

VENCLEXTA

Drug Interactions

A summary of drug interactions and recommendations for management

Indications and Select Important Safety Information

Indications

VENCLEXTA is indicated:

- For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who:
 - are 75 years of age or older, or
 - have comorbidities that preclude the use of intensive induction chemotherapy.

This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- In patients with CLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2 to 3 week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.
- VENCLEXTA poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.
- Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.

Please see additional Important Safety Information throughout this brochure. Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclxexta.pdf.



Effects of other drugs on VENCLEXTA

These tables provide recommendations for management of potential interactions with cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp) inhibitors and examples of drugs that interact with VENCLEXTA

- VENCLEXTA is predominantly metabolized by CYP3A in vitro¹
- P-gp is a transmembrane efflux pump that affects uptake of drugs such as VENCLEXTA from the gut²
- Concomitant use of VENCLEXTA with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax C_{max} and AUC_{inf} which may increase VENCLEXTA toxicities, including the risk of tumor lysis syndrome (TLS)¹
- Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A¹

Dose modifications for managing potential interactions¹

Coadministered Drug	CLL/SLL		AML	
	Initiation and ramp-up phase	Steady daily dose after ramp-up phase	Initiation and ramp-up phase	Steady daily dose after ramp-up phase
Posaconazole	Contraindicated	Reduce VENCLEXTA dose to 70 mg.	Day 1 : 10 mg Day 2 : 20 mg Day 3 : 50 mg Day 4 : 70 mg	Reduce VENCLEXTA dose to 70 mg.
Other strong CYP3A inhibitor	Contraindicated	Reduce VENCLEXTA dose to 100 mg.	Day 1 : 10 mg Day 2 : 20 mg Day 3 : 50 mg Day 4 : 100 mg	Reduce VENCLEXTA dose to 100 mg.
Moderate CYP3A inhibitor	Reduce VENCLEXTA dose by at least 50%.			
P-gp inhibitor	Reduce VENCLEXTA dose by at least 50%.			
Strong CYP3A inducer	Avoid concomitant use of VENCLEXTA with strong CYP3A inducers.			
Moderate CYP3A inducer	Avoid concomitant use of VENCLEXTA with moderate CYP3A inducers.			

- In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities¹
- In patients with AML, adjust the VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities¹
- Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor¹
- Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity

Important Safety Information (cont'd)

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies.
- In patients with AML, baseline neutrophil counts worsened in 97% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy.
- Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

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Examples of CYP3A and P-gp inhibitors/inducers^{3-5*}

Coadministered Drug	Name		
Other strong CYP3A inhibitor	Clarithromycin Conivaptan Diltiazem Indinavir	Itraconazole Ketoconazole Lopinavir	Ritonavir Telaprevir Voriconazole
Moderate CYP3A inhibitor	Aprepitant Cimetidine Ciprofloxacin	Cyclosporine Dronedarone Erythromycin	Fluconazole Isavuconazole Verapamil
P-gp inhibitor	Amiodarone Carvedilol Clarithromycin Cyclosporine	Dronedarone Itraconazole Ketoconazole Quinidine	Ranolazine Ritonavir Verapamil
Strong CYP3A inducer	Carbamazepine Phenytoin	Rifampin St. John's wort	
Moderate CYP3A inducer	Bosentan Efavirenz	Etravirine Modafinil	

*This is not an exhaustive list and is intended only to complement, not replace, clinical judgment during treatment of patients with VENCLEXTA. Please refer to the FDA website for more examples.

Effects of VENCLEXTA on other drugs¹

Warfarin: Closely monitor international normalized ratio (INR) in patients using warfarin concomitantly with VENCLEXTA.

P-gp substrates: Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Important Safety Information (cont'd)

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid pregnancy during treatment.



Important Safety Information (cont'd)

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

- In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- In patients with CLL receiving combination therapy with obinutuzumab, serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%).
- In patients with CLL receiving combination therapy with rituximab, the most frequent serious adverse reaction ($\geq 5\%$) was pneumonia (9%). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), cough (22%), and nausea (21%).
- In patients with CLL/SLL receiving monotherapy, the most frequent serious adverse reactions ($\geq 5\%$) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%).
- In patients with AML receiving combination therapy with azacitidine, the most frequent serious adverse reactions ($\geq 5\%$) were febrile neutropenia, pneumonia (excluding fungal), sepsis (excluding fungal), respiratory failure, and multiple organ dysfunction syndrome. The most common adverse reactions ($\geq 30\%$) of any grade were nausea (58%), diarrhea (54%), constipation (49%), neutropenia (49%), thrombocytopenia (49%), hemorrhage (46%), peripheral edema (46%), vomiting (40%), fatigue (36%), febrile neutropenia (36%), rash (33%), and anemia (30%).
- In patients with AML receiving combination therapy with decitabine, the most frequent serious adverse reactions ($\geq 5\%$) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, cellulitis, and localized infection. The most common adverse reactions ($\geq 30\%$) of any grade were febrile neutropenia (69%), constipation (62%), fatigue (62%), thrombocytopenia (54%), abdominal pain (46%), dizziness (46%), hemorrhage (46%), nausea (46%), pneumonia (excluding fungal) (46%), sepsis (excluding fungal) (46%), cough (38%), diarrhea (38%), neutropenia (38%), back pain (31%), hypotension (31%), myalgia (31%), oropharyngeal pain (31%), peripheral edema (31%), pyrexia (31%), and rash (31%).
- In patients with AML receiving combination therapy with low-dose cytarabine, the most frequent serious adverse reactions ($\geq 5\%$) were febrile neutropenia, sepsis (excluding fungal), hemorrhage, pneumonia (excluding fungal), and device-related infection. The most common adverse reactions ($\geq 30\%$) of any grade were nausea (64%), thrombocytopenia (59%), hemorrhage (49%), febrile neutropenia (46%), neutropenia (46%), diarrhea (44%), fatigue (44%), constipation (33%), and dyspnea (31%).

Drug Interactions

- Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Adjust VENCLEXTA dosage and closely monitor patients for signs of VENCLEXTA toxicities. Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.
- Monitor international normalized ratio (INR) closely in patients receiving warfarin.

Lactation

- Advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.
- Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

AML=acute myeloid leukemia; AUC_{inf} =area under the curve to infinite time;
CLL=chronic lymphocytic leukemia; C_{max} =maximum serum concentration;
SLL=small lymphocytic lymphoma.

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References: 1. VENCLEXTA [package insert]. North Chicago, IL: AbbVie Inc. 2. The International Transporter Consortium. Membrane transporters in drug development. *Nat Rev Drug Discov.* 2010;9(3):215-236. 3. Drug development and drug interactions: table of substrates, inhibitors and inducers. US Food and Drug Administration website. <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>. Updated November 14, 2017. Accessed February 20, 2019. 4. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. *J Am Coll Cardiol.* 2013;61(25): 2495-2502. 5. CRESEMBA [package insert]. Northbrook, IL; Astellas Pharma.

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