VENCLEXTA® (venetoclax tablets)
For first-line use in acute myeloid leukemia (AML)

INITIATION CHECKLIST AND MONITORING GUIDE FOR HEALTHCARE PROFESSIONALS

A stepwise tool for initiating and monitoring AML patients on treatment with VENCLEXTA

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 throughout this guide.
Please see accompanying full Prescribing Information or visit **www.rxabbvie.com/pdf/venclexta.pdf.**

abbvie | Genentech
A Member of the Roche Group

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

Initiating Therapy

Key considerations before starting VENCLEXTA

VENCLEXTA is an oral treatment that targets BCL-2 to help restore the process of apoptosis. VENCLEXTA is indicated in combination with azacitidine, 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 who have comorbidities that preclude use of intensive induction chemotherapy.

Before administering the first dose of VENCLEXTA, confirm that all considerations listed below have been addressed and note any concerns or follow-up that may be required.

Treatment considerations	
☐	**Review and assess patient medical history and current medications.** • VENCLEXTA may interact with some drugs and cause side effects • Have your patient inform you of their current medications, including over-the-counter medicines, vitamins, and herbal supplements
☐	**Baseline blood chemistry levels have been evaluated.** • Focus on potassium, uric acid, phosphorus, calcium, and creatinine • Correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA
☐	**White blood cell (WBC) counts do not exceed 25 x 10^9/L.** • Cytoreduction prior to treatment may be required
☐	**Assess patient-specific tumor lysis syndrome (TLS) risk factors.** • Premedicate with anti-hyperuricemics and ensure adequate hydration (6 to 8 glasses of water/day, starting 2 days before and on the day of the first dose, and every time the dose is increased) • Implement more intensive TLS prophylaxis and monitoring for patients with reduced renal function (CLcr <80 mL/min) • 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 (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 VENCLEXTA starting dose • Employ more intensive measures as overall risk increases
☐	**Assess baseline absolute neutrophil counts (ANC).** • Neutrophil counts may worsen in patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine • Advise patients of the need for periodic monitoring • Advise patients to contact their HCP immediately if they develop a fever or any signs of infection

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. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.

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

Key considerations when initiating VENCLEXTA

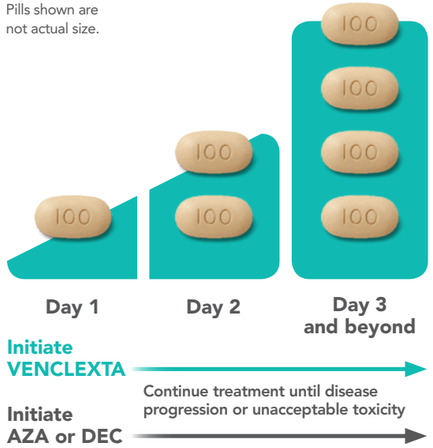
Dosing and administration of VENCLEXTA is dependent upon the combination agent with which VENCLEXTA is administered. Use the following table to determine the recommended dosing schedule (including ramp-up) for your patient.

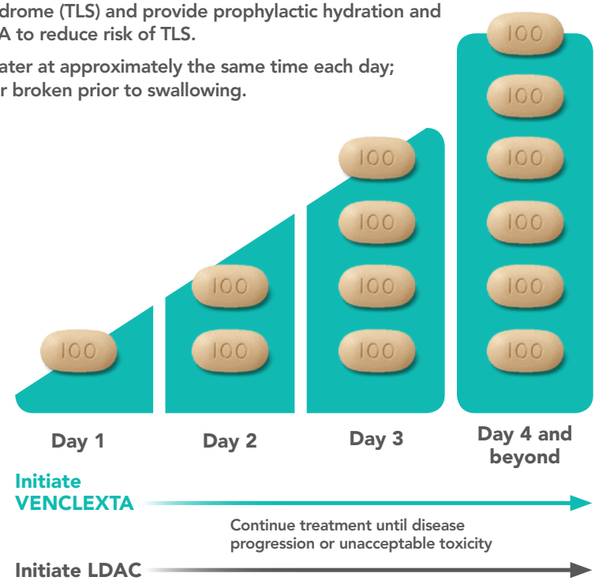
DAILY DOSING SCHEDULE INCLUDING RAMP-UP FOR VEN + AZA* or DEC,† or VEN + LDAC‡

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; tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Pills shown are not actual size.





No biomarker or cytogenetic testing required prior to initiation

*In study M14-358, which evaluated the efficacy and safety of VENCLEXTA, AZA 75 mg/m^2 was administered (IV or SC) on Days 1-7 of each 28-day cycle, beginning on Cycle 1, Day 1.
†In study M14-358, which evaluated the efficacy and safety of VENCLEXTA, DEC 20 mg/m^2 was administered (IV) on Days 1-5 of each 28-day cycle, beginning on Cycle 1, Day 1.
‡In study M14-387, which evaluated the efficacy and safety of VENCLEXTA, LDAC 20 mg/m^2 was administered (SC) on Days 1-10 of each 28-day cycle, beginning on Cycle 1, Day 1.

Additional AML clinical study data

Patients initiated VENCLEXTA via a daily ramp-up to final dose depending on the combination agent. During the VENCLEXTA ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity (see full azacitidine Prescribing Information). Dose reduction for decitabine was not implemented in the clinical trial. Dose reduction for low-dose cytarabine was not implemented in the clinical trials.

Additional guidance on administration of VENCLEXTA with other medications

VENCLEXTA may have certain effects on other drugs. Assess any other medications that your patient is taking and use the chart below for additional treatment instructions.

Administration instructions for patients taking certain other medications	
☐	**If patient is being treated with a P-gp substrate:** • Avoid concomitant use of VENCLEXTA with a P-gp substrate. Concomitant use of VENCLEXTA increases P-gp substrate exposure, which may increase toxicity of these substrates • If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before administration of VENCLEXTA
☐	**If patient is being treated with warfarin:** • Closely monitor international normalized ratio (INR) in patients using warfarin concomitantly with VENCLEXTA. Concomitant use with VENCLEXTA increases warfarin exposure, which may increase the risk of bleeding

IV=intravenous; SC=subcutaneous.

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

Dosing Adjustments

Key dosing modifications with concomitant medications

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS, and require dose adjustment. See below for dose modifications based on concomitant use with strong or moderate CYP3A or P-gp inhibitors, and concomitant use with strong or moderate CYP3A inducers.

Dose modifications for managing potential interactions

Coadministered Drug	Initiation and ramp-up phase	Steady daily dose after ramp-up phase
Posaconazole	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	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	Reduce the VENCLEXTA dose by at least 50%.	
P-gp inhibitor		
Strong CYP3A inducer	Avoid concomitant use of VENCLEXTA with strong CYP3A inducers.	
Moderate CYP3A inducer	Avoid concomitant use of VENCLEXTA with moderate CYP3A inducers.	

- Adjust the VENCLEXTA dose and closely monitor 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.
- 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
- Instruct patients to avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA as they contain inhibitors of CYP3A.

Key instructions for missed doses

Inform patients about the appropriate responses if they miss a dose of VENCLEXTA.

Circumstance leading to missed dose	Recommended patient response
Patient misses a dose by less than 8 hours from the time it is usually taken	• Patient should take the missed dose right away and take the next dose as usual
Patient misses a dose by more than 8 hours from the time it is usually taken	• Patient should not take the missed dose and should take the next dose at the usual time
Patient vomits following a dose	• No additional dose should be taken that day. The next prescribed dose should be taken at the usual time the next day

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

Key recommended dose modifications for managing toxicities*

Management of some adverse reactions may require dose interruptions or permanent discontinuation. See below for recommended dose adjustments based on time of occurrence.

Dose modifications for 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 lasting at least 7 days	☐ Delay subsequent treatment cycle of VENCLEXTA and combination agent ☐ Monitor blood counts ☐ Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia ☐ Resume VENCLEXTA therapy at the same dose with combination agent once toxicity resolves to Grade 1 or 2
Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	☐ Delay subsequent treatment cycle of VENCLEXTA and combination agent ☐ Monitor blood counts ☐ Administer G-CSF if clinically indicated for neutropenia ☐ Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose and reduce duration by 7 days for each subsequent cycle

Closely monitor your patients for signs of VENCLEXTA toxicities. Monitor blood counts frequently through resolution of cytopenias.

*Adverse reactions were graded using NCI CTCAE version 4.0.

Important Safety Information (cont'd)

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 and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

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

Monitoring Treatment Responses

Key considerations for measuring efficacy

To evaluate the effectiveness of treatment, monitor blood count and patient progress throughout treatment. Use the tables below to track and determine if your patient has achieved complete remission (CR) or complete remission with partial hematological recovery (CRh).

CR is defined as:	
☐	Absolute neutrophil count >1,000/microliter
☐	Platelets >100,000/microliter
☐	Red blood cell transfusion independence
☐	Bone marrow contains <5% blasts
☐	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease

CRh is defined as:	
☐	Bone marrow contains <5% blasts
☐	No evidence of disease
☐	**Partial recovery of peripheral blood counts** • Platelets >50,000/microliter • ANC >500/microliter

In the AML clinical studies:

- Median time to first CR or CRh for patients treated with VENCLEXTA in combination with azacitidine was 1.0 month (range: 0.7 to 8.9 months)
- Median time to first CR or CRh for patients treated with VENCLEXTA in combination with decitabine was 1.9 months (range: 0.8 to 4.2 months)
- Median time to first CR or CRh for patients treated with VENCLEXTA in combination with low-dose cytarabine was 1.0 month (range: 0.8 to 9.4 months)

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

Monitoring Side Effects

Key considerations when monitoring for side effects

VENCLEXTA may cause serious side effects. Monitor complete blood counts throughout the treatment period and use the chart below to track patient side effects and adverse events.

Most common adverse reactions (≥30%) in combination with azacitidine or decitabine or low-dose cytarabine

- ☐ Nausea
- ☐ Diarrhea
- ☐ Thrombocytopenia
- ☐ Constipation
- ☐ Neutropenia
- ☐ Febrile neutropenia
- ☐ Fatigue
- ☐ Vomiting
- ☐ Peripheral edema
- ☐ Pyrexia
- ☐ Pneumonia
- ☐ Dyspnea
- ☐ Hemorrhage
- ☐ Anemia
- ☐ Rash
- ☐ Abdominal pain
- ☐ Sepsis
- ☐ Back pain
- ☐ Myalgia
- ☐ Dizziness
- ☐ Cough
- ☐ Oropharyngeal pain
- ☐ Hypotension

All potential VENCLEXTA side effects are not listed. Use the space below to note additional side effects that your patient experiences:

_____

_____

_____

_____

_____

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 avoid pregnancy during treatment.

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

Indication and Important Safety Information

Indication

VENCLEXTA® (venetoclax tablets) 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.

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. 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 and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

Immunization

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

Embryo-Fetal Toxicity

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

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 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 (≥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%).

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

- **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 (64%), thrombocytopenia (59%), hemorrhage (49%), febrile neutropenia (46%), neutropenia (46%), diarrhea (44%), fatigue (44%), constipation (33%), and dyspnea (31%).

Drug Interactions

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

Lactation

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

Females and Males of Reproductive Potential

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

Hepatic Impairment

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

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

IMPORTANT INFORMATION

VENCOMPASS®

Dedicated VENCLEXTA support from oncology nurses

(844) 9-COMPASS/(844) 926-6727 | www.VENCLEXTA.com

VENCLEXTA® venetoclax | ACCESS SOLUTIONS®

Your resource for reliable, effective access and reimbursement support

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

BioOncology® Co-pay Card

Helping eligible patients with out-of-pocket costs for VENCLEXTA

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

Contact your AbbVie or Genentech representative

to learn more about VENCLEXTA
or ask questions about treatment initiation.

Reference: 1. VENCLEXTA [package insert]. North Chicago, IL: AbbVie Inc.

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

abbvie | Genentech
A Member of the Roche Group

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

Distributed and marketed by AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064
Marketed by Genentech USA, Inc., 1 DNA Way, South San Francisco, CA 94080-4990