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

# 1L AML treatment with an approved VENCLEXTA combination[1]

# DOSING AND ADMINISTRATION GUIDE

**National Comprehensive Cancer Network® (NCCN®) Recommendations* for Venetoclax Combination-Based Regimens[2]**

- For patients ≥60 years of age who are not candidates for intensive induction chemotherapy in first-line AML

| For patients **with or without actionable mutations†** | |
|---|---|
| | **VENETOCLAX + AZACITIDINE:** THE ONLY CATEGORY 1 PREFERRED |
| | **VENETOCLAX + DECITABINE:** CATEGORY 2A PREFERRED |
| | **VENETOCLAX + LOW-DOSE CYTARABINE:** CATEGORY 2A RECOMMENDED |

*See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML, Version 3.2021, for complete recommendations. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

†Actionable mutations include *IDH1/2* and *FLT3*.

1L=first line; *IDH*=isocitrate dehydrogenase; *FLT*=fms-like tyrosine kinase.

## Select Important Safety Information

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA. 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, 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 reduction.
- 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.

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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[1]

- Evaluate TLS risk in all patients and provide prophylactic measures
- 3-day dose ramp-up for VEN+HMA or 4-day dose ramp-up for VEN+LDAC. Monitor blood chemistries
- Dose-reduce for concomitant use with P-gp inhibitors or strong or moderate CYP3A inhibitors or for severe hepatic impairment

### Assessment[1]

- Assess and monitor for common and serious adverse reactions (ARs)
- Bone marrow assessment as clinically indicated
  - In AML clinical trials, bone marrow assessment was conducted following Cycle 1 treatment to assess for remission

### Management[1]

- Manage hematologic ARs with dose modifications based on remission status*
  - May include VENCLEXTA pause or change in VENCLEXTA duration
- Manage non-hematologic ARs with dose modifications*

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

This content is not a substitute for independent medical judgment.

PI=Prescribing Information; TLS=tumor lysis syndrome; P-gp=P-glycoprotein; CYP3A=cytochrome P450 3A.

## 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 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.

**Please see additional Important Safety Information throughout.**
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VIALE-A studied newly diagnosed AML patients who were ≥75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy[1]

### 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 AML who were ≥75 years of age, or had comorbidities (based on at least one of the following criteria: baseline ECOG performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity) that precluded the use of intensive induction chemotherapy. Patients received VENCLEXTA 400 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule or placebo in combination with azacitidine 75 mg/m$^2$ on Days 1-7 of each 28-day cycle beginning on Cycle 1, Day 1 until disease progression or unacceptable toxicity. The primary endpoint was overall survival.

### Select clinical endpoints[1,3,4]

**Primary endpoint:**

**OS**
OVERALL SURVIVAL

**Select secondary endpoints:**

- CR
- CR+CRh
- CR+CRh by initiation of Cycle 2

### Efficacy was based on OS, measured from the date of randomization to death from any cause[1]

**Overall survival, median number of months and (95% CI):** 14.7 (11.9, 18.7) for VEN+AZA vs 9.6 (7.4, 12.7) for AZA; HR=0.66 (0.52, 0.85); *P*<0.001

**Response rates:**

- **CR (95% CI):** 37% (31, 43) for VEN+AZA vs 18% (12, 25) for AZA; *P*<0.001
- **CR+CRh (95% CI):** 65% (59, 70) for VEN+AZA vs 23% (16, 30) for AZA; *P*<0.001

CR was defined as absolute neutrophil count (ANC) >1,000/microliter, platelets >100,000/microliter, RBC transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

### VIALE-C phase 3 trial: VEN + low-dose cytarabine (LDAC)

Efficacy of VEN+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, VEN+LDAC did not significantly improve OS versus placebo plus LDAC.**[1]

### M14-358 phase 1b trial: VEN+AZA or decitabine (DEC)

VENCLEXTA was studied in a non-randomized, open-label trial that evaluated the efficacy of VENCLEXTA in combination with AZA (N=84) or DEC (N=31) in patients with newly diagnosed AML. Overall survival benefit was not evaluated for VENCLEXTA in combination with decitabine.[1]

ECOG=Eastern Cooperative Oncology Group; CLcr=creatinine clearance; CR=complete remission; CRh=complete remission with partial hematologic recovery; mOS=median overall survival; CI=confidence interval; HR=hazard ratio; RBC=red blood cell.

## Important Safety Information (cont'd)

### Neutropenia

- 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. 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 dose.

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**VENCLEXTA IS FDA-APPROVED REGARDLESS OF MUTATION STATUS**

## Complete the pretreatment checklist for tumor lysis syndrome (TLS)[1]

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 and continue during ramp-up to reduce risk of TLS:

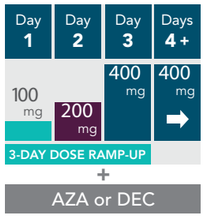
- ☐ **Confirm** that the patient's white blood cell count is **less than 25 × 10⁹/L.** Cytoreduction prior to treatment may be required
- ☐ **Provide appropriate prophylactic measures** including adequate hydration and anti-hyperuricemic agents prior to first VENCLEXTA dose, and continue during ramp-up 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 or 4-day dose ramp-up for VEN regimens[1]

### VENCLEXTA is taken orally once daily in combination with AZA, DEC, or LDAC

- Continue treatment until disease progression or unacceptable toxicity




- If dosing **in combination with azacitidine**, administer azacitidine at 75 mg/m², IV or subcutaneous, once daily on Days 1–7 of each 28-day cycle beginning on Cycle 1, Day 1
- If dosing **in combination with decitabine**, administer decitabine at 20 mg/m², IV, once daily on Days 1–5 of each 28-day cycle beginning on Cycle 1, Day 1

- If dosing **in combination with low-dose cytarabine**, follow the 4-day dose ramp-up schedule, for VENCLEXTA (Day 1: 100mg, Day 2: 200 mg, Day 3: 400 mg, Day 4+: 600 mg) and administer low-dose cytarabine at 20 mg/m² subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1, Day 1

LDH=lactate dehydrogenase; IV=intravenous.

## 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.**



## Reduce the VENCLEXTA dose for drug-drug interactions and hepatic impairment[1]

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including risk of TLS. See below for dose modifications based on drug-drug interactions.[1]

### Dose modifications with select inhibitors[1]

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.

| | Initiation and ramp-up phase | | | | Steady daily dose (after ramp-up phase) |
|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 | |
| Posaconazole | 10 mg | 20 mg | 50 mg | 70 mg | Reduce VENCLEXTA dose to 70 mg |
| Other strong CYP3A inhibitor* | 10 mg | 20 mg | 50 mg | 100 mg | Reduce VENCLEXTA dose to 100 mg |

**For moderate CYP3A† and P-gp inhibitors,‡ reduce the VENCLEXTA dose by at least 50%**

*Clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, telaprevir, voriconazole.[5,6§]
†Aprepitant, ciprofloxacin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil.[5,6§]
‡Amiodarone, carvedilol, clarithromycin, cyclosporine, dronedarone, itraconazole, ketoconazole, quinidine, ranolazine, ritonavir, verapamil.[5,6§]
§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.

### Ensure additional measures for other potential drug interactions[1]

- ☐ **Reduce the VENCLEXTA dose** and monitor more frequently for adverse reactions
- ☐ **Avoid grapefruit products, Seville oranges, and starfruit** during treatment with VENCLEXTA, as they contain inhibitors of CYP3A
- ☐ **Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers.** Concomitant use of VENCLEXTA with strong CYP3A inducers decreases VENCLEXTA exposure, which may decrease VENCLEXTA efficacy
- ☐ **Monitor international normalized ratio (INR) more frequently in patients using warfarin** concomitantly with VENCLEXTA. Concomitant use of VENCLEXTA increases warfarin exposure, which may increase the risk of bleeding
- ☐ **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. Concomitant use of VENCLEXTA increases exposure of P-gp substrates, which may increase toxicities of these substrates

### Dose modifications for patients with severe hepatic impairment[1]

- 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

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## A tolerable, manageable, and predictable safety profile[1]

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 | | | | | |
|---|---|---|---|---|---|
| | | VEN+AZA (N=283) | | PBO+AZA (N=144) | |
| **Body system** | **Adverse reaction** | **All Grades (%)** | **Grade 3 or 4 (%)** | **All Grades (%)** | **Grade 3 or 4 (%)** |
| **Gastrointestinal disorders** | Nausea | 44 | 2 | 35 | <1 |
| | Diarrhea† | 43 | 5 | 33 | 3 |
| | Vomiting† | 30 | 2 | 23 | <1 |
| | Stomatitis† | 18 | 1 | 13 | 0 |
| | Abdominal pain† | 18 | <1 | 13 | 0 |
| **Blood and lymphatic system disorders** | Febrile neutropenia | 42 | 42 | 19 | 19 |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain† | 36 | 2 | 28 | 1 |
| **General disorders and administration site conditions** | Fatigue† | 31 | 6 | 23 | 2 |
| | Edema† | 27 | <1 | 19 | 0 |
| **Vascular disorders** | Hemorrhage† | 27 | 7 | 24 | 3 |
| | Hypotension† | 12 | 5 | 8 | 3 |
| **Metabolism and nutrition disorders** | Decreased appetite† | 25 | 4 | 17 | <1 |
| **Skin and subcutaneous tissue disorders** | Rash† | 25 | 1 | 15 | 0 |
| **Infections and infestations** | Sepsis† (excluding fungal) | 22 | 22 | 16 | 14 |
| | Urinary tract infection† | 16 | 6 | 9 | 6 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea† | 18 | 4 | 10 | 2 |
| **Nervous system disorders** | Dizziness† | 17 | <1 | 8 | <1 |

*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 (≥10%)** 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%.

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## Duration of exposure and serious adverse reactions[1,3,7]

Patients maintained treatment with VEN in the VEN+AZA arm for a median of 7.6 months[1]

**Median duration of exposure to VEN or PBO**

| VEN+AZA[1] | PBO+AZA[7] |
|---|---|
| **7.6** months (range: <0.1-30.7) | **4.3** months (range: 0.1-24.0) |

**Median number of cycles**

| VEN+AZA[3] | PBO+AZA[3] |
|---|---|
| **7.0** cycles (range: 1.0-30.0) | **4.5** cycles (range: 1.0-26.0) |

| Rate of serious adverse reactions | | | | |
|---|---|---|---|---|
| | VEN+AZA (N=283)[1] | | PBO+AZA (N=144)[3,7] | |
| | (%) occurrence | Most frequent adverse reaction(s) | (%) occurrence | Most frequent adverse reaction(s) |
| **Serious ARs** | 83 | ≥5%: febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), hemorrhage (6%) | 73 | ≥5%: pneumonia (22%), febrile neutropenia (10%), sepsis (8%) |
| **Fatal ARs** | 23 | ≥2%: pneumonia (4%), sepsis (excluding fungal; 3%), hemorrhage (2%) | 20 | ≥2%: sepsis (4%), pneumonia (2%) |

| Discontinuation, reduction, and interruption rates of VEN or PBO | | | | |
|---|---|---|---|---|
| | VEN | VEN+AZA | PBO | PBO+AZA |
| **ARs leading to permanent drug discontinuation** | 24 | ≥2%: sepsis (excluding fungal; 3%), pneumonia (2%) | 20 | ≥2%: sepsis (4%), pneumonia (3%), thrombocytopenia (2%), malignant neoplasm progression (2%) |
| **Most frequent AR leading to dose reductions** | 3[7] | pneumonia (0.7%) | 4 | pneumonia (1%) |
| **ARs leading to dose interruptions** | 72 | ≥5%: febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), sepsis (excluding fungal; 11%), thrombocytopenia (10%) | 57 | ≥5%: pneumonia (13%), neutropenia (10%) |

- In the VEN+AZA arm, among patients who achieved bone marrow clearance of leukemia, 53% (114/216)* underwent dose interruptions for ANC <500/microliter[1,8]
- Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50,000/microliter[1]
- Azacitidine was resumed on the same day as VENCLEXTA or placebo following interruption[1]
- Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity[1]

*Of patients who achieved a morphologic leukemia-free state of response or better.[8]
AR=adverse reaction.

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## 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[1]

**In AML clinical trials, 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.[1]**

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

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

In VIALE-A, 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[1,4]

**Secondary endpoint: CR+CRh by initiation of Cycle 2[4]**

- **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[4]:**

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

ITT=intention to treat.

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

## 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.

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## Recommended dose modifications for cytopenias and non-hematologic adverse reactions in AML[1]

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

**Is the patient in remission?*†**

**NO**

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

**YES**

❚❚ **DELAY SUBSEQUENT** cycle of VENCLEXTA regimen and monitor blood counts

| For 1st occurrence (lasting at least 7 days) | For subsequent occurrences (lasting at least 7 days) |
|---|---|
| ▶ **RESUME VENCLEXTA** therapy at 400 mg‡ in combination with azacitidine or decitabine or at 600 mg‡ in combination with low-dose cytarabine upon resolution to Grade 1 or 2 and resume 28-day treatment cycle | ▶ **RESUME VENCLEXTA** therapy at 400 mg‡ in combination with azacitidine or decitabine or at 600 mg‡ in combination with low-dose cytarabine upon resolution to Grade 1 or 2<br>▼ **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)* |

**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[4]

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

❚❚ **INTERRUPT VENCLEXTA** if not resolved with supportive care

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

*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.

## Important Safety Information (cont'd)

### Adverse Reactions

- **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%).

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## Advise patients[1]:

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 their risk of getting 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

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 for periodic monitoring of blood counts and that dosing may be paused

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[1]

**If a patient misses a dose by <u>less than 8 hours</u> 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 <u>more than 8 hours</u>**

The patient should not take the missed dose and should take the next dose at the usual time.

**If a <u>patient vomits</u> following dosing**

No additional dose should be taken that day. The next prescribed dose should be taken at the usual time the next day.

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## 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; 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.
- **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 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: 1.** VENCLEXTA [package insert]. North Chicago, IL: AbbVie Inc. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2021. © National Comprehensive Cancer Network, Inc 2021. All rights reserved. Accessed March 30, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **3.** DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. **4.** Data on file, ABVRRTI71211. AbbVie Inc. **5.** 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 March 6, 2020. Accessed December 1, 2020. **6.** CRESEMBA [package insert]. Northbrook, IL: Astellas Pharma. **7.** Data on file, ABVRRTI71272. AbbVie Inc. **8.** Data on file, ABVRRTI71500. AbbVie Inc.

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

## VENCLEXTA PATIENT SUPPORT PROGRAMS

VENCOMPASS®

### Providing one-to-one product-related support for patients taking VENCLEXTA®.

This program can provide one-to-one support to help patients taking VENCLEXTA to follow the treatment plan you've prescribed.* VENCOMPASS Nurses† may help educate patients and may help them feel more prepared for upcoming appointments with their care team.

*For an approved use only.

†VENCOMPASS Nurses are provided by AbbVie and do not work under the direction of the patient's healthcare professional (HCP) or give medical advice. They are trained to direct patients to speak with their HCP for treatment-related advice, including further referrals.

For VENCOMPASS, please visit **www.VENCLEXTA.com**
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**Please see Important Safety Information throughout.**
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