swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tibsovo

International non-proprietary name: ivosidenib
Pharmaceutical form: film-coated tablets
Dosage strength(s): 250 mg
Route(s) of administration: oral
Marketing authorisation holder: Servier (Suisse) SA
Marketing authorisation no.: 69077
Decision and decision date: approved on 13 June 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AML	Acute myeloid leukaemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CCA	Cholangiocarcinoma
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IDH1	Isocitrate dehydrogenase-1
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event

SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for ivosidenib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 24 October 2022 and 12 January 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) presenting an isocitrate dehydrogenase-1 (IDH1) R132 mutation, who do not fulfil the conditions to receive intensive induction chemotherapy (see section *« Properties/Effects »*).

Tibsovo as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma presenting an IDH1 R132 mutation, who have previously been treated with at least one previous line of systemic treatment (see section *"Properties/Effects"*).

2.2.2 Approved indication

Acute myeloid leukaemia

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 intensive induction chemotherapy. Patients with acute promyelocytic leukaemia (APL) are excluded. (see "*Properties/Effects*").

Cholangiocarcinoma

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation whose disease has progressed after at least one line of systemic therapy (see "*Properties/Effects*").

2.2.3 Requested dosage

Summary of the requested standard dosage

Before taking Tibsovo, the presence of an IDH1 R132 mutation in patients should be confirmed using an appropriate diagnostic test.

Acute myeloid leukaemia

The recommended dose is 500 mg of ivosidenib (2 x 250 mg tablets) taken orally once daily.
Ivosidenib should be started on Day 1 of Cycle 1 in combination with azacitidine 75 mg/m^2 body surface area, intravenously or subcutaneously, once daily on Days 1 to 7 of each 28-day cycle.

Cholangiocarcinoma

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 December 2022
Formal control completed	30 December 2022
List of Questions (LoQ)	28 April 2023
Response to LoQ	27 July 2023
Preliminary decision	25 October 2023
Response to preliminary decision	26 December 2023
Labelling corrections	25 March 2024
Response to labelling corrections	24 April 2024
Final decision	13 June 2024
Decision	approval

3 Medical context

Acute myeloid leukaemia

Acute myeloid leukaemia (AML) is a neoplastic disorder of haematopoiesis characterised by clonal expansion of myeloid progenitor cells (blasts), which replace normal haematopoietic tissue in the bone marrow, resulting in pancytopenia, and therefore death by bleeding or infection. AML is universally fatal without treatment, with a median survival of approximately 2 months. With treatment, the 5-year relative survival rate is around 15% to 20% in Europe.

The treatment for newly diagnosed AML is intensive chemotherapy followed by consolidation therapy for patients in complete response. For patients not eligible for intensive treatment, azacitidine and decitabine are still considered treatment options; however, recently venetoclax in combination with azacitidine or decitabine has shown a prolongation in overall survival and has been approved in Switzerland. Currently there are no molecularly targeted combination therapies approved in Switzerland for patients with IDH1-mutated AML.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) which includes intrahepatic CCA and extrahepatic CCA, is a cancer with a dismal prognosis, with a 5-year survival of 10%. The standard first-line treatment for unresectable or metastatic disease is the combination of cisplatin and gemcitabine +/- immunotherapy, followed by mFOLFOX in second line.

Genomic alterations are present in up to 40% of all patients with CCA and are more frequent for intrahepatic CCA.

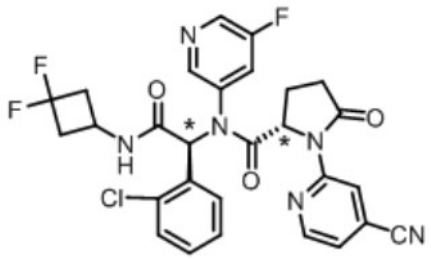
Isocitrate dehydrogenase 1 (IDH1) and IDH2 mutations are the most frequent alterations in CCA with an incidence of 10-20% in intrahepatic CCA and 1% in extrahepatic CCA.

Currently, there are no molecularly targeted combination therapies approved in Switzerland for patients with IDH1-mutated CCA.

4 Quality aspects

4.1 Drug substance

INN:	Ivosidenib
Chemical name:	(2S)-N-{(1S)-1-(2-chlorophenyl)-2-[(3,3- difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridine-2-yl)-N- (5-fluoropyridine-3-yl)-5-oxopyrrolidine-2-carboxamide
Molecular formula:	$C_{28}H_{22}ClF_3N_6O_3$
Molecular mass:	583.0 g/mol
Molecular structure:	



* denotes stereocenter

Physico-chemical properties:

Ivosidenib is a crystalline white to light yellow solid compound and is sparsely hygroscopic. It exhibits stereoisomerism due to the presence of 2 chiral centres; the isomer with S configuration at both centres is the active substance. Based on the low aqueous solubility of the drug substance coupled with the high permeability across Caco-2 cells, ivosidenib is classified as a Biopharmaceutical Classification System (BCS) Class II compound. Polymorphism has been observed for the active substance.

Synthesis:

The drug substance is manufactured by multiple step chemical synthesis. The synthesis of the drug substance and the necessary in-process controls are described in detail. Confirmation of the chemical structure is provided by elemental and spectroscopic analysis.

Specification:

In order to ensure a consistent quality of ivosidenib, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines, such as appearance, identity (FT-IR), assay (HPLC), related impurities (HPLC), chiral impurities (HPLC), residual solvents (GC), water content (Karl-Fischer titration), residue on ignition (Ph. Eur.), and elemental impurities (ICP-MS).

Stability:

The drug substance is packaged in double LDPE bags. A stability study, according to the current guideline recommendations, was carried out. Based on the results of this study, a satisfactory retest period was established for ivosidenib drug substance.

4.2 Drug product

Description and composition:

Ivosidenib tablets are presented as immediate-release 250 mg film-coated tablets for oral administration. The tablets are oval, blue, and debossed with “IVO” on one side and “250” on the other side. The excipients of the tablet cores are: hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, anhydrous colloidal silica, and magnesium stearate.

Pharmaceutical development:

A traditional pharmaceutical development approach with elements of enhanced/systematic (Quality by Design) components (e.g. risk assessments and DOE) was utilised for the development of ivosidenib tablets, 250 mg.

Manufacture:

Ivosidenib tablets are manufactured in a 2-stage process: the manufacture of the finished product intermediate and the manufacture of the finished product. The manufacturing process is described with a sufficient level of detail. In order to achieve a consistent quality of the tablets, appropriate in-process controls are applied.

Specification:

For the control of the finished product, adequate tests and criteria for release and at shelf-life are established. The specifications contain the typical parameters for a tablet formulation such as appearance, identification (HPLC/UV and HPLC/DAD), assay (HPLC), impurities (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), water content (Karl-Fischer titration), and microbiological purity (Ph. Eur.).

Container closure system:

Ivosidenib tablets are packed in HDPE bottles with polypropylene child-resistant closures. Each bottle contains 60 tablets and 1.0 g silica gel desiccant.

Stability:

Appropriate stability studies were conducted. Based on the data from these studies, a shelf-life was established for the immediate-release tablets. The storage recommendation is “Do not store above 30°C, keep the container closed in the outer carton to protect the contents from light and humidity”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Tibsovo, the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the CHMP assessment report (23.02.2023).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Tibsovo in the proposed indications. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are low, but can be accepted considering the proposed indications. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment report and respective product information from the EMA and FDA were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology see the information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

Acute myeloid leukaemia

The dosage of ivosidenib in monotherapy in patients with advanced haematologic malignancies was investigated in Study AG120-C-001, which included a dose escalation and a dose expansion phase. The maximum tolerated dose (MTD) was not reached. The data demonstrated clinical activity of ivosidenib for the treatment of subjects with relapsed/refractory AML with any IDH1 mutation. In light of these observations, the dose of 500 mg QD was selected for the expansion phase of the trial.
Considering the lack of anticipated clinically significant overlapping toxicities and low drug-drug interaction risk for azacitidine and ivosidenib, the chosen dosage of azacitine for the pivotal study was 75 mg/m^2 SC or IV for 7 days of each 4-week cycle, which has a proven clinical benefit in subjects with AML.

Cholangiocarcinoma

The dosage of ivosidenib in monotherapy in subjects with advanced solid tumours with IDH1 mutation was investigated in Study AG120-C-002, which included a dose escalation and a dose expansion phase. The maximum tolerated dose was not reached. The starting dose recommended for the expansion phase of the study was 500 mg QD, based on the PK/PD, safety, and clinical activity associated with ivosidenib from the dose escalation phase of this study.

6.3 Efficacy

Acute myeloid leukaemia

Study AG120-C-009 (AGILE) was a Phase 3, multicentre, double-blind, randomized, placebo-controlled clinical trial designed to evaluate the efficacy and safety of ivosidenib + azacitidine (IVO + AZA) vs placebo + azacitidine (PBO + AZA) in adult subjects with previously untreated IDH1-mutated AML and who are not considered eligible for intensive therapy.
A total of 146 patients were randomised (72 in the IVO + AZA arm and 74 in the PBO + AZA arm). The treatment arms were balanced in terms of demographics and baseline characteristics; 56.8% of the population was recruited in Europe.

The primary endpoint of the study was to compare event-free survival (EFS) between IVO + AZA and PBO + AZA. EFS was a composite endpoint and was defined as the time from randomisation until treatment failure (failure to achieve complete response (CR) by Week 24), relapse from remission, or death from any cause, whichever occurred first. In addition, CR and overall survival (OS) were among the secondary endpoints.

At the data cut-off (DCO) of 18 March 2021 a clinically relevant improvement in the primary endpoint of EFS was observed in the IVO + AZA arm compared with the PBO + AZA arm (HR = 0.33; 95% CI: 0.16-0.69). This analysis was not pre-planned and was triggered by a recommendation of the independent data monitoring committee (IDMC) of the study due to the observation of a greater number of deaths on the PBO + AZA arm compared with the IVO + AZA arm.

The complete response (CR) rate by 24 weeks was 37.5% in the IVO + AZA arm and 10.8% in the PBO + AZA arm.

At the most recent DCO in 30 June 2022 a clinically relevant improvement in OS was demonstrated for subjects randomised to the IVO + AZA arm compared with the PBO + AZA arm (HR = 0.42; 95% CI, 0.27-0.65), with a median follow-up of 29.3 months in the IVO + AZA arm and 26.7 months in the PBO + AZA arm. The median OS was 29.3 months in the IVO + AZA arm and 7.9 months in the PBO + AZA arm. The Kaplan-Meier plot shows the durability of the effect over at least 36 months.

Cholangiocarcinoma

Study AG120-C-005 (ClarIDHy) was a Phase 3, multicentre, double-blind, randomised, placebo-controlled clinical trial designed to evaluate the efficacy and safety of ivosidenib vs placebo in adult subjects with advanced IDH1-mutated CCA who have progressed on at least 1 previous treatment.
The ClarIDHy study randomised 187 patients in a 2:1 ratio to receive ivosidenib 500 mg QD or placebo in addition to best supportive care. Although a standard of care for the second-line treatment of CCA was not established at the time of the study design, a comparator arm of treatment of physician's choice would have been preferable in this setting. Crossover from the placebo arm to the ivosidenib arm was allowed upon progression.
The primary endpoint was progression-free survival (PFS); overall survival (OS) was a key secondary endpoint.

At the DCO of 31 January 2019, a statistically significant improvement in the primary endpoint PFS was demonstrated in favour of ivosidenib compared with placebo. The median PFS was 2.7 months in the ivosidenib arm and 1.4 months in the placebo arm, with an HR of 0.37 (95% CI: 0.25, 0.54; 1-sided p-value <0.0001). The Kaplan Meier curves separate at around 2 months and do not cross for the length of the follow-up. The benefit in PFS was confirmed at the database lock date of 21 June 2020, when nearly all patients had progressed in both arms.

The key secondary endpoint OS was analysed at the OS interim analysis and the final OS analysis, as preplanned. In both analyses the results excluded a detrimental effect of the treatment with ivosidenib and showed a numerically longer overall survival in favour of the ivosidenib arm compared with the placebo arm; however, the preplanned boundaries for statistical significance were not met in either of the OS analyses. At the final OS analysis (DCO 31 May 2020), OS events were 79.4% in the ivosidenib arm and 82.0% in the placebo arm, and the median OS was 10.3 months in the ivosidenib arm and 7.5 months in the placebo arm, with an HR of 0.79 (95% CI 0.56-1.12). The Kaplan Meier curves separate early and did not cross for the entire length of the OS follow up. Taking into account the relevant limitations of a cross-trial comparison, the OS results of the treatment with ivosidenib compare favourably with the result of the currently recommended second-line treatment with mFOLFOX.

6.4 Safety

Acute myeloid leukaemia

Treatment emergent adverse events (TEAEs) in the IVO + AZA arm were mainly related to haematological and gastrointestinal toxicities;the most frequently reported TEAEs in the experimental arm were nausea (42.3%), vomiting (40.8%), diarrhoea (35.2%), pyrexia (33.8%), anaemia (31.0%), febrile neutropenia (28.2%), neutropenia (28.2%), thrombocytopenia (28.2%), constipation (26.8%), and pneumonia (23.9%). In addition, electrocardiogram QT prolongation (19.7%) and differentiation syndrome (14.1%) were also frequently observed.

Overall, the incidence of Grade ≥3 TEAEs reported in each arm was comparable. Grade ≥3 TEAEs reported more frequently in the IVO + AZA arm included neutropenia (26.8%), electrocardiogram QT prolonged (9.9%), and differentiation syndrome (4.2%). Serious adverse events (SAEs) and deaths due to AEs were reported less frequently in the IVO + AZA arm than in the PBO + AZA arm.

TEAEs that led to dose interruption of both study medications were more frequent in the experimental arm than in the control arm (52.1% vs. 38.4%).

Bleeding events occurred in 40.8% of subjects in the AZA + IVO arm and in 28.8% in the PBO + AZA arm; however, G3 bleeding events had similar frequency in the 2 arms.

Cholangiocarcinoma

The most frequent TEAEs that occurred in subjects exposed to ivosidenib were fatigue (30.9%), decreased appetite (24.4%), cough (25.2%), and gastrointestinal events (nausea [42.3%], vomiting [22.8%], diarrhoea [35.0%], abdominal pain [24.4%], and ascites [22.8%]).

The incidence of Grade ≥3 TEAEs was higher in the ivosidenib arm compared with the placebo arm (51.2% vs 37.3%). The most frequent Grade ≥3 TEAEs were ascites (8.9%), anaemia (7.3%), blood bilirubin increased (5.7%), and hyponatremia (5.7%).

The incidence of SAEs was also higher in the ivosidenib arm compared with placebo (35.0% and 23.7%, respectively).

Notably, there were 6 (4.9%) fatal TEAEs in the ivosidenib arm and 2 (4.7%) after crossover: 2 deaths were due to sepsis, 2 to intestinal pseudo-obstruction or obstruction, 2 to hepatic cirrhosis or encephalopathy, 1 to pneumonia, and 1 to pulmonary embolism. There were no fatal TEAEs in the placebo arm.

TEAEs that led to dose interruption of study treatment were more frequent in the ivosidenib arm than in the placebo arm (30.1% vs 18.6%).

Regarding QTc prolongation, 9.8% of subjects in the ivosidenib arm experienced QT prolongation compared with 3.4% of subjects in the placebo arm.

6.5 Final clinical benefit-risk assessment

Acute myeloid leukaemia

The evaluation of the primary endpoint EFS in the AGILE trial is limited by multiple factors, including the unplanned nature of the analysis and the EFS being a composite endpoint, which impacts the statistical interpretation of the analysis.

However, the OS results are clinically relevant, with a 58% reduction in the risk of death and a prolongation of median survival by 21 months in a frail patient population.

The toxicity is acceptable overall in the setting of AML and manageable by an experienced physician.

The benefit-risk for the use of IVO+ AZA for the treatment of patients with newly diagnosed AML with IDH1 mutation who are not eligible for intensive chemotherapy is positive.

Cholangiocarcinoma

A numerically longer OS was observed in patients treated with ivosidenib compared with patients treated with placebo, with an HR at the final analysis of 0.82 and an early and consistent separation of the Kaplan Meier curves. Taking into account the high crossover rate of the placebo arm and the poor prognosis of patients in this clinical setting, as well as the limitation of other therapeutic options, this result, although not statistically significant, reasonably excludes a detrimental effect of treatment with ivosidenib and supports a potential prolongation in survival. Further, the statistically significant primary endpoint PFS supports the OS results. The toxicity is acceptable overall in the setting of advanced CCA and manageable by an experienced physician. The benefit-risk for the use of ivosidenib in the second-line setting of CCA with IDH1 mutation is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Tibsovo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

WARNING for the use of **TIBSOVO:**

DIFFERENTIATION SYNDROME IN ACUTE MYELOID LEUKEMIA

Patients treated with Tibsovo have experienced symptoms of differentiation syndrome, which can be life-threatening or fatal if not treated.

Symptoms can include: non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and increased creatinine.

If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution and for at a minimum 3 days (see "Warnings and Precautions" and "Adverse Reactions").

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.*

Tibsovo

Composition

Active substances

Ivosidenib

Excipients

Tablet core

Microcrystalline cellulose, Croscarmellose sodium, Hypromellose acetate succinate, Colloidal silicon dioxide , Magnesium stearate , Sodium lauryl sulfate (E487)

Film-coating

Hypromellose, Titanium dioxide (E171), Lactose (as lactose monohydrate) (10 mg), Triacetin, Indigo carmine aluminum lake (E132)

Contains a maximum of 5.2mg of sodium per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet 250mg Ivosidenib

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

Indications/Uses

Acute myeloid leukaemia

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 intensive induction chemotherapy. Patients with acute promyelocytic leukaemia (APL) are excluded. (see "*Properties/Effects*").

Cholangiocarcinoma

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation whose disease has progressed after at least one line of systemic therapy (see "*Properties/Effects*").

Dosage/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 R132 mutation using a validated diagnostic test (see section "*Clinical efficacy*").

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/m2 of body surface area, intravenously or subcutaneously, once daily on Days 1-7 of each 28-day cycle. For the posology and method of administration of azacitidine, please refer to the full product information for azacitidine.

Cholangiocarcinoma

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

Duration of treatment

Acute myeloid leukaemia

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.
It is recommended that patients be treated for a minimum of 6 cycles.

Cholangiocarcinoma

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, then monthly and whenever is clinically recommended if the QTc interval remains ≤ 480 msec. QTc interval abnormalities should be managed promptly (see Table 1 and "*Warnings and precautions*").
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 monthly and whenever is clinically recommended (see below and sections "*Warnings and precautions*", “*Interactions*” and "*Undesirable effects*").

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, then monthly and at each medical visit for the duration of therapy as clinically indicated.

Dose modification for concomitant administration of moderate and strong CYP3A4 inhibitors
If use of moderated 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 moderated or strong CYP3A4 inhibitor is discontinued, increase the dose of ivosidenib to 500 mg after at least 5 half-lives of the CYP3A4 inhibitor (see above and "*Warnings and precautions*" and "*Interactions*").

Dose modifications and management recommendations for adverse reactions

Table 1 - Recommended dose modifications for adverse reactions

Adverse reaction	**Recommended action**
Differentiation syndrome (see "*Warnings and precautions*" and "*Undesirable effects*")	• 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 "*Warnings and precautions"* and "*Undesirable effects*")	• 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 "*Warnings and precautions*", *"Interactions*" and "*Undesirable effects*")	• Monitor and supplement electrolyte levels as clinically indicated to correct levels. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects (see "*Interactions*"). • 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 "*Warnings and precautions*", "*Interactions*" and "*Undesirable effects*")	• Monitor and supplement electrolyte levels as clinically indicated to correct levels. • Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see "*Interactions*"). • Interrupt Tibsovo and perform ECG monitoring every 24 hours 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 "*Warnings and precautions*", "*Interactions*" and "*Undesirable effects*")	• Permanently discontinue treatment.
Guillain-Barré syndrome (see "*Warnings and precautions*" and "*Undesirable effects*")	• Permanently discontinue treatment
Posterior Reversible Encephalopathy Syndrome (see "*Warnings and precautions*" and "*Undesirable effects*")	• Permanently discontinue treatment
Progressive Multifocal Leukoencephalopathy (see "*Warnings and precautions*" and "*Undesirable effects*")	• 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 "*Warnings and precautions*" and "*Pharmacokinetics*").
No data are available for patients older than 85.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh classes A).
A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child Pugh class 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 "*Warnings and precautions*", "*Pharmacokinetics*" and "*Undesirable effects*").

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 "*Warnings and precautions*" and "*Pharmacokinetics*")

Paediatric population

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

Mode 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 tablets (see "*Interactions*" and "*Pharmacokinetics*"). The tablets should be swallowed whole with water. Do not split, crush or chew.

Patients should be advised to avoid grapefruit and grapefruit juice during (see "*Interactions*"). Patients should also be advised not to swallow the silica gel desiccant found in the tablet bottle (see "*Instructions for holding*").

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in "Composition".
Concomitant administration of strong CYP3A4 inducers or dabigatran (see "*Interactions*").
Congenital long QT syndrome.
Familial history of sudden death or polymorphic ventricular arrhythmia.

QT/QTc interval > 500 msec, regardless of the correction method (see “*Dosage/Administration*” and “*Warnings and precautions*”).

Warnings and precautions

Differentiation syndrome in patients with Acute Myeloid Leukaemia

Differentiation syndrome has been reported following treatment with ivosidenib (see “*Undesirable effects*”). Differentiation syndrome may be life-threatening or fatal if not treated (see below and “*Dosage/Administration*”). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. Symptoms include: noninfectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased. Patients should be informed of signs and symptoms of differentiation syndrome and be advised to contact their physician immediately if these occur.

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 "*Dosage/Administration*").

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, concentration-dependent, has been reported following treatment with ivosidenib (see "*Undesirable effects*").
An ECG should be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and thereafter monthly if the QTc interval remains ≤ 480 msec (see “*Dosage/Administration*”). Any abnormalities should be managed promptly (see “*Dosage/Administration*”). 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 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 "*Dosage/Administration*" and "*Interactions*").
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 "*Dosage/Administration*").

Ivosidenib should be used with caution in patients with albumin levels below normal range and underweight patients.

Guillain-Barré syndrome
Guillain-Barré syndrome has been reported in less than 1% of the AML patients treated with Tibsovo in the clinical development program.

Patients taking Tibsovo should be monitored for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue Tibsovo in patients who are diagnosed with Guillain-Barré syndrome (see section “*Dosage and Administration*”).

Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) has been reported in less than 1% of the AML patients treated with Tibsovo in the clinical development program.
Patients taking Tibsovo should be monitored for any unexpected neurological or psychiatric symptoms/signs, any symptom/sign suggestive of an increase of intracranial pressure or accelerated neurological deterioration. If such symptoms/signs occur, promptly schedule a complete physical and neurological examination, and consider an MRI. If PRES is suspected, discontinue Tibsovo.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JCV virus that typically only occurs in patients who are immunocompromised. PML has been reported in less than 1% of the AML patients treated with Tibsovo in the clinical development program. Patients taking Tibsovo should be monitored for symptoms suggestive of PML (e.g., cognitive, neurological, or psychiatric signs). If such symptoms/signs occur, consider referral to a neurologist and appropriate diagnostic measures for PML/JCV. If PML is suspected, Tibsovo must be suspended until PML has been excluded. If confirmed, discontinue Tibsovo.

Haemorrhage

Tibsovo has been associated with an increased incidence of haemorrhagic events (see "*Undesirable effects*"). Patients taking Tibsovo should be monitored for signs and symptoms of Central Nervous System (CNS) bleeding, Gastro-intestinal (GI) bleeding and other severe bleeding (see section "*Dosage/Administration*" for "Other Grade 3 or higher adverse reactions recommended dose modifications").

Hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child Pugh class 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 "*Dosage/ Administration*" and "*Pharmacokinetics*").

Tibsovo should be used with caution in patients with mild hepatic impairment (Child-Pugh class A) (see *"Undesirable effects"*).

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.

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 "*Dosage/ Administration*" and "*Pharmacokinetics*").

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 "*Pregnancy, lactation*").

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 "*Interactions*" and "*Pregnancy, lactation*").

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, i.e. it is essentially 'sodium-free'.

Interactions

Effect of other medicinal products on ivosidenib

Concomitant use contraindicated

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 "*Contraindications*"). Clinical studies evaluating the pharmacokinetics of ivosidenib in the presence of a CYP3A4 inducer have not been conducted.

Concomitant use to be avoided

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, with a geometric mean AUC ratio of 269% (90% CI: 245%, 295%) 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. 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 "*Dosage/Administration*"and "*Warnings and precaution*s"). Patients should be treated with

caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible.

- Moderate CYP3A4 inhibitors include for example: aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice, isavuconazole, verapamil.
- Strong CYP3A4 inhibitors include for example: 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 or appropriate alternatives should be considered 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 "*Dosage/Administration*" and "*Warnings and precautions*").

Effect of ivosidenib on other medicinal products

Concomitant use contraindicated

Interactions with transporters

P-gp substrates

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 "*Contraindications*").

Concomitant use to be avoided

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 "*Pharmacokinetics*").

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

- CYP2C19 substrates include for example: 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 during treatment with Tibsovo and for at least 1 month after the last dose (see "*Warnings and precautions*" and "*Pregnancy, lactation*")

OAT3 or OATP1B1/1B3 substrates
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 "*Pharmacokinetics*"). 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.

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 "*Pharmacokinetics*").

Pregnancy, 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 "*Warnings and precautions*").

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 "*Warnings and precautions*" and "*Interactions*").

Pregnancy

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

Tibsovo is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception. 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, they should be informed of the potential risk to the foetus.

Lactation

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 "Preclinical data"). The clinical relevance of these effects is unknown.

Effects on ability to drive and use machines

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

Undesirable effects

Newly Diagnosed Acute Myeloid Leukaemia in Combination with Azacitidine

Summary of the safety profile

The safety profile of Tibsovo in patients with newly diagnosed acute myeloid leukaemia in combination with azacitidine is based on data from 404 patients with hematologic malignancies treated with Tibsovo 500 mg once daily in clinical trials in combination (in the pivotal study Phase III AG120-C-009, randomized and placebo control in combination with azacitidine, and in a non-randomized, non-controlled phase I study AG120-221-C-001 in combination with cytarabine with either daunorubicin or

idarubicin) or as monotherapy (in non-randomized, non-controlled phase I study AG120-C-001, and CS3010-101). The median duration of treatment with Tibsovo 500 mg once daily was 4.5 months (range 0 to 104).

The most common adverse reactions in patients with hematologic malignancies treated with Tibsovo in combination or as monotherapy were fatigue (27%), vomiting (25%), electrocardiogram QT prolonged (23%) and leukocytosis (21%).

The most common serious adverse reactions in patients with hematologic malignancies treated with Tibsovo in combination or as monotherapy were differentiation syndrome (9%), leukocytosis (5%) and electrocardiogram QT prolonged (4%).

In patients with hematologic malignancies treated with Tibsovo in monotherapy or in combination, the frequency of discontinuation of ivosidenib due to adverse reactions was 4%. Adverse reactions leading to discontinuation were haemorrhage intracranial (1%), Guillain-Barre syndrome (< 1%), pulmonary embolism (< 1%) and thrombocytopenia (< 1%).

The frequency of dose interruption of ivosidenib due to adverse reactions in patients with hematologic malignancies with at least one adverse drug reaction was20%. The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%) and neutropenia (4%).

Dose reductions due to adverse events in patients with hematologic malignancies treated with Tibsovo in combination or as monotherapy were reported in 6% of patients. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3%), neutropenia (2%), thrombocytopenia (<1%), platelet count decreased (<1%), differentiation syndrome (< 1%) and fatigue (<1%).

List of adverse reactions

The adverse reaction frequencies are based on all-cause treatment emergent 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.

Adverse reactions are classified by MedDRA organ system class and by frequency according to the following convention. The frequency of adverse reactions was categorised as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and unknown (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 - Adverse drug reactions reported in patients with hematological malignancies (including newly diagnosed AML) treated with ivosidenib 500 mg daily in monotherapy or in combination with azacitidine (N=404)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Leukocytosis (21%), Thrombocytopenia (19%), Platelet count decreased (16%), Neutropenia (13%), White blood cell count decreased (11%), Differentiation Syndrome (11%),
	Common	Neutrophil count decreased, Leukopenia
Cardiac disorders	Very common	Electrocardiogram QT prolonged (23%)
Psychiatric disorders	Very common	Insomnia (12%)
Nervous system disorders	Very common	Dizziness (17%), Headache (16%)
	Common	Neuropathy Peripheral, Haemorrhage intracranial
	Uncommon	Guillain-Barre syndrome, Posterior reversible encephalopathy syndrome, Progressive multifocal leukoencephalopathy
Gastrointestinal disorders	Very common	Vomiting[1] (25%),
	Common	Oropharyngeal pain, Gingival bleeding
Musculoskeletal and connective tissue disorders	Very common	Arthralgia (18%), Back pain (17%), Pain in extremity (12%).
General disorders and administration site conditions	Very common	Fatigue (27%)
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis (15%)
	Common	Pulmonary embolism
Skin and subcutaneous tissue disorders	Common	Petechiae
Vascular disorders	Common	Haematoma

[1] Grouped term includes vomiting and retching.

Previously treated, locally advanced or metastatic cholangiocarcinoma

Summary of the safety profile

The safety profile of Tibsovo in patients with Locally Advanced or Metastatic Cholangiocarcinoma is based on data from 310 patients with solid tumors, treated with Tibsovo 500 mg once daily as monotherapy in clinical trials (in the randomized Phase III AG120-C-005 placebo controlled pivotal study, and in non-randomized, non-controlled phase I study AG120-C-002 and AG120-881-C-001). The median duration of treatment with Tibsovo 500 mg once daily was 3.7 months (range 0.1 to 45.1).

The most common adverse reactions in patients with solid tumors treated with Tibsovo as monotherapy were fatigue (40%), nausea (33%), diarrhoea (31%), abdominal pain (30%), decreased appetite (20%), vomiting (19%), anaemia (15%), headache (15%), ascites (14%) and rash (13%).

The most common serious adverse reactions in patients with solid tumors treated with Tibsovo as monotherapy were ascites (2%), blood bilirubin increased (1%), vomiting (1%), hyperbilirubinemia (1%), and jaundice cholestatic (1%).

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

The frequency of dose interruption of Tibsovo in patients with solid tumors treated with Tibsovo as monotherapy due to adverse reactions was 13%. The most common adverse reactions leading to dose interruption were fatigue (2%), hyperbilirubinemia (2%), aspartate aminotransferase increased (2%), alanine aminotransferase increased (2%), nausea (2%) and vomiting (2%).

Dose reductions due to adverse reactions in patients with solid tumors treated with Tibsovo as monotherapy were reported in 2% of patients. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (1%), neuropathy peripheral (<1%), blood bilirubin increased (<1%) and fatigue (<1%).

List of adverse reactions

The adverse reaction frequencies are based on all-cause treatment emergent 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.

Adverse reactions are classified by MedDRA organ system class and by frequency according to the following convention. The frequency of adverse reactions was categorised as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and unknown (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 - Adverse drug reactions reported in patients with solid tumors (including locally Advanced or Metastatic Cholangiocarcinoma) treated with ivosidenib 500 mg daily as monotherapy (N=310)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Anaemia (15%)
	Common	White blood cell count decreased, Platelet count decreased
Cardiac disorders	Common	Electrocardiogram QT prolonged
Metabolism and nutrition disorders	Very common	Decreased appetite (20%)
Nervous system disorders	Very common	Headache (14%)
	Common	Neuropathy peripheral[1]
Gastrointestinal disorders	Very common	Nausea (33%), Abdominal pain[2] (30%), Diarrhoea (31%), Vomiting (19%), Ascites (14%)

	Common	Rectal haemorrhage, Gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage
Hepatobiliary disorders	Common	Aspartate aminotransferase increased, Alanine aminotransferase increased, Hyperbilirubinemia, Jaundice cholestatic
Skin and subcutaneous tissue disorders	Very common	Rash[3] (13%)
General disorders and administration site conditions	Very common	Fatigue[4] (40%)
	Common	Fall
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis, Pulmonary embolism

[1] Grouped term includes neuropathy peripheral, peripheral sensory neuropathy and paraesthesia

[2] Grouped term includes abdominal pain, abdominal distension, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort and abdominal tenderness

[3] Grouped term includes rash, rash maculo-papular, erythema, rash erythematous, rash macular, rash pustular, urticaria, dermatitis allergic, dermatitis exfoliative generalized, drug eruption, drug hypersensitivity, rash pruritic and rash vesicular

[4] Grouped term includes fatigue and asthenia

Description of selected adverse reactions and additional information

Description of selected adverse reactions

Differentiation syndrome in patients with Acute Myeloid Leukaemia (see "Dosage/Administration" and "Warnings and precautions")

In the pivotal study AG120-C-009, in the 72 patients with newly diagnosed AML treated with Tibsovo in combination with azacitidine, 14% experienced differentiation syndrome, with a median time to onset of differentiation syndrome of 20 days. Differentiation syndrome occurred as early as 3 days and up to one month after treatment initiation with or without concomitant leukocytosis. 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 in the development program.

No cases of differentiation syndrome were reported in the clinical Study AG120-C-005 for patients with locally advanced or metastatic cholangiocarcinoma.

QTc interval prolongation (see "Dosage/Administration", "Warnings and precautions" and "interactions")

In the pivotal 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 22%, 11% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 17% 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, 26% 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 8% 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 27 months after treatment initiation.

In the pivotal 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 or 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 as compared to the patients with normal hepatic function (Child-Pugh class A) (see "*Dosage/Administration*" and "I*nteractions*").

In patients with hematologic malignancies treated with Tibsovo in combination or as monotherapy, the following adverse reactions were reported with a higher incidence in patient mild hepatic impairment compared to patients with normal hepatic function: arthralgia (27 vs 16%), electrocardiogram QT prolonged (29 vs 22%), haematoma (10 vs 4%), leukocytosis (38 vs 18%) and petechiae (16 vs 6%). Grade 3 adverse reactions were reported with a higher incidence in patient mild hepatic impairment: electrocardiogram QT prolonged (13 vs 8%), fatigue (10 vs 2%), differentiation syndrome (10 vs 4%).

In patients with solid tumors treated with Tibsovo 500 mg as monotherapy, the following adverse reactions were reported with a higher incidence in patients with mild hepatic impairment as compared to patients with normal hepatic function: abdominal pain (39 vs 24%), alanine aminotransferase increased (10 vs 4%), anaemia (21 vs 12%), ascites (25 vs 7%), blood bilirubin increased (12 vs 3%), decreased appetite (23 vs 18%), electrocardiogram QT prolonged (11 vs 6%), vomiting (23 vs 16%). Grade 3 adverse events were reported with a higher incidence in patient mild hepatic impairment: anaemia (9 vs 2%), ascites (10 vs 4%), blood bilirubin increased (8 vs 1%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with ivosidenib (see "*Undesirable effects*"). Patients should be closely monitored and provided with appropriate supportive care (see "*Dosage/Administration*" and "*Warnings and precautions*"). There is no specific antidote for ivosidenib overdose.

Properties/Effects

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.

Pharmacodynamics

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 "*Dosage/Administration*" and "*Warnings and precautions*").

Clinical efficacy

Newly Diagnosed Acute Myeloid Leukaemia in Combination with Azacitidine

The efficacy of Tibsovo was evaluated in a randomised, multicenter, double-blind, placebo-controlled clinical trial (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 test. 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) was a key secondary efficacy endpoint (Table 4).

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 (%) Treatment Failure Relapse Death	46 (63.9) 42 (58.3) 3 (4.2) 1 (1.4)	62 (83.8) 59 (79.7) 2 (2.7) 1 (1.4)
Hazard ratio[1] (95% CI)	0.33 (0.16, 0.69)	
p-value[2]	0.0011	
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)	
p-value[2]	0.0005	

CI: confidence interval; OS = Overall survival, DCO: 18 march 2021
[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] P-value is calculated from the 1-sided log-rank test stratified by the randomisation stratification factors (AML status and geographic region).

An updated OS analysis (DCO 30 June 2022), 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 with a life expectancy of 3 months or more.

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 OncomineTM 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, 8% locally advanced disease 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. No patient with an IDH1 R132H mutation was randomized to ivosidenib.

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 (%) Progressive Disease Death	76 (61) 64 (52) 12 (10)	50 (82) 44 (72) 6 (10)
Median PFS, months (95% CI)	2.7 (1.6, 4.2)	1.4 (1.4, 1.6)
Hazard ratio (95% CI)[1]	0.37 (0.25, 0.54)	
P-value[2]	<0.0001	
	Ivosidenib (500 mg daily)	**Placebo**
Overall Survival[3,4]	**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.

[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. Stratification factor is the number of prior line of therapies at randomisation.

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

[4]After adjustment of the OS estimation in the placebo arm for crossover (70.5% of patients in the placebo arm crossed over to ivosidenib at time of disease progression), the median OS in the placebo arm was 5.1 months (HR = 0.49, p value < 0.0001).

An updated OS analysis at the final database lock date of 21 June 2021, carried out at 153 deaths confirmed a consistent benefit with the final analysis of OS (data cutoff date: 31 May 2020) and showing a median OS of 10.3 months for Tibsovo vs 7.5 months for placebo, (HR = 0.82; 95% CI: 0.58, 1.14; p value = 0.118).

Paediatrics

The European Medicines Agency has waived the obligation to submit the results of studies with Tibsovo in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) and in the treatment of malignant neoplasms of the central nervous system.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tibsovo in one or more subsets of the paediatric population in the treatment of acute myeloid leukaemia (see "*Dosage/Administration*" for information on paediatric use).

Pharmacokinetics

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 "*Dosage/ Administration*").

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.

Metabolism

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.

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

Hepatic impairment

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. The pharmacokinetics of ivosidenib in patients with severe hepatic impairment (Child Pugh class C) are unknown (see "*Dosage/Administration*").

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 "*Dosage/Administration*").

Elderly

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on age (see "*Dosage/Administration*").

Other

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

Preclinical 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.

Repeated-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

Ivosidenib was not mutagenic or clastogenic in conventional *in vitro* and *in vivo* genotoxicity assays.

Carcinogenicity

Carcinogenicity studies have not been conducted with ivosidenib.

Reproductive 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 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.

Other information

Stability Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.

Keep container closed and in carton to protect contents from light and moisture.

Use within 30 days of opening.

Keep out of reach of children.

Authorisation number

69077 (Swissmedic).

Packs

Tibsovo 250mg: each bottle contains 60 film-coated tablets and a silica gel desiccant in a HDPE canister. [A]

Marketing authorisation holder

Servier (Suisse) S.A. 1202 Genève.

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