VENCLEXTA®
(venetoclax tablets)
DRUG INTERACTIONS

A summary of drug interactions and recommendations for management

Indications and Important Safety Information[1]

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:
  - 75 years or older, or
  - who have comorbidities that preclude use of intensive induction chemotherapy.

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 treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. 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. TLS, including fatal cases, has been reported after a single 20 mg dose.
- In patients with CLL/SLL 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/SLL monotherapy trials. 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.
- In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine. In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine.
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.

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

VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

VENCLEXTA dose should be modified for concomitant use with certain medications[1,2]

VENCLEXTA is metabolized by the CYP3A enzyme; the dose should be reduced when used with P-gp inhibitors or strong or moderate CYP3A inhibitors

This table provides 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.

- **Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in the treatment of CLL/SLL due to the potential for increased risk of TLS**

Dose modifications for managing potential interactions

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 the VENCLEXTA dose to 70 mg	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 70 mg	Reduce the VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitor Ceritinib, clarithromycin, cobicistat, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, ritonavir*	Contraindicated	Reduce the VENCLEXTA dose to 100 mg	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg	Reduce the VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitor Aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, erythromycin, fluconazole, grapefruit juice, imatinib*	Reduce the VENCLEXTA dose by at least 50%			
P-gp inhibitor Amiodarone, cyclosporine, dronedarone, quinidine, ranolazine, verapamil*				

*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.

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma; AML=acute myeloid leukemia.

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Additional instructions for dose modifications for VENCLEXTA[1]

- In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions
- In patients with AML, adjust the VENCLEXTA dose and monitor more frequently for adverse reactions
- 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
- Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A
- Concomitant use of VENCLEXTA with strong CYP3A inducers decreases VENCLEXTA exposure, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers

Dose modifications for patients with severe hepatic impairment

- Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions

Important Safety Information (cont'd)

Tumor Lysis Syndrome (cont'd)

- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

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.
- In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia. In CLL, resume at same or reduced dose. In AML, resume at same dose then reduce duration based on remission status and first or subsequent occurrence of neutropenia. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

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 use effective contraception during treatment and for 30 days after the last dose.

Effects of VENCLEXTA on other drugs[1]

Warfarin

Concomitant use of VENCLEXTA increases warfarin exposure, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA.

P-gp substrates

Concomitant use of VENCLEXTA increases exposure of P-gp substrates, which may increase toxicities of these 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)

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 (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.
- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of the last rituximab were reported in 2% (4/194) of patients.
- **In patients with CLL/SLL receiving monotherapy,** the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥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%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.
- **In patients with AML receiving combination therapy with azacitidine,** the most frequent serious adverse reactions (≥5%) were febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). The most common adverse reactions including hematological abnormalities (≥30%) of any grade were neutrophils decreased (98%), platelets decreased (94%), lymphocytes decreased (91%), hemoglobin decreased (61%), nausea (44%), diarrhea (43%), febrile neutropenia (42%), musculoskeletal pain (36%), pneumonia (33%), fatigue (31%), and vomiting (30%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).
- **In patients with AML receiving combination therapy with decitabine,** the most frequent serious adverse reactions (≥10%) were sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). The most common adverse reactions including hematological abnormalities (≥30%) of any grade were neutrophils decreased (100%), lymphocytes decreased (100%), white blood cells decreased (100%), platelets decreased (92%), hemoglobin decreased (69%), febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

- **In patients with AML receiving combination therapy with low-dose cytarabine,** the most frequent serious adverse reactions (≥10%) were pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). The most common adverse reactions including hematological abnormalities (≥30%) of any grade were platelets decreased (97%), neutrophils decreased (95%), lymphocytes decreased (92%), hemoglobin decreased (63%), nausea (42%), and febrile neutropenia (32%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A 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.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.
- 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.

Lactation

- Advise nursing women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

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

Hepatic Impairment

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

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

References: 1. VENCLEXTA [package insert]. North Chicago, IL: AbbVie Inc. **2.** For healthcare professionals: FDA's examples of drugs that interact with CYP enzymes and transporter systems. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems. Updated March 8, 2024. Accessed April 5, 2024.

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