DRUG NAME: Ivosidenib

SYNONYM(S): AG-120[1]

COMMON TRADE NAME(S): TIBSOVO®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Ivosidenib is an orally administered small molecule inhibitor of mutant isocitrate dehydrogenase 1 (IDH1). Mutant IDH1 enzyme converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG). Overproduction of 2-HG impairs cellular differentiation and promotes tumorigenesis in hematologic and non-hematologic malignancies. By inhibiting mutant IDH1 enzyme activity, ivosidenib reduces 2-HG levels and restores cell differentiation. In IDH1-mutated acute myeloid leukemia, ivosidenib has demonstrated its ability to reduce blast counts and promote maturation of myeloid cells.[2,3]

PHARMACOKINETICS:

Oral Absorption[3]	T_{max} = 2-3 h; high fat meal significantly increases ivosidenib C_{max} (98%) and AUC (26%)	
Distribution	highly bound to plasma proteins	
	cross blood brain barrier?	yes[4]
	volume of distribution	403-706 L
	plasma protein binding	92-96%
Metabolism	primarily metabolized by CYP3A4, with minor contributions by N dealkylation and hydrolytic pathways	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily by fecal elimination	
	urine	17% (10% as unchanged drug)
	feces	77% (67% as unchanged drug)
	terminal half life	58-129 h
	clearance	4.6-6.1 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:
Leukemia, acute myeloid*
Biliary tract cancer*

Other uses:
Myelodysplastic syndromes[5]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- congenital long QT syndrome or family history of sudden death or polymorphic ventricular arrythmia[3]

Caution:
- ivosidenib is not recommended in patients with ***QT/QTc interval*** greater than 500 msec; monitor ECG and correct electrolytes prior to treatment initiation[3]
- ivosidenib dose reduction may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[3]

Carcinogenicity: Carcinogenicity studies have not been conducted.[3]

Mutagenicity: Not mutagenic in Ames test. Ivosidenib was not clastogenic in the mammalian *in vitro* and *in vivo* chromosome tests.[3,5]

Fertility: In animal studies, uterine atrophy was observed in female test subjects at exposures 1.7 times higher than those seen following human clinical exposure. The effect was reversible after a 14 day recovery period. Testicular degeneration was observed in male test subjects at exposures 1.2 times higher than those seen following human clinical exposure. The clinical relevance of these effects in humans is unknown.[3,6]

Pregnancy: In animal studies, oral administration of ivosidenib during the period of organogenesis caused decreased fetal body weights, delayed skeletal ossification, skeletal variations, visceral variations, and spontaneous abortions at 2 to 3.9 times the exposures of those seen following human clinical exposure. Ivosidenib was shown to cross the placenta and was detected in fetal plasma. Pregnancy tests are recommended prior to treatment for female patients of childbearing potential. Contraception is recommended during treatment and for at least 1 month after the last dose for female patients of childbearing potential and male patients with female partners of childbearing potential. Ivosidenib may decrease the systemic concentrations of some hormonal contraceptives (e.g., norethisterone, ethinyl estradiol) via CYP 3A4 inhibition; therefore, non-hormonal methods of contraception are recommended.[3,5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 1 month after the last dose of ivosidenib.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (5-18%, severe 7%)
	leukocytosis (16-38%, severe 8%); occurs with differentiation syndrome
	leukopenia (3%)
cardiac	***ventricular fibrillation***
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (10-35%, severe 1-4%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ascites (1-23%, severe 9%)
	constipation (16-21%, severe 1-4%)
	diarrhea (23-61%, severe 2-7%)
	dyspepsia (11%)
	mucositis (21-28%, severe 3%)
	nausea (16-41%, severe 2-7%)
	vomiting (10-21%, severe 1-4%)[5]
general disorders and administration site conditions	chest pain (16%, severe 3%); includes angina pectoris and non-cardiac chest pain
	edema (32-43%, severe 1%); includes peripheral edema, face edema, and fluid overload
	fatigue (20-50%, severe 3-14%)
	pyrexia (23%, severe 1%)
hepatobiliary	jaundice cholestatic (1%)
investigations	albumin decrease (37%)
	alkaline phosphatase increase (16-27%, severe 1%)
	ALT increase (2-21%, severe 1-5%)
	AST increase (5-37%, severe 1-5%)
	blood bilirubin increase (16-30%, severe 1-13%)
	creatinine increase (23-95%, severe 1-5%)
	QTc prolongation (7-26%, severe 2-10%); see paragraph following **Side Effects** table
	uric acid increase (29-32%, severe 4-6%)
metabolism and nutrition	appetite decrease (9-39%, severe 2-4%)
	hypocalcemia (25%, severe 4%)
	hypokalemia (31-43%, severe 6-11%)
	hyperkalemia (16%)
	hypomagnesemia (21-38%)
	hyponatremia (39%, severe 4%)
	hypophosphatemia (21-26%, severe 8%)
	tumour lysis syndrome (8%, severe 6%)
	weight loss (11%)
musculoskeletal and connective tissue	arthralgia (32-42%, severe 4-16%)
	myalgia (18-26%, severe 1%)
nervous system	dizziness (21%)
	headache (8-16%)
	Guillain-Barré syndrome (<1%)[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neuropathy (11-14%, severe 1%); includes peripheral sensory and motor neuropathy
	progressive multifocal leukoencephalopathy
renal and urinary	acute kidney injury (2%)
respiratory, thoracic, and mediastinal	***cough*** (14-32%, severe <1%)
	differentiation syndrome (11-25%, severe 11-13%)[5]; see paragraph following Side Effects table
	dyspnea (21-33%, severe 9%); includes respiratory failure and hypoxia
	pleural effusion (13%, severe 3%)
skin and subcutaneous tissue	***rash*** (6-26%, severe 2-4%)
	pruritus (14-26%, severe 4%)
vascular	hypertension (16%, severe 16%)
	hypotension (12%, severe 4%)

Adapted from standard reference[3,5] unless specified otherwise.

Differentiation syndrome (formerly known as retinoic acid syndrome[10]) has been reported with ivosidenib in patients with acute myeloid leukemia and myelodysplastic syndromes.[3,5] Differentiation syndrome is a group of symptoms associated with rapid proliferation and differentiation of myeloid cells. Although the pathophysiology is not fully understood, it is suggested that it is caused by release of inflammatory vasoactive cytokines and tissue infiltration by rapidly maturing cells.[11] Clinical presentation may include fever, dyspnea, cough, rash, hypotension, pleural or pericardial effusion, pulmonary or peripheral edema, rapid weight gain, and renal dysfunction with or without leukocytosis. Symptoms can be fatal if not treated.[3] The median time to onset is usually reported as 15-29 days[12,13]; however, onset can be delayed up to 3-4 months after initiation of ivosidenib.[5,14] Recurrent episodes of differentiation syndrome can also occur.[15] If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring. If signs or symptoms persist for longer than 48 hours after corticosteroid initiation, ivosidenib dose interruption is recommended until symptoms improve to grade 2 or less. Continue corticosteroids for at least 3 days after symptom resolution as premature corticosteroid taper or discontinuation may result in symptom recurrence. If concomitant leukocytosis occurs, consider hydroxyurea or leukapheresis as clinically indicated.[3,5]

QTc interval prolongation is a concentration-dependent effect of ivosidenib. Although rare, ventricular fibrillation has also been reported.[5] Median time to onset of QTc prolongation is 30 days (range 1 day-23 months).[3] Monitor ECG and correct electrolyte abnormalities prior to ivosidenib initiation and monitor regularly throughout treatment. More frequent monitoring may be required for patients with known risk factors for QT prolongation (e.g., congestive heart failure, known drug interactions, etc.). Management of QTc prolongation may include dose interruption and/or dose reduction. Permanently discontinue ivosidenib in patients who develop life-threatening arrythmias with QTc prolongation.[3]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acid reducing agents[5]	no clinically significant changes in the pharmacokinetics of ivosidenib	reduced solubility of ivosidenib with increasing pH	no management required
fluconazole[3,5]	173% increase in ivosidenib AUC with no change in C_{max} following single dose ivosidenib; magnitude of effect is *predicted* to be greater following coadministration multiple daily doses of ivosidenib (190% increase in ivosidenib AUC and 152% increase in C_{max}	moderate inhibition of CYP 3A4 by fluconazole	avoid concurrent use; if unavoidable, decrease ivosidenib dose to 250 mg once daily and monitor ECG and observe for ivosidenib toxicity
grapefruit juice[3]	may increase plasma level of ivosidenib	may inhibit CYP 3A4 metabolism of ivosidenib in the intestinal wall	avoid grapefruit juice for the duration of treatment with ivosidenib
itraconazole[3,5]	169-269% increase in ivosidenib AUC with no change in C_{max}	strong inhibition of CYP 3A4 by itraconazole	avoid concurrent use; if unavoidable, decrease ivosidenib dose to 250 mg once daily and monitor ECG and observe for ivosidenib toxicity
rifampin[5]	*predicted*: 33% decrease in ivosidenib AUC	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Ivosidenib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of ivosidenib. Avoid concurrent use with ***strong or moderate*** CYP 3A4 inhibitors. If coadministration with a ***strong or moderate*** CYP 3A4 inhibitor cannot be avoided, decrease ivosidenib dose to 250 mg once daily.[3] Monitor for ivosidenib toxicity. If the CYP 3A4 inhibitor is discontinued, ivosidenib may be resumed at the prior dose after a washout period of at least 5 half-lives of the inhibitor.[5] ***CYP 3A4 inducers*** may decrease the plasma concentration of ivosidenib. Avoid concurrent use with strong CYP 3A4 inducers.[3]

In vitro, ivosidenib induces CYP 3A4, CYP 2B6, CYP 2C8, CYP 2C9 and CYP 2C19. Ivosidenib may also induce UGT enzymes. Use caution when ivosidenib is coadministered with sensitive substrates of these enzymes, where a minimal concentration change may lead to therapeutic failure of the substrate drug.[3,5]

In vitro, ivosidenib inhibits OAT3, OATP1B1, and OATP1B3. Ivosidenib inhibits P-gp and has potential to induce P-gp. If coadministered with a P-gp substrate that has a narrow therapeutic index, monitor for toxicity and efficacy of the substrate.[3,5]

SUPPLY AND STORAGE:

Oral: Servier Canada Inc. supplies ivosidenib as 250 mg film-coated tablets. Store at room temperature. Store in the original bottle with desiccant. Tablets contain lactose.[3,5]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

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Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[1,3,5,16]*:*	***500 mg*** (range 250-500 mg) ***PO once daily**** *dose adjustment may be required for some drug interactions Administer on an empty stomach (at least 1 hour before meals or 2 hours after), at approximately the same time each day. Do not take with grapefruit or grapefruit juice.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3] CrCl <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild impairment (Child-Pugh Class A): no adjustment required[3] moderate to severe impairment (Child Pugh classes B and C): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

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