Select Important Safety Information

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA. Assess all patients for risk, including evaluation of tumor burden and comorbidities, and provide 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 ramp-up phase, and requires VENCLEXTA dose adjustment.

- 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 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.

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

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

Please see additional Important Safety Information throughout. Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.
### Study design

**Primary endpoint:**
- OS (overall survival)
- CR (complete remission)
- CR+CRh (complete remission with partial hematologic recovery)

**Select secondary endpoints:**
- HR (hazard ratio)
- mOS (median overall survival)
- CI (confidence interval)
- P (p-value)

**VIALE-A:**
- A randomized (2:1), double-blind, placebo-controlled, multicenter, phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine (VEN+AZA, N=286) vs placebo with azacitidine (PBO+AZA, N=145) in adults with newly diagnosed or relapsed/refractory AML who were ≥75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy. The primary endpoint was overall survival (OS). Following VENCLEXTA dose ramp-up, patients received VENCLEXTA 400 mg daily or placebo in combination with azacitidine 75 mg/m² on Days 1–7 per cycle until disease progression or unacceptable toxicity.

**VIALE-C:**
- A randomized phase 3 trial that evaluated VENCLEXTA in combination with low-dose cytarabine (LDAC) in patients with AML who were ≥75 years of age and who had comorbidities that precluded the use of intensive induction chemotherapy. The primary endpoint was overall survival (OS). Efficacy of VENCLEXTA+LDAC regimen was based on CR rate and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. In the VIALE-C trial, VENCLEXTA+LDAC did not significantly improve OS vs PBO+LDAC.³

### Important Safety Information

**Tumor Lysis Syndrome**
- Tumor lysis syndrome (TLS), 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. 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.
- 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.
- Assess all patients for risk and provide prophylactic measures.
- Monitor complete blood counts throughout the treatment period. For severe neutropenia, interrupt dosing or reduce duration based on remission status and occurrence. 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 based on occurrence.

**Dose modifications**
- Dose-reduce for concomitant use with P-gp inhibitors or strong or moderate CYP3A inhibitors or for severe hepatic impairment.

**Management**
- Manage hematologic ARs with dose modifications based on remission status.
- Manage non-hematologic ARs with dose modifications.

*See Table 6 in the full Prescribing Information for dose modifications.*

**Note:**
- This content is not a substitute for independent medical judgement.
- All patients should be monitored for TLS.
- Use prophylactic measures for TLS.

**Additional important information:**
- Please see accompanying full Prescribing Information or visit www.rxbv.com/pdf/venclexta.pdf.

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**Using This Guide**

This guide provides PI-based direction for initiation, assessment, and management for select VENCLEXTA regimens, including safety, dosing, dose adjustments, and management of select cytopenias.
**Initiation**

Reduce VENCLEXTA dose to 70 mg

400

4

1

Day 2

Day 3

Day 4

Complete the pretreatment checklist for tumor lysis syndrome (TLS)

- Confirm that the patient’s white blood cell count is less than 25 \times 10^9/L. Cytoreduction prior to treatment may be required.
- Provide appropriate prophylactic measures including adequate hydration and anti-hyperuricemics prior to first VENCLEXTA dose, and continue during ramp-up phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistries 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 (eg, circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment LDH levels, or reduced renal function), consider additional measures, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

- In the VIALE-A (VEN+AZA) and M14-358 (VEN+AZA or VEN+DEC) trials, during the VENCLEXTA ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring.

- 1.1% of patients who followed the 3-day dose ramp-up and TLS prophylaxis and monitoring measures experienced TLS in the VIALE-A study.

Initiate AML dosing with a 3-day dose ramp-up for VEN+AZA or DEC

VENCLEXTA is taken orally once daily in combination with AZA or DEC.

**Important Safety Information (cont’d)**

- 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 and for at least 30 days after the last dose.

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

<table>
<thead>
<tr>
<th>Initiation and ramp-up phase</th>
<th>Steady daily dose (after ramp-up phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
</tr>
<tr>
<td></td>
<td>70 mg</td>
</tr>
<tr>
<td>Other strong CYP3A inhibitor</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
</tr>
</tbody>
</table>

For VEN+LDAC dosing, please see Section 2.3 of the full Prescribing Information.

LDH= lactate dehydrogenase; DEC= decitabine; V= intravenous; LDAC= low-dose cytarabine.

VENCLEXTA is FDA-APPROVED REGARDLESS OF MUTATION STATUS

No need to wait for biomarker test results.
A tolerable, manageable, and predictable adverse reaction profile

No additional warnings or precautions for VENCLEXTA were observed in the AML trials.

The safety profile of VEN+AZA was consistent with the known side effect profile of both agents.

Adverse reactions (≥10%) in patients with AML who received VEN+AZA with a difference between arms of ≥5% for all grades or ≥2% for Grade 3 or 4 reactions compared with PBO+AZA.

### Adverse reaction by body system

<table>
<thead>
<tr>
<th>Body system</th>
<th>Adverse reaction</th>
<th>VEN+AZA (N=283)</th>
<th>PBO+AZA (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Feverl neutropenia</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>27</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>Sepsis (excluding fungal)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>17</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Patients who received at least one dose of either treatment.
†Includes multiple adverse reaction terms.

### Hematologic laboratory abnormalities

New or worsening Grade 3 or 4 hematologic laboratory abnormalities in VIALE-A with a difference between arms of ≥2% for VEN+AZA vs PBO+AZA, respectively: neutrophils decreased 98% vs 81%, platelets decreased 88% vs 80%, lymphocytes decreased 71% vs 39%, hemoglobin decreased 57% vs 52%.


Patients maintained treatment with VEN in the VEN+AZA arm for a median of 7.6 months.

#### Duration of exposure and occurrence of adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>VEN+AZA (N=283)</th>
<th>PBO+AZA (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of exposure to VEN or PBO</td>
<td>7.6 months (range: 0.1-30.7)</td>
<td>4.3 months (range: 0.1-24.0)</td>
</tr>
<tr>
<td>Median number of cycles</td>
<td>7.0 cycles (range: 1.0-30.0)</td>
<td>4.5 cycles (range: 1.0-26.0)</td>
</tr>
</tbody>
</table>

### Rate of serious adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>VEN+AZA (N=283)</th>
<th>PBO+AZA (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%) occurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most frequent adverse reaction(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious ARs</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>Fatal ARs</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>VEN+AZA</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation, reduction, and interruption rates of VEN or PBO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ars leading to permanent drug discontinuation</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Most frequent AR leading to dose reductions</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ars leading to dose interruptions</td>
<td>72</td>
<td>57</td>
</tr>
</tbody>
</table>

*Of patients who achieved a morphologic leukemia-free state of response or better.

**Please see important Safety Information throughout. Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.**
Responses for CR and CRh were reached at different times throughout treatment; management of Grade 4 neutropenia or thrombocytopenia differs before and after remission is achieved. 

In VIALE-A, bone marrow assessment was conducted following Cycle 1 treatment. Once bone marrow assessment confirmed a remission, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50,000/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. 

When treating AML with VENCLEXTA regimens, monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status.

*See facing page for information to help manage patients who experience cytopenias and non-hematologic toxicities

**Defined as less than 5% leukemia blasts with cytopenia.

See page 3 of this guide for select secondary endpoint results (CR and CR+CRh).

The median time to first response of CR or CRh was 1.0 months (range: 0.6-14.3 months) with VEN+AZA treatment; some patients achieved CR/CRh in later cycles. 

Secondary endpoint: CR+CRh by initiation of Cycle 2:

- 40% (n=114/286) with VEN+AZA (95% CI: [34, 46]; P<0.001)

In an exploratory post hoc analysis of CR+CRh in the VEN+AZA ITT population:

- 47% (134/286) achieved CR+CRh by the beginning of Cycle 3
- 50% (143/286) achieved CR+CRh by the beginning of Cycle 4

For any occurrence of Grade 3 or 4 non-hematologic toxicities

RESUME VENCLEXTA at the same dose upon resolution to Grade 1 or baseline level

INTERRUPT VENCLEXTA if not resolved with supportive care

RESUME VENCLEXTA regimen and monitor blood counts

If not resolved with supportive care, REDUCE TREATMENT CYCLE by 7 days for each subsequent cycle (eg, for 2nd occurrence, VENCLEXTA would be dosed for 21 days of a 28-day cycle)

STAY ON VENCLEXTA REGIMEN: In most instances, do not interrupt the VENCLEXTA regimen due to cytopenias

For subsequent occurrences (lasting at least 7 days)

RESUME VENCLEXTA therapy at 400 mg

in combination with azacitidine or decitabine upon resolution to Grade 1 or 2

REDUCE TREATMENT CYCLE by 7 days for each subsequent cycle (eg, for 2nd occurrence, VENCLEXTA would be dosed for 21 days of a 28-day cycle)

For 1st occurrence (lasting at least 7 days)

RESUME VENCLEXTA therapy at 400 mg

in combination with azacitidine or decitabine upon resolution to Grade 1 or 2 and resume 28-day treatment cycle

**Recommend bone marrow evaluation.

†Remission is defined as achieving a CR or CRh.

‡Dose may vary based on drug-drug interactions or severe hepatic impairment.

For VEN+LDAC dosing, please see Section 2.5 of the full Prescribing Information.

Recommended dose modifications for cytopenias and non-hematologic adverse reactions in AML

Managing Grade 4 neutropenia with or without fever or infection, or Grade 4 thrombocytopenia

In an exploratory post hoc analysis of VIALE-A:

- 75% of patients in remission (139/186) had at least 1 pause in dosing lasting ≥7+ days

**Variable involvement in 21% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥3%) being pneumonia (4%), sepsis (excluding fungal) (3%), and hemorrhage (2%).

Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.
Advise patients:

- Of the risks and review the Medication Guide with patients before they start VENCLEXTA.
- Of the potential risk of TLS, particularly at treatment initiation, during the ramp-up phase, and with resumption after an interruption and to immediately report any signs and symptoms associated with this event (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their health care provider (HCP) for evaluation.
- Let patients know that they can expect their HCP to:
  - Do tests to check for TLS before they start taking VENCLEXTA.
  - Do blood tests to check for TLS when they first start treatment and during treatment with VENCLEXTA.
  - Delay or decrease their dose, or stop treatment with VENCLEXTA if they have side effects.

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.

To take VENCLEXTA orally once daily with a meal and water at approximately the same time each day.

To swallow tablets whole, and to not chew, crush, or break the tablets.

To contact their HCP immediately if they develop a fever or any signs of infection. Advise patients of the need of the importance of keeping scheduled appointments for blood work or other laboratory tests.

To contact their HCP immediately if they develop a fever or any signs of infection. Advise patients of the need of the importance of keeping scheduled appointments for blood work or other laboratory tests.

To take VENCLEXTA exactly as prescribed and not to change their dose or stop taking VENCLEXTA unless they are told to do so by their doctor.

Missed dose:

- 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.

Important Safety Information (cont’d)

Adverse Reactions (cont’d):

- In patients with AML receiving combination therapy with decitabine, the most frequent serious adverse reactions (≥10%) were sepsis (excluding fungal; 44%), febrile neutropenia (38%), and pneumonia (31%). The most common adverse reactions (≥30%) of any grade were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (44%), 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.

- 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 (≥30%) of any grade were platelets decreased (97%), neutrophils decreased (95%), lymphocytes decreased (92%), hemoglobin decreased (63%), nausea (43%), 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.

- 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 at least 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 signs of adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

References:

VENCLEXTA PATIENT SUPPORT PROGRAMS

VENCOMPASS®

Providing product-related support for patients taking VENCLEXTA

Patients will be matched with a VENCOMPASS Nurse for dedicated 1:1 support throughout their treatment.

This program is intended to provide product-related education and support to your patients taking VENCLEXTA for an approved use during the ramp-up phase and throughout their therapy. VENCOMPASS does not provide medical advice and will direct patients to speak with their healthcare provider for all treatment-related questions. Information provided is based on the full Prescribing Information and Medication Guide for VENCLEXTA.

For VENCOMPASS, please visit www.VENCLEXTA.com or call (844) 9-COMPASS/(844) 926-6727 for more information.

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(888) 249-4918
Genentech-Access.com/VENCLEXTA

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The Genentech Oncology Co-pay Assistance Program provides financial assistance to eligible commercially insured patients to help with their co-pays, co-insurance, or other out-of-pocket (OOP) costs

(855) MY-COPAY/(855) 692-6729
CopayAssistanceNow.com

Visit venclextahcp.com/aml or contact a rep to learn more

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