DRUG NAME: Venetoclax

SYNONYM(S): ABT-199, GDC-0199, RG7601[1]

COMMON TRADE NAME(S): VENCLEXTA®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Venetoclax is an oral small-molecule inhibitor which selectively binds and inhibits the anti-apoptotic protein B-cell lymphoma 2 (BCL-2), restoring apoptosis in BCL-2 dependent cancer cells. Cytotoxicity has been demonstrated against a variety of tumour cells derived from B-cell and other hematologic malignancies.[2,3]

PHARMACOKINETICS:

Oral Absorption	extent of absorption: >65%[4]; time to peak concentration: 5-8 h; food increases bioavailability[5]	
Distribution	highly protein bound	
	cross blood brain barrier?	no
	volume of distribution	256 to 321 L
	plasma protein binding	>99%[6]
Metabolism	mainly by CYP 3A4/5 *in vitro*[3,6]	
	active metabolite(s)	M27 (weak activity, not likely clinically significant)[2,4]
	inactive metabolite(s)	several (unnamed)[4]
Excretion	first order elimination[2,7]	
	urine	<0.1%
	feces	>99.9% (20.8% as parent drug)
	terminal half life	26 h
	clearance	16.5 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Leukemia, chronic lymphocytic
*Leukemia, acute myeloid

Other uses:
Lymphoma, non-Hodgkin's[7]
Multiple myeloma[7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- ***tumour lysis syndrome*** has been reported with venetoclax; gradual dose escalation (ramp-up) and prophylaxis with hydration and anti-hyperuricemic drugs starting prior to treatment is recommended for all patients[2]
- in patients with ***CLL***, concurrent use of ***strong CYP 3A inhibitors*** is contraindicated during initiation and ramp-up; concurrent use of ***moderate CYP 3A inhibitors*** and ***P-gp inhibitors*** requires venetoclax dose reduction[8]

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- in patients with ***AML***, concurrent use with ***moderate and strong CYP 3A inhibitors*** and ***P-gp inhibitors*** requires venetoclax dose reduction[8]
- immune response to ***vaccines*** may be diminished by venetoclax[2,3,6]
- ***live attenuated vaccines*** should not be administered prior to, during, or after treatment until B-cell recovery has occurred due to risk of enhanced vaccine adverse effects[2,3,6]

Carcinogenicity: Basal cell carcinoma and squamous cell carcinoma of the skin have been reported following venetoclax treatment. Formal carcinogenicity studies have not been done.[2]

Mutagenicity: Not mutagenic in the Ames test; not clastogenic in mammalian *in vitro* and *in vivo* assays.[2]

Fertility: Testicular germ cell depletion was observed in dogs.[2]

Pregnancy: In animal studies, increased rates of postimplantation loss, reduced fetal weight, and dead/resorbed embryos were observed. Pregnancy testing prior to treatment is recommended for females of reproductive potential. Contraception should be used during treatment and for at least 30 days after the last dose of venetoclax.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.

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.[9,10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (25-53%, severe 12-29%)[11,12]
	autoimmune hemolytic anemia (2-8%, severe 2-7%)[12,13]
	febrile neutropenia (5-13%, severe 5-13%)[3,12]
	immune thrombocytopenic purpura (3-5%, severe 3-5%)[11,13]
	leukopenia (5-34%, severe 5-18%)[12,13]
	lymphocytosis (8%, severe 4%)[12]
	lymphopenia (3-25%, severe 3-15%)[12,13]
	neutropenia (43-62%, severe 40-51%)[2,12]
	thrombocytopenia (19-48%, severe 12-29%)[2,12]
cardiac	atrial fibrillation (6%, severe 2%)[13]
eye	cataract (2%, severe 2%)
gastrointestinal	*emetogenic potential:* low[14]
	abdominal pain (14-21%, severe 2-4%)[2,12]
	constipation (10-21%, severe 1%)[2,11]
	diarrhea (29-52%, severe 2-7%)[2,11,12]
	nausea (29-57%, severe ≤2%)[2,3,11,12]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	vomiting (15-23%, severe ≤2%)[2,12]
general disorders and administration site conditions	chills (12%, severe 1%)[12]
	fatigue (21-42%, severe 2-6%)[3,12]
	fluid overload (2%, severe 2%)[11]
	edema, peripheral (11-23%)[3,12]
	pyrexia (16-26%, severe ≤2%)[3,11]
infections and infestations	cellulitis (5%, severe 3%)[12]
	lower respiratory tract infection (3-6%, severe 2%)[12,13]
	nasopharyngitis (9-14%)
	pneumonia (7-10%, severe 4-6%)[11,12]
	sinusitis (11%)
	upper respiratory tract infection (15-48%, severe 1-3%)[2,11]
	urinary tract infection (6-9%, severe 2%)[2,12]
injury, poisoning, and procedural complications	bruising (17%)[12]
	fall (5%, severe 3%)[12]
investigations	ALT increase (15%, severe 3%)[12]
	AST increase (14-20%, severe 2%)[2,12]
	bilirubin increase (2-13%, severe 1-2%)[12,13]
	lactate dehydrogenase increase (5%, severe 2-5%)[2,13]
	weight decrease (5%, severe 2%)[13]
metabolism and nutrition	dehydration (9%, severe 2%)[12]
	hypercalcemia (6%, severe 2%)[12]
	hyperglycemia (10-16%, severe 5-9%)[2,11,12]
	hyperkalemia (15-20%, severe 1-2%)[2,12]
	hyperphosphatemia (12-16%, severe 1-3%)[2,12]
	hyperuricemia (6-13%, severe 2%)[2,12]
	hypoalbuminemia (16%, severe 2%)[12]
	hypocalcemia (5-23%, severe 2-4%)[2,12,13]
	hypokalemia (10-16%, severe 3-7%)
	hyponatremia (19%, severe 7%)[12]
	hypophosphatemia (3-18%, severe 2-13%)[12,13]
	tumour lysis syndrome (3-6%, severe 3-6%)[2,11]; see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (18-19%, severe 1-2%)[2,11]
	back pain (10-18%, severe 2%)[2,12]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	extremity pain (13%)[12]
neoplasms	basal cell carcinoma (7%, severe 5%)
	squamous cell carcinoma of the skin (4-14%, severe 1-9%)[2,12,13]
nervous system	dizziness (13-14%)[2,12]
	headache (11-28%, severe ≤2%)^{2,3}
	syncope (2%, severe 2%)[12]
respiratory, thoracic and mediastinal	cough (13-30%)[3,11]
	dyspnea (15%, severe 2%)[12]
	hypoxia (4%, severe 4%)[12]
	nasal congestion (11%)
skin and subcutaneous tissue	pruritus (14%)
	rash (12%)[12]
vascular	hypertension (6-12%, severe 4-7%)[12,13]

Adapted from standard reference[2] unless specified otherwise.

Hyperuricemia and ***tumour lysis syndrome (TLS)*** may result from cell lysis by venetoclax and may lead to electrolyte disturbances or acute renal failure.[15] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. TLS incidence has been reported as high as 13%, including fatalities. This risk is reduced by dose modification, prophylaxis, and monitoring.[2] Blood chemistry changes consistent with TLS have occurred as early as six hours following the first dose of venetoclax and with each dose increase; prompt management is required. All patients require prophylaxis for tumour lysis syndrome. **Hydration and anti-hyperuricemics should begin at least two days prior to dose initiation**. Patients should be stratified as either low, medium, or high risk based on their absolute lymphocyte count, lymph node size, and comorbidities, including renal function. Increase intensity of hydration and frequency of blood chemistry monitoring with increasing risk level. Hospitalization is recommended for high risk patients and those medium risk patients with CrCl 50-80 mL/minute at initiation and during the early weeks of dose escalation/ramp-up.[2,16] Suggested prophylactic treatment[17]:

- aggressive hydration: 1.5 to 2 L PO, with or without 150 to 200 mL/hr IV, as tolerated[2]
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid pre and post dose at initiation and with each dose escalation[2]
- replace electrolytes as required
- allopurinol 300 mg PO daily x 5-7 days[10]; may need to be continued for up to 5 weeks[13]

Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite.[18] Consider using rasburicase in high risk patients with elevated baseline uric acid levels. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[19]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
azithromycin[20,21]	25% decrease in C_{max} and 35% decrease in AUC of venetoclax	unknown; not consistent with P-glycoprotein (P-gp) inhibition by azithromycin	effect is considered modest; no dose adjustment needed
digoxin[20]	35% increase in C_{max} and 9% increase in AUC of digoxin	P-gp inhibition by venetoclax	administer digoxin at least 6 hours before venetoclax if concurrent administration unavoidable
grapefruit juice[2]	may increase plasma level of venetoclax	may inhibit CYP 3A4 metabolism of venetoclax in the intestinal wall	avoid grapefruit and grapefruit juice for the duration of treatment with venetoclax
ketoconazole[22]	2.3 fold increase in C_{max} and 6.4 fold increase in AUC of venetoclax	strong inhibition of CYP 3A by ketoconazole; possible P-gp and BCRP inhibition	avoid concurrent use if possible; **in CLL,** concurrent administration is contraindicated during venetoclax initiation and ramp-up; after ramp-up phase, reduce venetoclax dose to 100 mg or less **in AML,** concurrent administration during venetoclax initiation and ramp-up requires venetoclax dose reduction is required for days 1-4 (see notes below table); after ramp-up phase, reduce venetoclax dose to 100 mg or less [8]
posaconazole[22]	7.1 fold increase in C_{max} and 8.8 fold increase in AUC of venetoclax	strong inhibition of CYP 3A by posaconazole	avoid concurrent use if possible; **in CLL,** concurrent administration is contraindicated during venetoclax initiation and ramp-up; after ramp-up phase, reduce venetoclax dose to 100 mg or less **in AML**, concurrent administration during venetoclax initiation and ramp-up requires venetoclax dose reduction is required for days 1-4 (see notes below table); after ramp-up phase, reduce venetoclax dose to 100 mg or less [8]

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AGENT	EFFECT	MECHANISM	MANAGEMENT
proton pump inhibitors, H_2 blockers, antacids[7]	no effect on venetoclax pharmacokinetics		
rifampin[2]	42% reduction in venetoclax C_{max} and 71% reduction in venetoclax AUC	strong induction of CYP 3A by rifampin	avoid concurrent use
ritonavir[20]	2.4 fold increase in C_{max} and 7.9 fold increase in AUC of venetoclax	strong CYP 3A and P-gp inhibition by ritonavir	avoid concurrent use if possible; **in CLL,** concurrent administration is contraindicated during venetoclax initiation and ramp-up; after ramp-up phase, reduce venetoclax dose to 100 mg or less **in AML**, concurrent administration during venetoclax initiation and ramp-up requires venetoclax dose reduction is required for days 1-4 (see notes below table); after ramp-up phase, reduce venetoclax dose to 100 mg or less [8]
rituximab[7]	change in venetoclax C_{max} and AUC not statistically significant		
warfarin[23]	18-28% increase in C_{max} and AUC of R-warfarin and S-warfarin	unknown; not believed to be CYP2C9 mediated	increase frequency of INR monitoring and monitor for increased bleeding or other toxicity due to warfarin

Venetoclax is a ***substrate of CYP 3A4***. Concurrent administration with CYP 3A4 inhibitors may increase venetoclax exposure and the risk of venetoclax toxicity, including TLS during initiation and ramp-up phase. **In CLL,** concurrent administration with ***strong CYP 3A inhibitors*** is contraindicated during the venetoclax initiation and ramp-up phase. After ramp-up, if concurrent administration cannot be avoided, reduce venetoclax to 100 mg or less. **In AML**, concurrent administration with a ***strong CYP 3A inhibitor*** during the initiation and ramp-up phase requires venetoclax dose reduction as follows: Day 1 (10 mg); Day 2 (20 mg); Day 3 (50 mg); and Day 4 (100 mg or less). After ramp-up, reduce venetoclax dose to 100 mg or less. If a ***moderate CYP 3A inhibitor*** is used at any time during treatment, reduce venetoclax dose by at least 50%. Resume standard venetoclax dosing two to three days after the CYP 3A inhibitor is discontinued. Dose adjustment is not required for ***weak CYP 3A inhibitors***.[8] Avoid concurrent use with strong and moderate ***CYP 3A inducers*** if possible, as venetoclax exposure may be decreased.[24]

Venetoclax is a ***substrate*** of P-glycoprotein ***(P-gp)***. Concurrent administration with P-gp inhibitors may increase venetoclax exposure. Avoid concurrent administration if possible, particularly during initiation and dose escalation. If concurrent use is unavoidable, a 50% venetoclax dose reduction is suggested.[20] However, some P-gp inhibitors have been reported to decrease venetoclax exposure, suggesting that venetoclax dose adjustment may result in compromised efficacy.[21]

Venetoclax ***inhibits P-gp and BCRP*** *in vitro*. Venetoclax may inhibit intestinal P-gp and BCRP, altering the absorption of coadministered P-gp or BCRP substrates. For substrates of P-gp with a narrow therapeutic index, consider administering at least six hours before venetoclax.[2]

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SUPPLY AND STORAGE:

Oral: AbbVie Corp. supplies venetoclax as 10 mg, 50 mg, and 100 mg film-coated tablets. Store at room temperature.[8]

Additional information: For initiation and ramp-up dosing, venetoclax tablets are available as a 28 day starting pack containing four weekly wallet blister packs in a dose-specific compliance configuration. For maintenance doses, venetoclax tablets are supplied as unit dose blisters and in bulk bottles.[8,25]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

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

Oral:

Suggested initiation and ramp-up schedule* in CLL[8,26-28]:
week 1: ***20 mg PO once daily*** for 7 consecutive days ***starting on day 1***
week 2: ***50 mg PO once daily*** for 7 consecutive days ***starting on day 8***
week 3: ***100 mg PO once daily*** for 7 consecutive days ***starting on day 15***
week 4: ***200 mg PO once daily*** for 7 consecutive days ***starting on day 22***
week 5 and beyond: ***400 mg PO once daily starting on day 29***

in some combination regimens, initiation and ramp-up schedule for venetoclax may start on different day of cycle than above; refer to protocol by which patient is being treated.[8]

*concurrent administration with strong CYP 3A inhibitors is contraindicated during initiation and ramp-up phase; dose adjustment may be required for drug interactions[8]

Suggested initiation and ramp-up schedule* in AML[8,29]:
day 1: ***100 mg PO once***
day 2: ***200 mg PO once***
day 3: ***400 mg PO once***
day 4 and beyond: venetoclax dose is dependent upon the combination agent; refer to protocol by which patient is being treated
400 mg PO once daily (in combination with azacitidine)
or 600 mg PO once daily (in combination with cytarabine)

*dose adjustment may be required for drug interactions

Administer with food.[2] Swallow tablets whole (splitting, crushing, or chewing tablets may reduce venetoclax plasma concentration by up to 50%).[30]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

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

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[8]; NOTE: renal impairment increases TLS risk[2]

CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{\text{N* x (140 - Age) x weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

mild to moderate impairment: no adjustment required

severe impairment: 50% venetoclax dose reduction during initiation and ramp-up phase and at steady state[8]

Dosage in dialysis:

no information found

Children:

no information found

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