Indication

VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who:

• are age 75 years 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.

Select Important Safety Information

• Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA. 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. 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.

• Grade 3 or 4 neutropenia occurred in patients treated with VENCLEXTA. Monitor blood counts and for signs of infection; manage as medically appropriate.

• 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.

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

• Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs.

• VENCLEXTA may cause embryo-fetal harm. Advise females of reproductive potential to avoid pregnancy during treatment.

Please see additional Important Safety Information on pages 8 and 9. Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.
Recommended dosage for AML

- Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS
- Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing
- The dose of VENCLEXTA depends upon the combination agent
- The VENCLEXTA dosing schedules are shown below and on the next page
- Initiate azacitidine or decitabine or low-dose cytarabine on Day 1

VENCLEXTA IN COMBINATION WITH AZACITIDINE OR DECITABINE
Dosing in AML includes a 3-day ramp-up to safely attain the recommended daily dose

DAILY DOSING SCHEDULE INCLUDING RAMP-UP

Study M14-358: VENCLEXTA in combination with azacitidine or decitabine
- Patients received VENCLEXTA via a daily ramp-up to a final 400 mg once daily dose. During the VENCLEXTA ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring
- Azacitidine at 75 mg/m² was administered either intravenously or subcutaneously on Days 1–7 of each 28-day cycle beginning on Cycle 1 Day 1
- Decitabine at 20 mg/m² was administered intravenously on Days 1–5 of each 28-day cycle beginning on Cycle 1 Day 1
- Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity; see azacitidine full Prescribing Information for more details
- Dose reductions for decitabine were not implemented in the clinical trial

Recommended dosage for AML (cont’d)

VENCLEXTA IN COMBINATION WITH LOW-DOSE CYTARABINE
Dosing in AML includes a 4-day ramp-up to safely attain the recommended daily dose

DAILY DOSING SCHEDULE INCLUDING RAMP-UP

Study M14-387: VENCLEXTA in combination with low-dose cytarabine
- Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose. During the VENCLEXTA ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring
- Cytarabine at a dose of 20 mg/m² was administered subcutaneously once daily on Days 1–10 of each 28-day cycle beginning on Cycle 1 Day 1
- Dose reduction for low-dose cytarabine was not implemented in the clinical trials

Select Important Safety Information
Tumor Lysis Syndrome
- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- 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. Intermittent 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.
Risk assessment and prophylaxis for tumor lysis syndrome

Patients treated with VENCLEXTA may develop tumor lysis syndrome (TLS). Assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS.

Acute myeloid leukemia
- All patients should have white blood cell count <25 × 10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required.
- Collect blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistry for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing the VENCLEXTA starting dose.

TLS in VENCLEXTA clinical trials

Tumor lysis syndrome is an important risk when initiating treatment in patients with AML. The incidence of TLS was 3% (2/61) with VENCLEXTA in combination with low-dose cytarabine and with the use of dose ramp-up schedule in addition to standard prophylaxis and monitoring measures. All events were laboratory TLS, and all patients were able to reach the target dose.

Select Important Safety Information

Neutropenia
- 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.
- For patients with rapid increases in blast count, consider increased monitoring and dose interruptions or permanent discontinuations of VENCLEXTA.

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 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.

Dose modifications for VENCLEXTA in AML

Dose modifications based on toxicities for AML
- Monitor blood counts frequently through resolution of cytopenias.
- Management of some adverse reactions may require dose interruptions or permanent discontinuation of VENCLEXTA.

The following table shows the dose modification guidelines for hematologic toxicities.

<table>
<thead>
<tr>
<th>Event*</th>
<th>Occurrence</th>
<th>Action</th>
</tr>
</thead>
</table>
| Grade 4 neutropenia with or without fever or infection, or Grade 4 thrombocytopenia | Occurrence prior to achieving remission | Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission.

First occurrence after achieving remission and lasting at least 7 days | Delay subsequent treatment cycle of VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine until the neutrophil count >1.0 × 10^9/L and the platelet count >50 × 10^9/L. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine or decitabine or low-dose cytarabine.

Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer | Delay subsequent treatment cycle of VENCLEXTA and azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, VENCLEXTA therapy may be resumed at the same dose and the duration reduced by 7 days for each subsequent cycle.

*Adverse reactions were graded using NCI Common Terminology Criteria for Adverse Events version 4.0.

Select Important Safety Information

Adverse Reactions

- In patients with AML receiving combination therapy with azacitidine, the most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia (excluding fungal), sepsis (excluding fungal), respiratory failure, and multisystem organ dysfunction syndrome. The most common adverse reactions (≥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 (≥5%) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, cellulitis, and localized infection. The most common adverse reactions (≥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 (≥5%) were febrile neutropenia, sepsis (excluding fungal), hemorrhage, pneumonia (excluding fungal), and device-related infection. The most common adverse reactions (≥30%) of any grade were nausea (54%), thrombocytopenia (59%), hemorrhage (49%), febrile neutropenia (46%), neutropenia (46%), diarrhea (44%), fatigue (44%), constipation (33%), and dyspnea (31%).
Instructions for taking VENCLEXTA

Advise patients:

- To take VENCLEXTA exactly as prescribed and not to change their dose or to stop taking VENCLEXTA unless they are told to do so by their doctor.
- To be adequately hydrated every day when taking VENCLEXTA to reduce the risk of TLS. The recommended volume is 6 to 8 glasses (approximately 56 ounces total) of water each day. Patients should drink water starting 2 days before and on the day of the first dose, and every time the dose is increased.
- Of the importance of keeping scheduled appointments for blood work or other laboratory tests.
- To take VENCLEXTA orally once daily with a meal and water at approximately the same time each day.
- That VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken.
- If a patient misses a dose by less than 8 hours from the time it is usually taken, the patient should take the missed dose right away and take the next dose as usual.
- If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should take the next dose at the usual time.
- If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the next day.

Select Important Safety Information

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.

Dose modifications for use with a strong or moderate CYP3A inhibitor or P-gp inhibitor

- Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax Cmax and AUC, which may increase VENCLEXTA toxicities, including the risk of TLS.
- In patients with AML, adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities.
- Resume the VENCLEXTA dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

In AML patients: management of potential VENCLEXTA interactions with CYP3A and P-gp Inhibitors

<table>
<thead>
<tr>
<th>Coadministered drug</th>
<th>Initiation and ramp-up phase</th>
<th>Steady daily dose (after ramp-up phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg</td>
<td>Reduce VENCLEXTA dose to 70 mg</td>
</tr>
<tr>
<td>Other strong CYP3A inhibitor</td>
<td>Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 150 mg</td>
<td>Reduce the VENCLEXTA dose to 100 mg</td>
</tr>
<tr>
<td>Moderate CYP3A inhibitor</td>
<td>Reduce the VENCLEXTA dose by at least 50%</td>
<td></td>
</tr>
<tr>
<td>P-gp inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 signs of toxicity.

Select Important Safety Information

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.
Indication and Important Safety Information

Indication
VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who:
- are age 75 years or older, or
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Important Safety Information

Tumor Lysis Syndrome
- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- VENCLEXTA poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistry 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.

Neutropenia
- 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).

Infections
- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients closely for signs 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 use effective contraception during treatment with VENCLEXTA.
- Advise females of reproductive potential to discontinue breastfeeding during treatment with VENCLEXTA.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone
- In a randomized trial (BELLE-1, 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 AML receiving combination therapy with azacitidine, the most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia (excluding fungal), sepsis (excluding fungal), respiratory failure, and multiple organ dysfunction syndrome. The most common adverse reactions (≥20%) of any grade were nausea (58%), diarrhea (54%), constipation (49%), neutropenia (49%), thrombocytopenia (49%), hemophagocytosis (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 (≥5%) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, cellulitis, and localized infection. The most common adverse reactions (≥20%) of any grade were nausea (64%), 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 (≥5%) were febrile neutropenia, sepsis (excluding fungal), hemorrhage, pneumonia (excluding fungal), and device-related infection. The most common adverse reactions (≥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 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 CYP3A and P-gp substrates. If concomitant use is unavoidable, separate use of VENCLEXTA and the inhibitor by 2-3 hours.
- 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.

Contact your AbbVie or Genentech representative
to learn more about VENCLEXTA or ask questions about treatment initiation