Drug Monograph

A - Drug Name

ivosidenib

COMMON TRADE NAME(S): Tibsovo®

back to top

B - Mechanism of Action and Pharmacokinetics

Ivosidenib is an inhibitor of mutant isocitrate dehydrogenase (IDH1) enzymes. Mutant IDH1 increases the production of 2-hydroxyglutarate (2-HG), which plays a role in blocking cellular differentiation and promoting tumorigenesis. By inhibiting mutant IDH1, ivosidenib reduces 2-HG levels and restores cellular differentiation.

Absorption	Time to reach steady state	Within 14 days
	Effects with food	Significant increases in C_{max} (by ~98%) and AUC_T (by ~26%) were observed following administration with a high-fat, high-calorie meal.
	Peak plasma levels	~2 hours
Distribution	PPB	92-96%
Metabolism	Ivosidenib is primarily metabolized by CYP3A4 with minor contributions from N-dealkylation and hydrolytic pathways.	
Elimination	Half-life	98 hours (terminal; in combination with azacitidine in acute amyloid leukemia)

		129 hours (terminal; monotherapy in cholangiocarcinoma)
	Feces	77% (67% unchanged)
	Urine	17% (10% unchanged)

back to top

C - Indications and Status

Health Canada Approvals:

- Acute myeloid leukemia (AML)
- Cholangiocarcinoma

Refer to the product monograph for a full list and details of approved indications

back to top

D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 5% of patients with cholangiocarcinoma treated with ivosidenib versus placebo in a phase III study. It also includes severe or life-threatening effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (5%)	E
	QT interval prolonged (7%) (2% severe)	E
Dermatological	Rash (6%)	E
Gastrointestinal	Abdominal pain (10%)	E
	Anorexia (9%)	E
	Ascites (1%)	E

	Diarrhea (23%)	E
	Nausea, vomiting (23%)	E
General	Differentiation syndrome (14%) (8% severe) (in AML)	E
	Fatigue (20%)	E
Hematological	Anemia (5%)	E
	Leukocytosis (10%) (in AML)	E
	Myelosuppression (3%) (in AML - 19%; 1% severe)	E
Hepatobiliary	↑ Bilirubin (3%) , cholestatic jaundice	E
	↑ LFTs (5%)	E
Nervous System	Dizziness (4%) (in AML)	E
	Headache (8%)	E
	Insomnia (8%)	E
	Peripheral neuropathy (4%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ivosidenib include diarrhea, nausea/ vomiting, fatigue, and differentiation syndrome (in AML).

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells, and may be life-threatening or fatal if untreated. Signs and symptoms of differentiation syndrome include non-infectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. Differentiation syndrome may occur with or without concomitant leukocytosis. Differentiation syndrome can occur as early as 3 days after starting AML treatment and during the first month of treatment.

back to top

E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

IDH1 R132 mutation should be confirmed using an appropriate diagnostic test prior to starting ivosidenib.

QTc should be < 450 ms prior to starting ivosidenib. In the presence of an abnormal QTc 480-500 ms, treatment should only be initiated in exceptional cases if the benefits outweigh the risks.

Adults:

Oral: 500 mg Daily

Dosage with Toxicity:

Dose Level	Ivosidenib Dose (mg daily)
0	500
-1	250
-2	Discontinue

Toxicity	Grade/Severity	Action
Differentiation Syndrome	Any	If differentiation syndrome suspected, initiate systemic corticosteroids for a minimum of 3 days. Taper after toxicity resolves to prevent recurrence. Initiate hemodynamic monitoring until toxicity resolves and for a minimum of 3 days. Hold ivosidenib if toxicity is severe and persists for > 48 hours after initiating systemic corticosteroids. Resume at same dose once toxicity is no longer severe and clinically improved.

Leukocytosis	WBC > 25 x 10^9 /L OR an absolute increase in total WBC > 15 x 10^9 /L from baseline	Initiate hydroxyurea as per local guidelines. Taper after leukocytosis improves or resolves, to prevent recurrence. Initiate leukapheresis as clinically indicated. Hold ivosidenib if no improvement after initiating hydroxyurea. Resume at same dose once resolved.
QTc Interval Prolongation	QTc > 480 to 500 ms	Hold until QTc ≤ 480 ms.* Resume** at same dose.
	QTc > 500 ms	Hold.* Monitor ECG† every 24 hours until QTc ≤ 480 ms or within 30 ms of baseline. Resume** at 1 dose level ↓. May increase dose to 500 mg daily if alternative etiology for QTc prolongation is identified.
	QT prolongation with signs/symptoms of life-threatening ventricular arrhythmia	Discontinue.
Other Adverse Reactions	Grade 3	Hold until improvement to ≤ Grade 1 or baseline. Resume at same dose.
		First recurrence: Hold until improvement to ≤ Grade 1 or baseline. Resume at 1 dose level ↓, then return to original dose once toxicity resolves.
		Second recurrence: Discontinue.
	Grade 4	Hold until improvement to ≤ Grade 1 or baseline. Resume at 1 dose level ↓.
		Recurrence: Discontinue

* Monitor electrolyte levels and supplement as clinically indicated. Review and adjust concomitant medications known to prolong QTc intervals.

** Monitor ECGs at least weekly for 2 weeks and as clinically indicated.

† If QTc > 550 ms, consider continuous ECG monitoring until < 500 ms.

Dosage with Hepatic Impairment:

Hepatic Impairment	Ivosidenib Dose
Mild (Child-Pugh Class A)	No dose adjustment required.
Moderate (Child-Pugh Class B)	No data available. Use with caution and monitor closely.
Severe (Child-Pugh Class C)	

Dosage with Renal Impairment:

Creatinine Clearance*	Ivosidenib Dose
≥ 30	No dose adjustment required.
< 30	No data available. Use with caution and monitor closely.

*Reported as eGFR (mL/min/1.73 m^2)

Dosage in the elderly:

No dose adjustment is required. No overall differences in effectiveness or safety were observed between patients aged ≥ 65 years compared to younger patients. No data is available for patients ≥ 85 years old.

Dosage based on gender:

Gender does not have a clinically meaningful effect on the pharmacokinetics of ivosidenib.

Dosage based on ethnicity:

Ethnicity does not have a clinically meaningful effect on the pharmacokinetics of ivosidenib.

Children:

No data is available for patients < 18 years of age.

back to top

F - Administration Guidelines

- Administer each dose on an empty stomach, at least 1 hour before or 2 hours after a meal.
- Tablets should be swallowed whole with water. Do not split, crush, or chew the tablets.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during treatment, due to risk of increased toxicity.
- If a dose is missed, administer the dose as soon as possible within 12 hours of missed dose. If the dose is missed by more than 12 hours, skip the dose and administer the next dose at the next planned time. Do not give extra tablets to make up for the missed dose.
- If patient vomits after taking a dose, do not administer a replacement dose. The next regular daily dose should be given on the next day.
- Store at 15°C - 30°C. Keep the bottle tightly closed to protect tablets from moisture.

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Patients taking strong CYP3A4 inducers or dabigatran
- Patients with congenital long QT syndrome
- Patients with a family history of sudden death or polymorphic ventricular arrythmia
- Patients with a QT/QTc interval > 500 ms, regardless of the correction method used

Other Warnings/Precautions:

- Ivosidenib contains lactose and should not be used in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- QTc interval prolongation has been reported following treatment with ivosidenib, and can increase the risk of ventricular arrhythmias including torsades de pointes. Clinical trials excluded patients with baseline QTc ≥ 450 ms or other factors that increased the risk of QT prolongation (e.g. history or family history of long QT syndrome, uncontrolled or significant cardiovascular disease, heart failure, hypokalemia). Closely monitor patients who have congestive heart failure or electrolyte abnormalities. Use with caution in patients who have low albumin levels or are underweight.
- Caution with driving or using machinery as dizziness may occur with treatment.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
    - Ivosidenib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
    - Use of an additional non-hormonal (e.g., barrier) methods of contraception is recommended since ivosidenib may reduce the effectiveness of hormonal contraceptives (See Interactions section).
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **1 month** after the last dose.
- Fertility effects: Unknown

back to top

H - Interactions

Ivosidenib is:

- primarily metabolized by CYP3A4.
- an inducer of CYP3A4, including its own metabolism, as well as CYP2B6, CYP2C8, CYP2C9. It may also induce CYP2C19 and UGTs.
- a substrate and inhibitor of P-glycoprotein (P-gp), and a potential inducer of P-gp.
- an inhibitor of OAT3, OATP1B1, and OATP1B3.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort)	↓ ivosidenib concentration (e.g. ↓ AUC by 33% with rifampin) (theoretical)	↑ metabolism of ivosidenib	Coadministration is contraindicated.
P-glycoprotein (P-gp) substrates (e.g. dabigatran)	Alter exposure of P-gp substrates (theoretical)	Ivosidenib is a substrate and inhibitor of P-gp, and has the potential to induce P-gp.	Coadministration with dabigatran is contraindicated.
Strong and moderate CYP3A4 inhibitors (e.g. clarithromycin, ritonavir, aprepitant, cyclosporine, diltiazem, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ ivosidenib concentration and/or toxicity	↓ metabolism of ivosidenib	Avoid coadministration. If must co-administer, ↓ ivosidenib dose to 250 mg once daily and closely monitor for QTc prolongation. Resume ivosidenib dose at 500 mg once daily after inhibitor has been discontinued for at least 5 half-lives.
Medications known to prolong QTc interval (e.g. anti-arrhythmics, fluoroquinolones, 5 HT3 receptor antagonists)	↑ risk of QTc prolongation (theoretical)	Additive effect	Avoid coadministration. If must co-administer, use with caution and closely monitor for QTc prolongation.
OAT3 substrates, OR sensitive OATP1B1 and OATP1B3 substrates (e.g. benzylpenicillin,	↑ concentration and/or toxicity of OAT3 and OATP1B1/ OATP1B3 substrates (theoretical)	Ivosidenib is an inhibitor of OAT3, OATP1B1, OATP1B3	Avoid coadministration. If must co-administer, use with caution. If

furosemide, atorvastatin, pravastatin, rosuvastatin)			furosemide is clinically indicated to manage differentiation syndrome, closely monitor for electrolyte imbalances and QTc prolongation.
Anti-fungal agents that are CYP3A4 substrates (e.g. fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	↓ efficacy of antifungals (theoretical)	Ivosidenib is an inducer of CYP3A4	Avoid coadministration.
CYP3A4 substrates with a narrow therapeutic index (e.g. cyclosporine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)	↓ concentration and/or efficacy of CYP3A4 substrates (theoretical)	Ivosidenib is an inducer of CYP3A4	Avoid coadministration. If must co-administer, monitor for ↓ efficacy of substrates.
CYP2B6 substrates with a narrow therapeutic index (e.g. cyclophosphamide, ifosfamide, methadone)	↓ concentration and/or efficacy of CYP2B6 substrates (theoretical)	Ivosidenib is an inducer of CYP2B6	Avoid coadministration. If must co-administer, monitor for ↓ efficacy of substrates.
CYP2C8 substrates with a narrow therapeutic index (e.g. paclitaxel, pioglitazone, repaglinide)	↓ concentration and/or efficacy of CYP2C8 substrates (theoretical)	Ivosidenib is an inducer of CYP2C8	Avoid coadministration. If must co-administer, monitor for ↓ efficacy of substrates.
CYP2C9 substrates with a narrow therapeutic index (e.g. phenytoin, warfarin)	↓ concentration and/or efficacy of CYP2C9 substrates (theoretical)	Ivosidenib is an inducer of CYP2C9	Avoid coadministration. If must co-administer, monitor for ↓ efficacy of substrates.
CYP2C19 substrates (e.g. omeprazole)	↓ concentration and/or efficacy of CYP2C19 substrates (theoretical)	Ivosidenib may induce CYP2C19	Avoid coadministration. If must co-administer, monitor for ↓ efficacy of substrates.
Uridine diphosphate glucuronosyltransferases (UGTs) substrates (e.g.	↓ concentration of UGT substrates (theoretical)	Ivosidenib has the potential to induce UGTs and decrease	Avoid coadministration. If must co-administer,

lamotrigine, raltegravir)		systemic exposure of UGT substrates	monitor for ↓ efficacy of substrates.
Hormonal contraceptives (e.g. norethisterone and ethinyl estradiol)	↓ concentration and/or efficacy of hormonal contraceptives (theoretical)	Ivosidenib is an inducer of CYP3A4	Concomitant use of a non-hormonal (e.g. barrier) method of contraception is recommended during treatment and for at least 1 month after the last ivosidenib dose.
Medications that affect electrolytes (e.g. thiazide and related diuretics, laxatives and enemas, amphotericin B, high-dose corticosteroids, and proton pump inhibitors)	↑ risk of QTc prolongation	Medications that decrease electrolyte levels may ↑ the risk of QTc prolongation	Use with caution. Monitor and maintain electrolyte levels within the normal range.
Medications that reduce heart rate (e.g. diltiazem, verapamil, quinidine)	↑ risk of QTc prolongation	Bradycardia can ↑ the risk of QTc prolongation and torsades de pointes	Use with caution. Monitor and maintain heart rate within the normal range.

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit, and as clinically indicated (Consider additional testing for patients with AML, e.g. at least weekly for the first month, once every other week for the second month then monthly thereafter)
Liver function tests	Baseline, at each visit, and as clinically indicated
Renal function tests	Baseline, at each visit, and as clinically indicated
ECG	Baseline, at least weekly during the first 3 weeks of treatment, then at least monthly for the duration of treatment (More frequent monitoring may be necessary in patients with / at risk of QTc prolongation).
Electrolytes, including sodium, potassium, calcium or magnesium	Baseline, at each visit, and as clinically indicated
Clinical toxicity assessment for fatigue, GI effects, and differentiation syndrome (in AML)	Baseline, at each visit, and as clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- Ivosidenib in combination with Azacitidine (Outpatient) - Previously Untreated Acute Myeloid Leukemia

back to top

K - References

Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Jun;21(6):796-807. doi: 10.1016/S1470-2045(20)30157-1.

Ivosidenib [Drug information]. UpToDate Inc. (2025). Accessed March 19, 2025.

Montesinos P, Recher C, Vives S, et al. Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia. N Engl J Med. 2022 Apr 21;386(16):1519-1531. doi: 10.1056/NEJMoa2117344.

Prescribing Information: Tibsovo® (ivosidenib). Servier Pharmaceuticals LLC. October 2023.

Product Monograph: Tibsovo® (ivosidenib). Servier Canada Inc. July 10, 2024.

September 2025 New drug monograph

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top