1. NAME OF THE MEDICINAL PRODUCT

Tibsovo
film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of ivosidenib.

Excipient with known effect

Each film-coated tablet contains lactose monohydrate equivalent to 9.5 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

Patient safety information card
The marketing of Tibsovo is subject to a risk management plan (RMP) including a 'patient safety information card'. The patient safety information card , emphasize important information that the patient should be aware of before starting treatment.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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 in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy (see section 5.1).

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of physicians experienced in the use of anti-cancer medicinal products.

Before taking Tibsovo, patients must have confirmation of an IDH1 R132 mutation using an appropriate diagnostic test.

Posology

Acute myeloid leukaemia
The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily. Ivosidenib should be started on Cycle 1 Day 1 in combination with azacitidine at 75 mg/m^2 of body surface area, intravenously or subcutaneously, once daily on Days 1-7 (or days 1-5 and 8-9) of each

28-day cycle. The first treatment cycle of azacitidine should be given at 100% of the dose. It is recommended that patients be treated for a minimum of 6 cycles.

Refer to the Prescribing Information for azacitidine for additional dosing information

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Cholangiocarcinoma
The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily.

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Missed or delayed doses

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

If a dose is vomited, replacement tablets should not be taken. The tablets should be taken as usual the following day.

Precautions to be taken prior to administration and monitoring

An electrocardiogram (ECG) must be performed prior to treatment initiation. Heart rate corrected QT (QTc) should be less than 450 msec prior to treatment initiation and, in the presence of an abnormal QT, practitioners should thoroughly reassess the benefit/risk of initiating ivosidenib. In case QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with ivosidenib should remain exceptional and be accompanied by close monitoring.

An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec. QTc interval abnormalities should be managed promptly (see Table 1 and section 4.4). In case of suggestive symptomatology, an ECG should be performed as clinically indicated.

Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. An ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated (see below and sections 4.4, 4.5 and 4.8).

Complete blood count and blood chemistries should be assessed prior to the initiation of Tibsovo, at least once weekly for the first month of treatment, once every other week for the second month, and at each medical visit for the duration of therapy as clinically indicated.

Dose modification for concomitant administration of moderate or strong CYP3A4 inhibitors

If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250 mg (1 x 250 mg tablet) once daily. If the moderate or strong CYP3A4 inhibitor is discontinued, the dose of ivosidenib should be increased to 500 mg after at least 5 half-lives of the CYP3A4 inhibitor (see above and sections 4.4 and 4.5).

Dose modifications and management recommendations for adverse reactions

Table 1 - Recommended dose modifications for adverse reactions

Adverse reaction	Recommended action
Differentiation syndrome (see sections 4.4 and 4.8)	• If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of 3 days and taper only after symptom resolution. Premature discontinuation may result in symptom recurrence. • Initiate haemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt Tibsovo if severe signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume treatment at 500 mg ivosidenib once daily when signs/symptoms are moderate or lower and upon improvement in clinical condition.
Leukocytosis (white blood cell count > 25 x 10^9/L or an absolute increase in total white blood cell count > 15 x 10^9/L from baseline, see sections 4.4 and 4.8)	• Initiate treatment with hydroxycarbamide according to institutional standards of care and leukapheresis as clinically indicated. • Taper hydroxycarbamide only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence. • Interrupt Tibsovo if leukocytosis has not improved after initiation of hydroxycarbamide. • Resume treatment at 500 mg ivosidenib once daily when leukocytosis has resolved.
QTc interval prolongation > 480 to 500 msec (Grade 2, see sections 4.4, 4.5 and 4.8)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects (see section 4.5). • Interrupt Tibsovo until QTc interval returns to ≤ 480 msec. • Resume treatment at 500 mg ivosidenib once daily after the QTc interval returns to ≤ 480 msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to ≤ 480 msec.

QTc interval prolongation > 500 msec (Grade 3, see sections 4.4, 4.5 and 4.8)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see section 4.5). • Interrupt Tibsovo and monitor ECG every 24 h until QTc interval returns to within 30 msec of baseline or ≤ 480 msec. • In case of QTc interval prolongation > 550 msec, in addition to the interruption of ivosidenib already scheduled, consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec. • Resume treatment at 250 mg ivosidenib once daily after QTc interval returns to within 30 msec of baseline or ≤ to 480 msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to within 30 msec of baseline or ≤ 480 msec. • If alternative aetiology for QTc interval prolongation is identified, dose may be increased to 500 mg ivosidenib once daily.
QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4, see sections 4.4, 4.5 and 4.8)	• Permanently discontinue treatment.
Other Grade 3 or higher adverse reactions	• Interrupt Tibsovo 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.

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

Special populations

Elderly

No dose adjustment is required in elderly patients (≥ 65 years old, see sections 4.8 and 5.2). No data are available for patients aged 85 years or older.

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). Tibsovo should be used with caution in patients with severe renal impairment and this patient population should be closely monitored (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Tibsovo should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see sections 4.4 and 5.2).

Paediatric population

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

Method of administration

Tibsovo is for oral use.

The tablets are taken once daily at about the same time each day. Patients should not eat anything for 2 hours before and through 1 hour after taking the tablets (see section 5.2). The tablets should be swallowed whole with water.

Patients should be advised to avoid grapefruit and grapefruit juice during treatment (see section 4.5). Patients should also be advised not to swallow the silica gel desiccant found in the tablet bottle (see section 6.5).

4.3 Contraindications

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

Concomitant administration of strong CYP3A4 inducers or dabigatran (see section 4.5).

Congenital long QT syndrome.

Familial history of sudden death or polymorphic ventricular arrhythmia.

QT/QTc interval > 500 msec, regardless of the correction method (see section 4.2 and 4.4).

4.4 Special warnings and precautions for use

Differentiation syndrome in patients with acute myeloid leukaemia

Differentiation syndrome has been reported following treatment with ivosidenib (see section 4.8). Differentiation syndrome may be life-threatening or fatal if not treated (see below and section 4.2). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. Symptoms include: 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.
Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their physician immediately if these occur and the need to carry the Patient Alert Card with them at all times.

If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days.

If leukocytosis is observed, initiate treatment with hydroxycarbamide according to institutional standards of care and leukapheresis as clinically indicated (see section 4.5).

Taper corticosteroids and hydroxycarbamide only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxycarbamide treatment. Interrupt treatment with Tibsovo if severe signs/symptoms persist for more than 48 hours after the initiation of systemic corticosteroids and resume treatment at 500 mg ivosidenib once daily when the signs/symptoms are moderate or lower and upon improvement in the patient's clinical condition.

QTc interval prolongation

QTc interval prolongation has been reported following treatment with ivosidenib (see section 4.8). An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec (see section 4.2). Any abnormalities should be managed promptly (see section 4.2). In case of suggestive symptomatology, an ECG should be performed as clinically indicated. In case of severe vomiting and/or diarrhoea, an assessment of serum electrolytes abnormalities, especially hypokalaemia and magnesium, must be performed.

Patients should be informed of the risk of QT prolongation, its signs and symptoms (palpitation, dizziness, syncope or even cardiac arrest) and be advised to contact their physician immediately if these occur.

Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated. The recommended dose of ivosidenib should be reduced to 250 mg once daily if use of moderate or strong CYP3A4 inhibitors cannot be avoided (see sections 4.2 and 4.5).

If administration of furosemide (an OAT3 substrate) is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.

Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib.
Treatment with Tibsovo should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia (see section 4.2).

Ivosidenib should be used with caution in patients who have either albumin levels below the normal range or are underweight.

Severe 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). Tibsovo should be used with caution in patients with severe renal impairment and this patient population should be closely monitored
(see sections 4.2 and 5.2).

Hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Tibsovo should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see sections 4.2 and 5.2).
Tibsovo should be used with caution in patients with mild hepatic impairment (Child-Pugh class A) (see section 4.8).

CYP3A4 substrates

Ivosidenib induces CYP3A4 and it may, therefore, decrease systemic exposure to CYP3A4 substrates. Patients should be monitored for loss of antifungal efficacy if use of itraconazole or ketoconazole cannot be avoided (see section 4.5).

Women of childbearing potential / contraception

Women of childbearing potential should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during therapy (see section 4.6).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Tibsovo and for at least 1 month after the last dose.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended (see sections 4.5 and 4.6).

Lactose intolerance

Tibsovo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should avoid this medicinal product.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on ivosidenib

Strong CYP3A4 inducers

Ivosidenib is a CYP3A4 substrate. Concomitant administration of strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*)) is expected to decrease plasma concentrations of ivosidenib and is contraindicated during treatment with Tibsovo (see section 4.3). Clinical studies evaluating the pharmacokinetics of ivosidenib in the presence of a CYP3A4 inducer have not been conducted.

Moderate or strong CYP3A4 inhibitors

In healthy subjects, administration of a single dose of 250 mg ivosidenib and 200 mg itraconazole once daily for 18 days increased the ivosidenib AUC by 169% (90% CI: 145, 195) with no change in C_{max}. Concomitant administration of moderate or strong CYP3A4 inhibitors increases plasma concentrations of ivosidenib. This may increase the risk of QTc interval prolongation and suitable alternatives that are not moderate or strong CYP3A4 inhibitors should be considered whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250 mg once daily (see sections 4.2 and 4.4).

- Moderate CYP3A4 inhibitors include: aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice, isavuconazole, verapamil.
- Strong CYP3A4 inhibitors include: clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole.

Medicinal products known to prolong the QTc interval

Concomitant administration of medicinal products known to prolong the QTc interval (e.g. anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals) may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible (see sections 4.2 and 4.4).

Effect of ivosidenib on other medicinal products

Interactions with transporters

Ivosidenib inhibits P-gp and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp (e.g. dabigatran). Concomitant administration of dabigatran is contraindicated (see section 4.3).

Ivosidenib inhibits OAT3, organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3). Therefore, it may increase systemic exposure to OAT3 or OATP1B1/1B3 substrates. Concomitant administration of OAT3 substrates (e.g. benzylpenicillin, furosemide) or sensitive OATP1B1/1B3 substrates (e.g. atorvastatin, pravastatin, rosuvastatin) should be avoided whenever possible during treatment with Tibsovo (see section 5.2). Patients should be treated with caution if use of a suitable alternative is not possible. If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.

Enzyme induction

Cytochrome P450 (CYP) enzymes
Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Therefore, it may decrease systemic exposure to substrates of these enzymes. Suitable alternatives that are not CYP3A4, CYP2B6, CYP2C8 or CYP2C9 substrates with a narrow therapeutic index, or CYP2C19 substrates should be considered during treatment with Tibsovo. Patients should be monitored for loss of substrate efficacy if use of such medicinal products cannot be avoided (see section 5.2).

- CYP3A4 substrates with a narrow therapeutic index include: alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.
- CYP2B6 substrates with a narrow therapeutic index include: cyclophosphamide, ifosfamide, methadone.
- CYP2C8 substrates with a narrow therapeutic index include: paclitaxel, pioglitazone, repaglinide.
- CYP2C9 substrates with a narrow therapeutic index include: phenytoin, warfarin.
- CYP2C19 substrates include: omeprazole.

Itraconazole or ketoconazole should not be used concomitantly with Tibsovo due to the expected loss of antifungal efficacy.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended for at least 1 month after the last dose (see sections 4.4 and 4.6).

Uridine diphosphate glucuronosyltransferases (UGTs)
Ivosidenib has the potential to induce UGTs and it may, therefore, decrease systemic exposure to substrates of these enzymes (e.g. lamotrigine, raltegravir). Suitable alternatives that are not UGT substrates should be considered during treatment with Tibsovo. Patients should be monitored for loss of UGT substrate efficacy if use of such medicinal products cannot be avoided (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during therapy (see section 4.4).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Tibsovo and for at least 1 month after the last dose.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of an alternative contraceptive method such as barrier contraceptives is recommended (see sections 4.4 and 4.5).

Pregnancy

There are no adequate data on the use of ivosidenib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Tibsovo is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception. Patients should be informed of the potential risk to the foetus if it is used during pregnancy or if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose.

Breast-feeding

It is unknown whether ivosidenib and its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of ivosidenib and its metabolites in milk. A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Tibsovo and for at least 1 month after the last dose.

Fertility

There are no human data on the effect of ivosidenib on fertility. No fertility studies in animals have been conducted to evaluate the effect of ivosidenib. Undesirable effects on reproductive organs were observed in a 28-day repeat-dose toxicity study (see section 5.3). The clinical relevance of these effects is unknown.

4.7 Effects on ability to drive and use machines

Ivosidenib has minor influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients taking ivosidenib (see section 4.8) and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Newly diagnosed acute myeloid leukaemia in combination with azacitidine

Summary of the safety profile

The most common adverse reactions were vomiting (40%), neutropenia (31%), thrombocytopenia (28%), electrocardiogram QT prolonged (21%), insomnia (19%).

The most common serious adverse reactions were differentiation syndrome (8%) and thrombocytopenia (3%).

In patients treated with ivosidenib in combination with azacitidine, the frequency of discontinuation of ivosidenib due to adverse reactions was 6%. Adverse reactions leading to discontinuation were electrocardiogram QT prolonged (1%), insomnia (1%), neutropenia (1%) and thrombocytopenia (1%).

The frequency of dose interruption of ivosidenib due to adverse reactions was 35%. The most common adverse reactions leading to dose interruption were neutropenia (24%), electrocardiogram QT prolonged (7%), thrombocytopenia (7%), leukopenia (4%) and differentiation syndrome (3%).

The frequency of dose reduction of ivosidenib due to adverse reactions was 19%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (10%), neutropenia (8%) and thrombocytopenia (1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on Study AG120-C-009 which included 72 patients with newly diagnosed AML randomised to and treated with ivosidenib (500 mg daily) in combination with azacitidine. The median duration of treatment with Tibsovo was 8 months (range 0.1 to 40.0 months). The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than ivosidenib, such as the disease, other medicinal products or unrelated causes.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 - Adverse drug reactions reported in patients with newly diagnosed AML treated with ivosidenib in combination with azacitidine in clinical study AG120-C-009 (N=72)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Differentiation syndrome, Leukocytosis, Thrombocytopenia, Neutropenia
	Common	Leukopenia
Psychiatric disorders	Very common	Insomnia
Nervous system disorders	Very common	Headache, Dizziness
	Common	Neuropathy peripheral
Gastrointestinal disorders	Very common	Vomiting[1]
	Common	Oropharyngeal pain
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity, Arthralgia, Back pain
Investigations	Very common	Electrocardiogram QT prolonged

[1] Grouped term includes vomiting and retching.

Previously treated, locally advanced or metastatic cholangiocarcinoma

Summary of the safety profile

The most common adverse reactions were fatigue (43%), nausea (42%), abdominal pain (35%), diarrhoea (35%), decreased appetite (24%), ascites (23%), vomiting (23%), anaemia (19%) and rash (15%).

The most common serious adverse reactions were ascites (2%), hyperbilirubinemia (2%), and jaundice cholestatic (2%).

In patients treated with ivosidenib, the frequency of treatment discontinuation due to adverse reactions was 2%. Adverse reactions leading to discontinuation were ascites (1%) and hyperbilirubinemia (1%).

The frequency of dose interruption of ivosidenib due to adverse reactions was 16%. The most common adverse reactions leading to dose interruption were hyperbilirubinemia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), ascites (2%) and fatigue (2%).

The frequency of dose reduction of ivosidenib due to adverse reactions was 4%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3%) and neuropathy peripheral (1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on Study AG120-C-005 which included 123 patients with previously treated, locally advanced or metastatic cholangiocarcinoma, randomised to and treated with 500 mg ivosidenib once daily. The median duration of treatment with Tibsovo was 2.8 months (range 0.1 to 45.1 months; mean (standard deviation [SD]) 6.7 (8.2) months).

The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than ivosidenib, such as the disease, other medicinal products or unrelated causes.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 - Adverse drug reactions reported in patients with locally advanced or metastatic cholangiocarcinoma treated with ivosidenib in clinical study AG120-C-005 (N=123)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Neuropathy peripheral, Headache
Gastrointestinal disorders	Very common	Ascites, Diarrhoea, Vomiting, Nausea, Abdominal pain
Hepatobiliary disorders	Common	Jaundice cholestatic, Hyperbilirubinemia
Skin and subcutaneous tissue disorders	Very common	Rash[1]
General disorders and administration site conditions	Very common	Fatigue
	Common	Fall
Investigations	Very common	Aspartate aminotransferase increased, Blood bilirubin increased
	Common	Electrocardiogram QT prolonged, Alanine aminotransferase increased, White blood cell count decreased, Platelet count decreased

[1] Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.

Description of selected adverse reactions

Differentiation syndrome in patients with acute myeloid leukaemia (see sections 4.2 and 4.4)

In study AG120-C-009, in the 72 patients with newly diagnosed AML treated with Tibsovo in combination with azacitidine, 14% experienced differentiation syndrome. No patient discontinued ivosidenib treatment due to differentiation syndrome and dose interruptions (3%) to manage signs/symptoms were required in a minority of patients. Of the 10 patients who experienced

differentiation syndrome, all recovered after treatment or after dose interruption of Tibsovo. The median time to onset of differentiation syndrome was 20 days. Differentiation syndrome occurred as early as 3 days and up to 46 days after treatment initiation during combination therapy.

QTc interval prolongation (see sections 4.2, 4.4 and 4.5)

In Study AG120-C-009, in the 72 patients with newly diagnosed AML treated with ivosidenib in combination with azacitidine, electrocardiogram QT prolonged was reported in 21%; 11% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 15% of patients treated with ivosidenib in combination with azacitidine, who had at least one post-baseline ECG assessment, were found to have a QTc interval > 500 msec, 24% had an increase from baseline QTc > 60 msec. One percent (1%) of patients discontinued ivosidenib treatment due to electrocardiogram QT prolonged, dose interruption and reduction were required in 7% and 10% of patients, respectively. The median time to onset of QT prolongation in patients treated with ivosidenib was 29 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 18 months after treatment initiation.
In Study AG120-C-005, in the 123 patients with locally advanced or metastatic cholangiocarcinoma treated with ivosidenib monotherapy, electrocardiogram QT prolonged 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% QTc interval prolongation > 60 msec from baseline. Dose reduction to manage signs/symptoms was required in 3% of patients. The median time to onset of QT prolongation in patients treated with ivosidenib monotherapy was 28 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 23 months after treatment initiation.

Special populations

Hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). A trend to a higher incidence of adverse reactions was observed in patients with mild hepatic impairment (Child-Pugh class A) (See sections 4.2 and 5.2.).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with ivosidenib (see section 4.8). Patients should be closely monitored and provided with appropriate supportive care (see sections 4.2 and 4.4). 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 an inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib beyond its ability to reduce 2-HG and restore cellular differentiation is not fully understood across indications.

Pharmacodynamic effects

Multiple doses of ivosidenib 500 mg daily decreased plasma concentrations of 2-HG in patients with hematological malignancies and cholangiocarcinoma with mutated IDH1 to levels approximating those observed in healthy subjects. In bone marrow of patients with hematological malignancies and in tumour biopsy of patients with cholangiocarcinoma, the mean (% coefficient of variation [%CV]) reduction in 2-HG concentrations were 93.1% (11.1%) and 82.2% (32.4%), respectively.

Using an ivosidenib concentration-QTc model, a concentration-dependent QTc interval prolongation of approximately 17.2 msec (90% CI: 14.7, 19.7) was predicted at the steady-state C_{max} based on an analysis of 173 patients with AML who received 500 mg ivosidenib once daily. A concentration-dependent QTc interval prolongation of approximately 17.2 msec (90% CI: 14.3, 20.2) was observed at the steady-state C_{max} following a 500 mg daily dose based on an analysis of 101 patients with cholangiocarcinoma who received ivosidenib 500 mg daily (see sections 4.2 and 4.4).

Clinical efficacy

Newly diagnosed acute myeloid leukaemia in combination with azacitidine

The efficacy and safety of Tibsovo was evaluated in a randomised, multicenter, double-blind, placebo-controlled clinical study (AG120-C-009) of 146 adult patients with previously untreated AML with an IDH1 mutation who were ineligible for intensive induction chemotherapy, based on at least one of the following criteria: 75 years or older, 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. Gene mutation analysis for central confirmation of IDH1 mutation from bone marrow and/or peripheral blood were conducted for all subjects using the Abbott RealTime™ IDH1 Assay. Patients were randomised to receive either Tibsovo 500 mg or matched placebo orally once daily with azacitidine 75 mg/m^2/day subcutaneously or intravenously for 1 week every 4 weeks until the end of the study, disease progression or unacceptable toxicity.

The median age of patients treated with Tibsovo was 76 years (range: 58 to 84); 58% were male; 21% Asian, 17% were White, 61% not reported; and had an ECOG performance status of 0 (19%), 1 (44%), or 2 (36%). Seventy-five percent of patients had de novo AML. Overall, patients had documented favourable (4%), intermediate (67%) or poor/other (26%) cytogenetic risk as assessed by investigators based on the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology (2017).

Efficacy was based on the primary efficacy endpoint 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 (Table 4 and Figure 1).

Table 4 - Efficacy results in patients with newly diagnosed AML in combination with azacitidine

Endpoint	Ivosidenib (500 mg daily) + azacitidine N=72	Placebo + azacitidine N=74
Event-free survival, events (%)	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)	
OS events (%)	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)	
CR, n (%)	34 (47.2)	11 (14.9)
95% CI[2]	(35.3, 59.3)	(7.7, 25.0)
Odds ratio[3] (95% CI)	4.76 (2.15, 10.50)	
CR + CRh rate, n (%)	38 (52.8)	13 (17.6)
95% CI[2]	(40.7, 64.7)	(9.7, 28.2)
Odds ratio[3](95% CI)	5.01 (2.32, 10.81)	
CR + CRi rate, n (%)	39 (54.2)	12 (16.2)
95% CI[2]	(42.0, 66.0)	(8.7, 26.6)
Odds ratio[3] (95% CI)	5.90 (2.69, 12.97)	

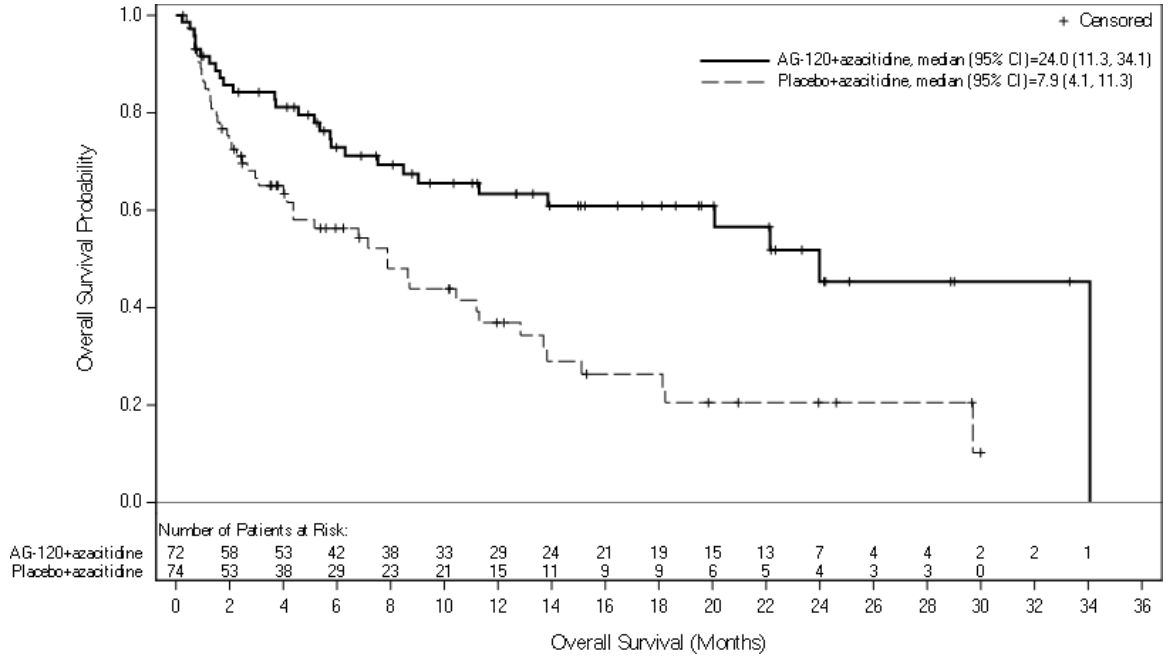
CI: confidence interval; CR = Complete remission; CRh = Complete remission with partial hematologic recovery; CRi = Complete remission with incomplete hematologic recovery; OS = Overall survival; PR = Partial response.

[1] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomisation stratification factors (AML status and geographic region) with PBO+AZA as the denominator.

[2] CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

[3] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with PBO+AZA as the denominator.

Figure 1: Kaplan Meier plot of overall survival (OS)



AG120=ivosidenib

An updated OS analysis, carried out at 64.2% (N = 95) of events, confirmed the overall survival benefit of Tibsovo in combination with azacitidine compared to placebo in combination with azacitidine with a median OS of 29.3 months vs 7.9 months, respectively (HR = 0.42; 95% CI: 0.27 to 0.65).

Previously treated, locally advanced or metastatic cholangiocarcinoma

The efficacy of Tibsovo was evaluated in a randomised (2:1), multicenter, double-blind, placebo-controlled, phase 3 clinical trial (Study AG120-C-005) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation whose disease had progressed following at least 1 but not more than 2 prior treatment regimens including at least one gemcitabine- or 5-FU-containing regimen and an expected survival of ≥ 3 months.

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. Gene mutation analysis for central confirmation of IDH1 mutation from tumour tissue biopsy were conducted on all subjects using the Oncomine™ Dx Target Test.

The median age was 62 years (range: 33 to 83). Majority of patients were female (63%), 57% were White and 37% had an ECOG performance status of 0 (37%) or 1 (62%). All patients received at least 1 prior line of systemic therapy and 47% received two prior lines. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. Across both arms, 70% 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.

The primary efficacy outcome measure was progression free survival (PFS) as determined by Independent Radiology Center (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, which was defined as time from randomisation to disease progression or death due to any cause.

Overall survival (OS) was a secondary efficacy endpoint. As allowed per protocol, a large proportion (70.5%) of patients in the placebo arm crossed over to receive Tibsovo following radiographic disease progression as assessed by the Investigator.

Efficacy results are summarised in Table 5.

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

Endpoint	**Ivosidenib (500 mg daily)**	**Placebo**
Progression-free survival (PFS) by IRC assessment	**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	
PFS rate (%)[3]		
6 months	32.0	NE
12 months	21.9	NE
	Ivosidenib (500 mg daily)	**Placebo**
Overall survival[4]	**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]	0.79 (0.56, 1.12)	
P-value[2]	0.093	

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

[1] Hazard ratio is calculated from stratified Cox regression model. Stratification factor is the number of prior line of therapies at randomisation.

[2] P-value is calculated from the one-sided stratified log-rank test without adjusting for crossover. Stratification factor is the number of prior line of therapies at randomisation.

[3] Based on Kaplan-Meier estimation. No patients randomised to placebo achieved PFS of 6 months or longer.

[4] OS results are based on the final analysis of OS (based on 150 deaths; data cut off: 30 May 2020) which occurred 16 months after the final analysis of PFS (data cut off: 31 January 2019).

Figure 2: Kaplan Meier plot of progression-free survival (PFS) per IRC

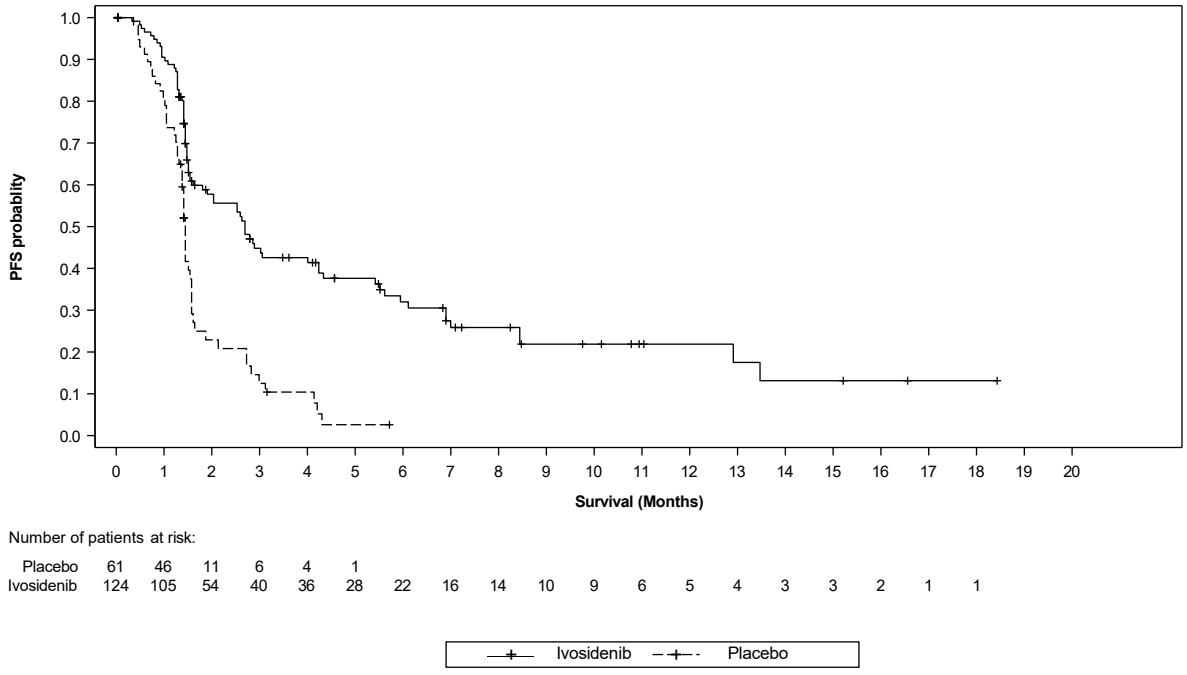
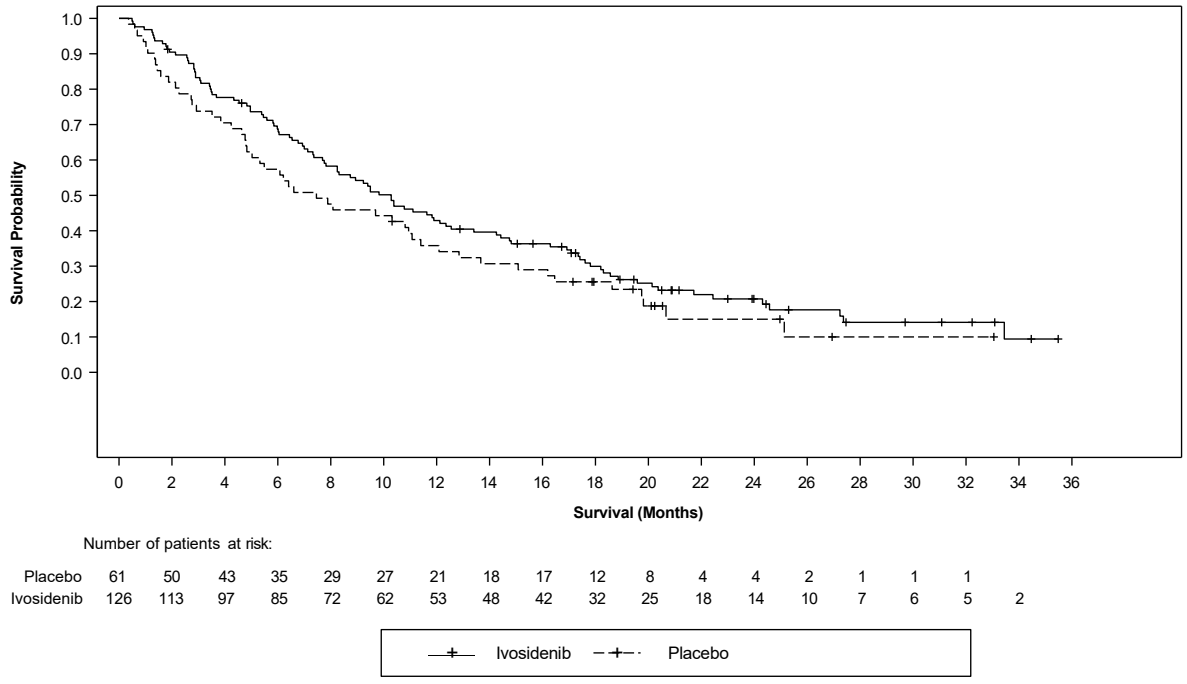


Figure 3: Kaplan-Meier plot of overall survival



5.2 Pharmacokinetic properties

A total of 10 clinical studies have contributed to the characterisation of the clinical pharmacology of ivosidenib. Five studies have been conducted in healthy subjects and 3 studies have been conducted in patients with advanced malignancies including 2 studies in patients with cholangiocarcinoma. Two studies have been conducted in patients with newly diagnosed AML receiving ivosidenib in combination with azacitidine. Pharmacokinetic endpoints have been assessed in plasma and urine. Pharmacodynamic endpoints have been assessed in plasma, urine, tumour biopsy, and bone marrow (for studies in patients with advanced malignancies only).
The steady-state pharmacokinetics of ivosidenib 500 mg were comparable between patients with newly diagnosed AML and cholangiocarcinoma.

Absorption

After a single 500 mg oral dose, the median time to C_{max} (T_{max}) was approximately 2 hours in newly diagnosed AML patients treated with a combination of ivosidenib and azacitidine and in cholangiocarcinoma patients.

In patients with newly diagnosed AML treated with a combination of ivosidenib (500 mg daily dose) and azacitidine, the mean steady-state C_{max} was 6,145 ng/mL (CV%: 34) and the mean steady-state AUC was 106,326 ng hr/mL (CV%: 41).

In patients with cholangiocarcinoma, the mean C_{max} was 4,060 ng/mL (%CV: 45) after a single dose of 500 mg and 4,799 ng/mL (CV%: 33) at steady state for 500 mg daily. The AUC was 86,382 ng·hr/mL (CV%: 34).

Accumulation ratios were approximately 1.6 for AUC and 1.2 for C_{max} in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and approximately 1.5 for AUC and 1.2 for C_{max} in patients with cholangiocarcinoma, over one month, when ivosidenib was administered at 500 mg daily. Steady-state plasma levels were reached within 14 days of once daily dosing.

Significant increases in ivosidenib C_{max} (by approximately 98%; 90% CI: 79, 119) and AUC_{inf} (by approximately 25%) were observed following administration of a single dose with a high-fat meal (approximately 900 to 1,000 calories, 56% to 60% fat) in healthy subjects (see section 4.2).

Distribution

Based on a population pharmacokinetic analysis the mean apparent volume of distribution of ivosidenib at steady-state (Vc/F) is 3.20 L/kg (CV%: 47.8) in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and 2.97 L/kg (CV%: 25.9) in patients with cholangiocarcinoma treated with ivosidenib monotherapy.

Biotransformation

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

Ivosidenib induces CYP3A4 (including its own metabolism), CYP2B6, CYP2C8, CYP2C9, and may induce CYP2C19 and UGTs. Therefore, it may decrease systemic exposure to substrates of these enzymes (see sections 4.4, 4.5 and 4.6).

Ivosidenib inhibits P-gp *in vitro* and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp (see sections 4.3 and 4.5).

In vitro data suggest that ivosidenib has the potential to inhibit OAT3, OATP1B1 and OATP1B3 at clinically relevant concentrations and it may, therefore, increase systemic exposure to OAT3, OATP1B1 or OATP1B3 substrates (see sections 4.5).

Elimination

In patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine, the mean apparent clearance of ivosidenib at steady state was 4.6 L/hour (35%) with a mean terminal half-life of 98 hours (42%).

In patients with cholangiocarcinoma, the mean apparent clearance of ivosidenib at steady state was 6.1 L/hour (31%) with a mean terminal half-life of 129 hours (102%).

In healthy subjects, 77% of a single ivosidenib oral dose was found in the faeces of which 67% was recovered unchanged. Approximately 17% of a single oral dose was found in the urine of which 10% was recovered unchanged.

Linearity/non-linearity

The AUC and C_{max} of ivosidenib increased 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).

Special populations

Elderly

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in older patients up to 84 years. The pharmacokinetics of ivosidenib in patients 85 years of age or older is unknown (see section 4.2).

Renal impairment

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2). The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or renal impairment requiring dialysis are unknown (see section 4.2).

Hepatic impairment

Using the NCI classification, no clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild hepatic impairment. The pharmacokinetics of ivosidenib in patients with moderate and severe hepatic impairment are unknown in patients with newly diagnosed AML and with cholangiocarcinoma (see section 4.2). No PK data in patients with hepatic impairment stratified by the Child-Pugh classification are available.

Other

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on gender, race, body weight or ECOG performance status.

5.3 Preclinical safety data

Safety pharmacology

The potential of ivosidenib for QT prolongation was evidenced in *in vitro* and *in vivo* preclinical studies at clinically relevant plasma levels.

Repeat-dose toxicity

In animal studies at clinically relevant exposures, ivosidenib induced haematologic abnormalities (bone marrow hypocellularity, lymphoid depletion, decreased red cell mass together with extramedullary haematopoiesis in the spleen), gastrointestinal toxicity, thyroid findings (follicular cell hypertrophy/hyperplasia in rats), liver toxicity (elevated transaminases, increased weights, hepatocellular hypertrophy and necrosis in rats and hepatocellular hypertrophy associated with increased liver weights in monkeys) and kidney findings (tubular vacuolation and necrosis in rats). Toxic effects observed on haematologic system, GI system and kidney were reversible whereas the toxic effects observed on liver, spleen and thyroid were still observed at the end of the recovery period.

Genotoxicity and carcinogenicity

Ivosidenib was not mutagenic or clastogenic in conventional *in vitro* and *in vivo* genotoxicity assays. Carcinogenicity studies have not been conducted with ivosidenib.

Reproductive and developmental toxicity

Fertility studies have not been conducted with ivosidenib. In the 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) in animals prematurely euthanized.

In embryofoetal development studies in rats, lower foetal body weights and delayed skeletal ossification occurred in the absence of maternal toxicity. In rabbits, maternal toxicity, spontaneous abortions, decreased foetal body weights, increased post implantation loss, delayed skeletal ossification and visceral development variation (small spleen) were observed. Animal studies indicate that ivosidenib crosses the placenta and is found in foetal plasma. In rats and rabbits, the no adverse effect levels for embryofoetal development were 0.4-fold and 1.4-fold the clinical exposure (based on AUC), respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose acetate succinate
Microcrystalline cellulose
Croscarmellose sodium
Colloidal silica, anhydrous
Magnesium stearate
Sodium lauryl sulfate Film-

coating

Hypromellose
Titanium dioxide Lactose
monohydrate Triacetin
Indigo carmine aluminum lake (FD&C Blue #2).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

The shelf life after first opening the container is 30 days, based on the administration of two tablets per day. After opening, the container should be stored at a temperature not exceeding 30°C.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach st, P.O.B, Petach Tikva
Israel

9. **REGISTRATION NUMBER**: 179-35-38216-99

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