DRUG NAME: Vorasidenib

SYNONYM(S): AG881[1]

COMMON TRADE NAME(S): VORANIGO®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Vorasidenib is an orally administered small molecule inhibitor that targets isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). Mutant IDH1 and IDH2 enzymes overproduce oncogenic metabolite 2-hydroxyglutarate (2-HG) which impairs cellular differentiation and promotes oncogenesis. By inhibiting mutant IDH1 and IDH2, vorasidenib reduces 2-HG levels, thereby restoring cellular differentiation and decreasing tumour cell proliferation.[2,3]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2 h; food increases vorasidenib exposure (1.4-fold increase in AUC and 2 to 3-fold increase in C_{max})	
Distribution	highly bound to plasma proteins	
	cross blood brain barrier?	yes
	volume of distribution	3,930 L
	plasma protein binding	97%
Metabolism	primarily metabolized by CYP 1A2, with minor contributions by CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4/5; also metabolized by non-CYP pathways	
	active metabolite(s)	AGI-69460[2]
	inactive metabolite(s)	no information found
Excretion	primarily by fecal elimination	
	urine	4.5% (no unchanged drug detected)
	feces	85% (55% as unchanged drug)
	terminal half life	238 h
	clearance	14 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

Brain tumour*

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***hepatotoxicity***, including hepatic failure, hepatic necrosis, and autoimmune hepatitis, has been reported with vorasidenib; close monitoring may be required in patients with pre-existing hepatic impairment[3]

Special populations: Female adolescent patients (≥12 years) weighing 40-50 kg may be at increased risk of adverse reactions of vorasidenib as higher exposure is predicted compared with adults.[3]

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

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

Fertility: Fertility studies have not been conducted. In animal toxicity studies, adverse effects on both female and male reproductive organs were observed. In female rats, uterine squamous metaplasia, decreased numbers of corpora lutea, estrous cycle variation, and atrophy of the ovaries, uterus, cervix and vagina were observed at exposures approximately 29 times the expected human exposure at the maximum clinical dose. In male rats, degeneration of seminiferous tubules, cellular debris in the epididymides, and atrophy of the testes, prostate, and seminal vesicles were observed. Partial recovery was observed in both sexes after a 4-week recovery period.[3]

Pregnancy: In animal studies, oral administration of vorasidenib during organogenesis caused embryo-fetal toxicity. In pregnant rats, increased resorptions, increased post-implantation loss, decreased fetal weight, and visceral/skeletal abnormalities were observed at exposures up to 118 times the expected human exposure at the maximum clinical dose, with skeletal abnormalities occurring at all dose levels. In pregnant rabbits, delayed ossification, skeletal variations, increased reportions, increased post-implantation loss, and decreased fetal weight were observed at exposures 5 to 12 times the expected human exposure at the maximum clinical dose. Pregnancy tests are recommended prior to treatment for female patients of childbearing potential. Contraception is recommended during treatment and for at least 3 months after the last dose for female patients of childbearing potential and male patients with female partners of childbearing potential. Vorasidenib may reduce the concentrations of hormonal contraceptives via CYP 3A induction; therefore, non-hormonal methods of contraception are recommended.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 2 months after the last dose of vorasidenib.[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.[4,5] 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	thrombocytopenia (12%)
gastrointestinal	*emetogenic potential:* minimal (rare)[2,6,7]
	abdominal pain (8-13%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (12-25%, severe <1%)
	gastroesophageal reflux (4%)
general disorders and administration site conditions	fatigue (23%)
hepatobiliary	***hepatotoxicity*** (<1%); see paragraph following **Side Effects** table
investigations	alkaline phosphatase increase (4-10%, severe 1%)
	ALT increase (37-59%, severe 10%); see paragraph following **Side Effects** table
	AST increase (25-46%, severe 5%); see paragraph following **Side Effects** table
	blood bilirubin increase (5%, severe <1%)
	gamma-glutamyl transferase increase (13-38%, severe 3%)
	hemoglobin increase (13%)
metabolism and nutrition	appetite decrease (5-9%)
	hyperglycemia (10%)

Adapted from standard references[3,8] unless specified otherwise.

Hepatotoxicity, including serious cases such as hepatic failure, hepatic necrosis, and autoimmune hepatitis, has been reported in patients treated with vorasidenib.[3] Median time to onset of increased ALT or AST is 57 days (range 1-1049 days).[8] Liver function tests are recommended at baseline and throughout treatment. Based on the severity and persistence of hepatotoxicity, vorasidenib dose interruption, dose reduction, and/or permanent discontinuation may be required.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ciprofloxacin[3]	2.5-fold increase in vorasidenib AUC and 1.3-fold increase in C_{max}	moderate inhibition of CYP 1A2 by ciprofloxacin	avoid concurrent use; if unavoidable, monitor for vorasidenib toxicity and consider vorasidenib dose reduction
fluvoxamine[3]	*predicted:* 7.2-fold increase in vorasidenib AUC and 5.7-fold increase in C_{max}	strong inhibition of CYP 1A2 by fluvoxamine	avoid concurrent use; if unavoidable, monitor for vorasidenib toxicity and consider vorasidenib dose reduction
omeprazole[3]	no clinically significant changes in the pharmacokinetics of vorasidenib	vorasidenib does not show pH-dependent solubility	no management required
phenytoin[3]	*predicted*: 40% decrease in vorasidenib AUC and 30% decrease in C_{max}	moderate induction of CYP 1A2 by rifampin	avoid concurrent use

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Vorasidenib is a substrate of ***CYP 1A2***. ***CYP 1A2 inhibitors*** may increase the plasma concentration of vorasidenib. Avoid concurrent use with *moderate or strong* CYP 1A2 inhibitors. If coadministration with a *moderate or strong* CYP 1A2 inhibitor cannot be avoided, monitor for increased toxicity of vorasidenib; consider dose reduction as indicated.[3]

CYP 1A2 inducers may decrease the plasma concentration of vorasidenib. Avoid concurrent use with *moderate or strong* CYP 1A2 inducers. Smoking tobacco may decrease the plasma concentration of vorasidenib via CYP 1A2 induction and lead to reduced efficacy of vorasidenib.[3]

In vitro, vorasidenib induces CYP 3A (strong), CYP 2C19 (weak to moderate), and CYP 2B6 (weak). Use caution when vorasidenib is coadministered with sensitive substrates of CYP 3A or CYP 2C19, where a minimal concentration change may lead to therapeutic failure of the substrate drug.[3]

In vitro, vorasidenib induces CYP 2C8, CYP 2C9, and UGT1A4 and inhibits BCRP; no clinically significant interactions have been reported.[3]

SUPPLY AND STORAGE:

Oral: Servier Canada Inc. supplies vorasidenib as 10 mg and 40 mg film-coated tablets. Tablets contain lactose. Store at room temperature.[3]

Additional information: Vorasidenib tablets do not require any special storage conditions[2,8,9]; the instruction to use the tablets within 60 days of opening[10,11] appears to be precautionary.

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

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

Oral[3,12,13]*:*	**≥*40 kg***: ***40 mg*** (range 10-40 mg) ***PO once daily*** ***<40 kg: 20 mg*** (range 10-20 mg) ***PO once daily*** Administer on an empty stomach (at least 1 hour before meals or 2 hours after), at approximately the same time each day.
Concurrent radiation:	no information found
Dosage in renal failure:	CrCl >40 mL/min: no adjustment required[3] CrCl ≤40 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 to moderate impairment (Child-Pugh A, B): no adjustment required[3] severe impairment (Child-Pugh C): no information found; monitor for toxicity[3]
Dosage in dialysis:	no information found

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Children:

Oral[3]*:*	children under 12 years of age: safety and efficacy have not been established adolescents 12 years and older: ≥40 kg: 40 mg (range 10-40 mg) PO once daily <40 kg: 20 mg (range 10-20 mg) PO once daily Administer on an empty stomach (at least 1 hour before meals or 2 hours after), at approximately the same time each day.

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