AML treated with TIBSOVO monotherapy, 63% were 65 years of age or older and 22% were 75 years or older. 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 QTc interval 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 TIBSOVO 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 certain mutant 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.

Acute myeloid leukaemia

Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels, reduced blast counts, and increased percentages of mature myeloid cells.

Pharmacodynamic effects

Multiple doses of ivosidenib 500 mg daily decreased plasma concentrations of 2-HG in patients with haematological malignancies and cholangiocarcinoma with mutated IDH1 to levels approximating those observed in healthy subjects. In tumour biopsies from patients with cholangiocarcinoma who received ivosidenib, the mean (coefficient of variation [CV]) reduction in 2-HG concentrations was 82% (32%). In

bone marrow biopsies from patients with haematological malignancies who received ivosidenib, the mean (CV) reduction in 2-HG concentrations was 93% (11%).

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 trials (efficacy)

Efficacy in previously treated, locally advanced or metastatic cholangiocarcinoma

The efficacy of TIBSOVO 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 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 TIBSOVO.

The study demonstrated a statistically significant improvement in PFS. The efficacy results for Study AG120-C-005 are summarised in Table 11 and

Figure **1**.

Table 11- Efficacy results in patients with locally advanced or metastatic cholangiocarcinoma (Study

AG120-C-005)

	TIBSOVO (500 mg daily)	Placebo
Progression-free survival (PFS) by IRC	**N=124**	**N=61**
Events, n (%)	76 (61)	50 (82)
Progressive Disease	64 (52)	44 (72)
Death	12 (10)	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	

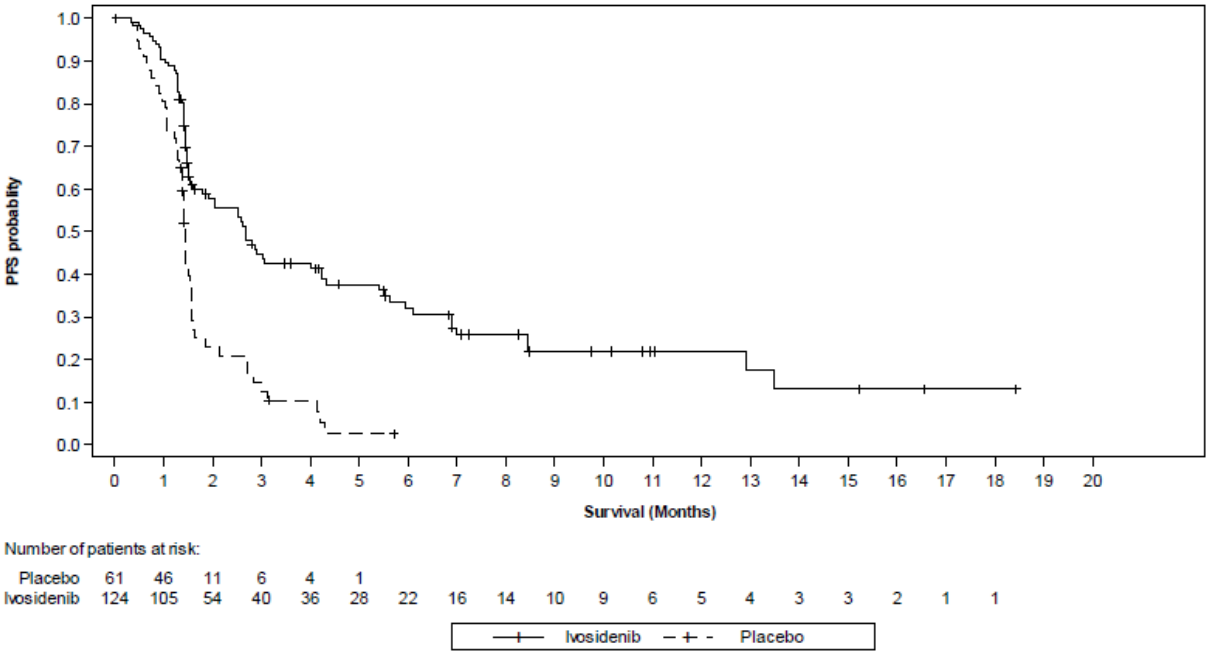
IRC: Independent Radiology Centre; CI: Confidence Interval; NE = not estimable.

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 in patients with locally advanced or metastatic cholangiocarcinoma (Study AG120-C-005)



Efficacy in newly diagnosed AML - TIBSOVO in combination with azacitidine

The efficacy and safety of TIBSOVO was evaluated in a randomised, multicentre, double-blind, placebo-controlled clinical trial (Study AG120-C-009) of 146 adult patients with newly diagnosed AML with an IDH1 mutation who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, creatinine clearance <45 mL/min, or other comorbidity. IDH1 mutations were confirmed centrally using the Abbott RealTime™ IDH1 Assay. Local diagnostic tests were permitted for screening and randomisation, provided a bone marrow or peripheral blood sample was sent for central confirmation. Gene mutation analysis to document IDH1 mutated disease from a bone marrow or peripheral blood sample was conducted for all patients. Patients were randomised to receive either TIBSOVO 500 mg, or matched placebo, orally once daily on Days 1-28, in combination with azacitidine 75 mg/m^2/day subcutaneously or intravenously on Days 1-7 or Days 1-5 and 8-9 of each 28-day cycle. Treatment was continued for a minimum of 6 cycles unless they experienced disease progression or unacceptable toxicity or underwent haematopoietic stem cell transplantation.

The primary efficacy outcome was event-free survival (EFS), measured from the date of randomisation until treatment failure, relapse from remission, or death by any cause. Treatment failure was defined as failure to achieve complete remission (CR) by week 24. Overall Survival (OS), CR rate, CR + CR with partial hematologic recovery (CR + CRh) rate and objective response rate (ORR) were key secondary efficacy endpoints.

Amongst patients randomised to receive TIBSOVO, the median age was 76 years (range: 58 to 84); 58% were male; 21% Asian and 17% were Caucasian, whilst ethnicity was not reported for 61%. ECOG performance status was 0 (19%), 1 (44%), or 2 (36%), and most patients (75%) had de novo AML. Cytogenetic risk (per National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, 2017), was intermediate for most patients (67%), with 4% having favourable and 26% having poor/other cytogenetic risk. According to the central testing, 63% of patients had an R132C mutation, 19% had an R132H mutation, 8% had an R132G mutation, 4% had an R132L mutation, and 3% had an R132H mutation.

The key efficacy findings of Study AG120-C-009 are summarised in

Table ***12*** and Figure 2.

Table 12- Efficacy results for TIBSOVO in combination with azacitidine in patients with newly diagnosed

AML (Study AG120-C-009)

	TIBSOVO (500 mg daily) + azacitidine N=72	**Placebo + azacitidine N=74**
Event-free survival (EFS) events, n (%)	46 (63.9)	62 (83.8)
Treatment failure	42 (58.3)	59 (79.7)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Hazard ratio[1] (95% CI)	0.33 (0.16, 0.69)	
p-value[2]	0.0011	
OS events, n (%)	28 (38.9)	46 (62.2)
Median OS (95% CI), months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
Hazard ratio[1] (95% CI)	0.44 (0.27, 0.73)	
p-value[2]	0.0005	
CR rate, n (%)	34 (47.2)	11 (14.9)
95% CI3	(35.3, 59.3)	(7.7, 25.0)
Odds Ratio[4] (95% CI)	4.76 (2.15, 10.50)	
p-value[2]	<0.0001	

	TIBSOVO (500 mg daily) + azacitidine N=72	**Placebo + azacitidine N=74**
CR + CRh rate, n (%)	38 (52.8)	13 (17.6)
95% CI[3]	(40.7, 64.7)	(9.7, 28.2)
Odds ratio4 (95% CI)	5.01 (2.32, 10.81)	
p-value[2]	<0.0001	
Objective response rate[5], n (%)	45 (62.5)	14 (18.9)
95% CI[3]	(50.3, 73.6)	(10.7, 29.7)
Odds Ratio[4] (95% CI)	7.15 (3.31, 15.44)	
p-value[2]	<0.0001	

CI: confidence interval; CR = complete remission; CRh = complete remission with partial haematological recovery; OS = overall survival.

1 Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomisation stratification factors (AML status and geographic region).

2 p-value is calculated from the 1-sided log-rank test stratified by the randomisation stratification factors (AML status and geographic region).

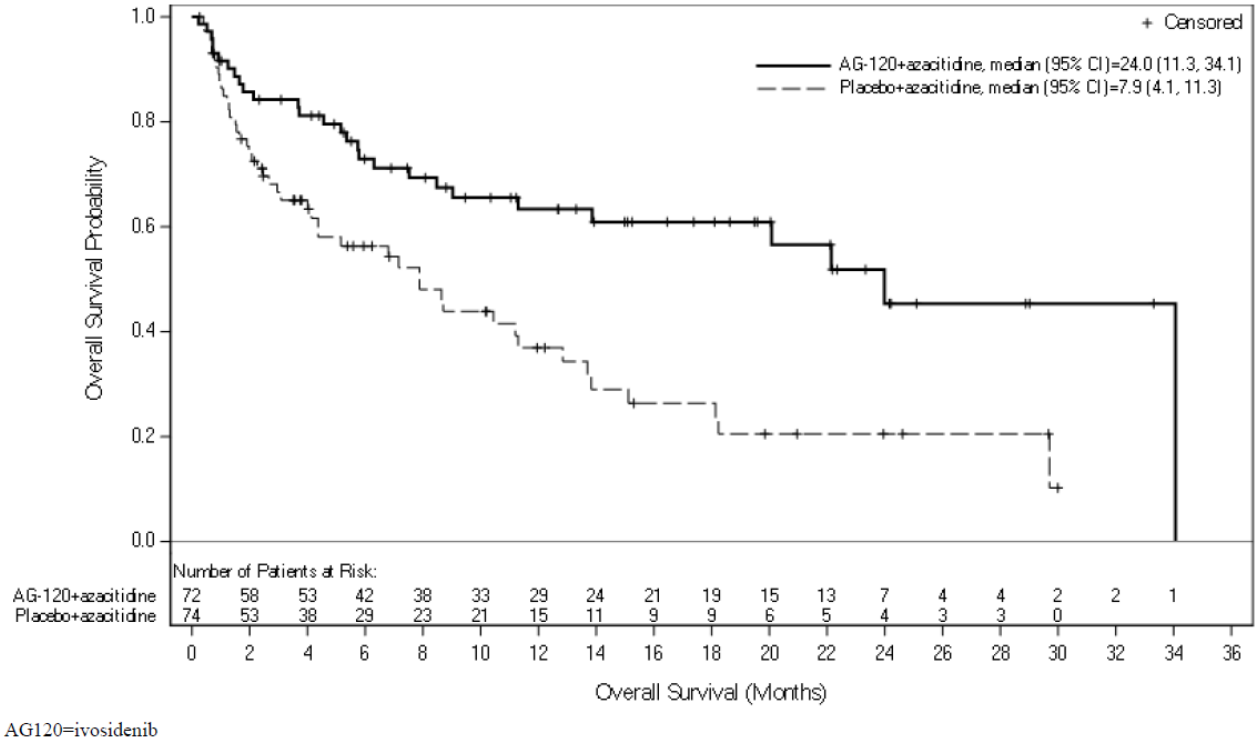
3 CI of percentage is calculated with the Clopper and Pearson (exact binomial) method.

4 Cochran-Mantel-Haenszel (CMH) estimate for odds ratio.

5 Objective response rate is defined as the rate of CR, complete remission with incomplete haematological recovery (CRi, including CR with incomplete platelet recovery [CRp]), partial response (PR), and morphologic leukaemia-free state (MLFS).

Figure 2- Kaplan-Meier plot of overall survival (OS) TIBSOVO in combination with azacitidine in patients

with newly diagnosed AML (Study AG120-C-009)



AG120=ivosidenib

The median time to first CR for TIBSOVO with azacitidine was four months (range, 1.7 to 9.2 months). The median time to first CR + CRh for TIBSOVO with azacitidine was four months (range, 1.7 to 8.6 months). The median time to first objective response (defined as CR, CRi (including CRp), PR or MLFS) was two months (range, 1.7 to 7.5 months) for TIBSOVO with azacitidine.

Efficacy in newly diagnosed AML - TIBSOVO monotherapy

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicentre clinical trial (Study AG120-C-001) that included 28 adult patients with newly diagnosed AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTime™ IDH1 Assay. The cohort included patients who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of ≥2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatinine clearance 45 mL/min. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing haematopoietic stem cell transplantation. Two (7%) of the 28 patients went on to stem cell transplantation following TIBSOVO treatment.

Amongst this group of patients, the median age was 77 years (range: 64 to 87). Most patients were male (54%), 87% were Caucasian, ECOG performance status was 0 in 37%, 1 in 62%, two in five patients (18%) and 3 in one patient (4%). Just under half (46%) had received a hypomethylating agent previously for an antecedent haematological disorder. Most patients (61%) were transfusion dependent at baseline, defined as receipt of any transfusion within 56 days prior to the first dose of TIBSOVO. Most patients had AML with myelodysplasia-related changes (68%), whilst 21% had de novo AML and 11% had therapy-related AML. European Leukaemia Net risk category was adverse for most patients (68%) and intermediate for the remaining 32%. According to the central retrospective confirmatory testing, 86% of patients had an R132C

mutation, 7% had an R132H mutation, there was 1 patient each with an R132G or R132L mutation, and no patients with an R132S mutation.

Efficacy was established on the basis of the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 13. The median follow-up was 8.1 months (range, 0.6 to 40.9 months) and median treatment duration was 4.3 months (range, 0.3 to 40.9 months).

Table 13- Efficacy results of TIBSOVO monotherapy in patients with newly diagnosed AML (Study AG120-C-001)

Endpoint	**TIBSOVO (500 mg daily) N=28**
CR[1] n (%)	8 (28.6)
95% CI	(13.2, 48.7)
Median DOCR[2] (months)	NE[3]
95% CI	(4.2, NE)
CRh[4] n (%)	4 (14.3)
95% CI	(4.0, 32.7)
Observed DOCRh[2] (months)	2.8, 4.6, 8.3, 15.7+
CR+CRh n (%)	12 (42.9)
95% CI	(24.5, 62.8)
Median DOCR+CRh[2] (months)	NE[3]
95% CI	(4.2, NE)

CI: confidence interval, NE: not estimable

[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier. + indicates censored observation.

[3] The median durations of CR and CR+CRh were not estimable, with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO treatment (treatment duration range: 20.3 to 40.9 months).

[4] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

For patients who achieved a CR or CRh, the median time to CR or CRh was 2.8 months (range, 1.9 to 12.9 months). Of the 12 patients who achieved a best response of CR or CRh, 11 (92%) achieved a first response of CR or CRh within six months of initiating TIBSOVO.

Among the 17 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, seven (41.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 11 patients who were independent of both RBC and platelet transfusions at baseline, six (54.5%) remained transfusion independent during any 56-day post- baseline period.

Efficacy in relapsed or refractory AML

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001) in 174 adult patients with relapsed or refractory AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*me*™ IDH1 Assay. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing haematopoietic stem cell transplantation. Twenty-one (12%) of the 174 patients went on to stem cell transplantation following TIBSOVO treatment.

Amongst this group of patients, the median age was 67 years (range: 18 to 87). Half of the group were male (51%), 62% were Caucasian, ECOG performance status was 0 in 21%; 1 in 56%; 2 in 22% and 3 in two patients (1%). Most patients had de novo AML (67%) and 33% had secondary AML. Relapse was primary refractory for 37%, untreated relapse for 37% and refractory relapse for 26% of patients. Most patients (63%) were transfusion dependent at baseline (defined as receipt of any transfusion within 56 days prior to the first dose of TIBSOVO), and the median number of prior therapies was 2 (range 1-6): 23% had received prior stem cell transplantation for AML. Cytogenetic risk was intermediate for most patients (60%), with 27% having poor cytogenetic risk and the remainder unknown. According to the central retrospective confirmatory testing, 59% of patients had an R132C mutation, 25% had R132H, 7% had R132G, 6% had R132S, and 4% had an R132L mutation.

Efficacy was established on the basis of the rate of complete remission (CR) plus complete remission with partial haematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 14. The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and median treatment duration was 4.1 months (range, 0.1 to 39.5 months).

Table 14- Efficacy results in patients with relapsed or refractory AML (Study AG120-C-001)

Endpoint	TIBSOVO (500 mg daily) N=174
CR[1] n (%)	43 (24.7)
95% CI	(18.5, 31.8)
Median DOCR[2] (months)	10.1
95% CI	(6.5, 22.2)
CRh[3] n (%)	14 (8.0)
95% CI	(4.5, 13.1)
Median DOCRh[2] (months)	3.6
95% CI	(1, 5.5)
CR+CRh[4] n (%)	57 (32.8)
95% CI	(25.8, 40.3)
Median DOCR+CRh[2] (months)	8.2
95% CI	(5.6, 12)

CI: confidence interval

[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier.

[3] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

[4] CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens.

For patients who achieved a CR or CRh, the median time to CR or CRh was two months (range, 0.9 to 5.6 months). Of the 57 patients who achieved a best response of CR or CRh, all achieved a first response of CR or CRh within six months of initiating TIBSOVO.

Among the 110 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (37%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59%) remained transfusion independent during any 56-day post-baseline period.

5.2 PHARMACOKINETIC PROPERTIES

A summary of ivosidenib pharmacokinetic (PK) parameters following administration of ivosidenib 500 mg as a single or daily dose (for steady state) is provided in Table 15. 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 15- Summary of plasma PK parameters of ivosidenib[a] after administration in clinical studies (cholangiocarcinoma and AML)

PK parameter	Cholangiocarcinoma (TIBSOVO monotherapy)	Relapsed or refractory AML (TIBSOVO monotherapy)	Newly diagnosed AML (TIBSOVO + Azacitidine)
Mean (CV) single dose C_{max} (ng/mL)	4,060 (45%)	4,503 (38%)	4,820 (39%)
Mean (CV) steady-state C_{max} (ng/mL)	4,799 (33%)	6,551 (44%)	6,145 (34%)
Mean (CV) steady-state AUC (ng/mL)	86,382 (34%)	117,348 (50%)	106,326 (41%)

PK parameter	Cholangiocarcinoma (TIBSOVO monotherapy)	Relapsed or refractory AML (TIBSOVO monotherapy)	Newly diagnosed AML (TIBSOVO + Azacitidine)
Accumulation ratio: C_{max}	1.2	1.5	1.2
Accumulation ratio: AUC	1.5	1.9	1.6
Absorption			
Median T_{max} (hours)	2 (range 0.5, 4.1)	3	2
Effect of food: [b] on Cmax	1.98-fold (90% CI: 1.79, 2.19)		
on AUC	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	403 (35%) L	504 (22%) L
Elimination			
Mean (CV) CL at steady state (L/hr)	6.1 (31%)	5.6 (35%)	4.6 (35%)
Mean (CV) T½ at steady state (hours)	129 (102%)	58 (42%)	98 (42%)
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

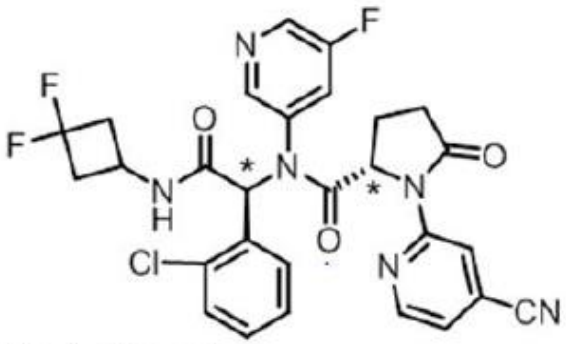
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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

For the treatment of Cholangiocarcinoma: 05 April 2023

For the treatment of Acute myeloid leukaemia: 20 September 2023

10 DATE OF REVISION

20 September 2023

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information
Sections 1 to 5 inclusive	New indication- treatment of Acute myeloid leukaemia (AML)