KEY INFORMATION TO HELP YOU SUCCESSFULLY INITIATE AND MANAGE YOUR PATIENTS' AML TREATMENT

A GUIDE TO TREATING WITH VENCLYXTO

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[Placeholder for indication statement, as per local regulation, and placeholder for safety statement, as per local regulation.]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

AML=acute myeloid leukaemia.

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USING THIS TOOL

This resource is designed to provide information on key areas that can help optimise treatment, including:

- Introduction to VENCLYXTO for AML
- Considerations before starting VENCLYXTO treatment
- How to start VENCLYXTO treatment, including the AML ramp-up dosing schedule
- Key safety information and dosing/schedule modifications during VENCLYXTO treatment
- Drug-drug interactions and VENCLYXTO dose modifications

This tool is for electronic use by healthcare professionals only. It must not be distributed in any format to patients.

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VENCLYXTO IS A FIRST-IN-CLASS, POTENT, AND SELECTIVE BCL-2 INHIBITOR

VENCLYXTO has been found in vitro to work synergistically with combination agents[1,2]

- VENCLYXTO in combination with a hypomethylating agent (AZA or DEC) is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy[3]
- VENCLYXTO in combination with LDAC is indicated for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy[4]
- VENCLYXTO is the first approved BCL-2 inhibitor that targets a key hallmark of cancer by inducing apoptosis[3,5]
- VENCLYXTO can be started without the requirement to wait for mutational or cytogenetic results[3]

AZA=azacitidine; BCL-2=B-cell lymphoma 2; DEC=decitabine; LDAC=low-dose cytarabine.

REFERENCES: 1. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood.* 2019;133(1):7-17. **2.** Ramsey HE, Fischer MA, Lee T, et al. A novel MCL1 inhibitor combined with venetoclax rescues venetoclax-resistant acute myelogenous leukemia. *Cancer Discov.* 2018;8(12):1566-1581. **3.** VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **4.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020. **5.** Lagadinou ED, Sach A, Callahan K, et al. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. *Cell Stem Cell.* 2013;12(3):329-341.

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VIALE-A: A PHASE 3 TRIAL COMPARING VENCLYXTO PLUS AZA VERSUS AZA ALONE IN PATIENTS WHO WERE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY[1]

A randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of VENCLYXTO in the first-line treatment of AML[1]

VENCLYXTO plus AZA reached its dual primary efficacy endpoints,* achieving statistically significant overall survival and remission rates. Patients treated with VENCLYXTO plus AZA experienced[1]:

Maximised overall survival vs AZA alone

- 5.1-month increase in median overall survival vs AZA alone (14.7 months vs 9.6 months, respectively [95% CI: 0.52-0.85; *P*<0.001])[1]

Maintained remission for longer

- More than DOUBLE the remission rate vs AZA alone (66% CR+CRi† vs 28%, respectively; *P*<0.001)[1,2]
- Longer remission rates among patients who achieved CR+CRi vs AZA alone (17.5 months vs 13.4 months, respectively)[1‡]

*The dual primary efficacy endpoints of the study were overall survival, measured from the date of randomisation to death from any cause, and composite complete remission rate (CR+CRi).[1]
†CR=absolute neutrophil count (ANC) >1000/microlitre, platelets >100,000/microlitre, RBC transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease. CRi=CR with incomplete blood count recovery (ANC <1000/microlitre or platelets <100,000/microlitre).[1]
‡Median duration of response is from Kaplan-Meier estimate and was defined as time from first response of CR or CRi to the first date of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression, whichever occurred earlier.[1]

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematological recovery.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med.* 2020;387(7):617-629.

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VIALE-C: A PHASE 3 TRIAL COMPARING VENCLYXTO PLUS LDAC VERSUS LDAC ALONE IN PATIENTS WHO WERE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY[1,2]

A randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of VENCLYXTO in the first-line treatment of AML[1,2]

At the time of the primary analysis, patients treated with VENCLYXTO plus LDAC experienced:

- A 3.1-month increase in median overall survival vs LDAC alone (7.2 months vs 4.1 months, respectively; HR=0.75 [95% CI: 0.52-1.07]; *P*=0.11 [not significant])—a 25% risk reduction of mortality[1]
- Increased remission rate (CR+CRi) vs LDAC alone (48% vs 13%, respectively; *P*<0.001)[1]*
  – By Cycle 2, 34% of patients achieved remission and 14% achieved remission after Cycle 2[1†]
- Median time to first response[‡] was 1.0 month[2]

*This *P* value is descriptive.
†The rate of CR+CRi after Cycle 2 was calculated by subtracting the rate of CR+CRi by Cycle 2 from the total CR+CRi rate.
‡Median time to first response (CR or CRh).[2]

HR=hazard ratio.

REFERENCES: 1. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020.

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M14-358: A PHASE 1/2 TRIAL EVALUATING VENCLYXTO PLUS DEC IN PATIENTS WHO WERE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY

A nonrandomised study in the first-line treatment of AML

In M14-358, VENCLYXTO plus DEC demonstrated a high remission rate. Patients treated with VENCLYXTO plus DEC experienced:

- A 74% remission rate (CR+CRi) (95% CI: 55-88)

REFERENCE: VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021.

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VENCLYXTO AML DOSAGE AND ADMINISTRATION

Step-wise patient management approach[1,2]

1 PREPARE

- Evaluate TLS risk in all patients and provide prophylactic measures (eg, hydration and anti-hyperuricaemics)

2 INITIATE

- 3-4 day dose ramp-up
- Monitor blood chemistry pre and 6-8 hours post each ramp-up dose

3 ADJUST

- Test blood counts regularly and monitor for AEs
- Manage AEs with dose modifications.
  For grade 4 cytopaenia, consider bone marrow assessment:

Pre-remission

- **Maintain dose and cycle length**

Post-remission

- **Delay next cycle** to allow for count recovery
- 21-day cycle for recurrent cytopaenia

In VIALE-A and VIALE-C, bone marrow assessments were conducted following Cycle 1 of treatment to assess for remission.

4 CONTINUE

- **Continue treatment** until disease progression or unacceptable toxicity

First response of CR or CRi as late as Month 10 with VENCLYXTO plus AZA treatment.

If CYP3A inhibitors (eg, antifungals) are required temporarily, **reduce to appropriate VENCLYXTO dose.**

AE=adverse event; CYP3A=cytochrome P450 3A; TLS=tumour lysis syndrome.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020.

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MANAGEMENT OF TLS IN PATIENTS TREATED WITH VENCLYXTO

PROPHYLAXIS MEASURES[1]

PRIOR TO INITIATION	DURING RAMP-UP PERIOD AND AFTER REACHING RECOMMENDED DOSE
• All patients should have a WBC count <25 × 10^9/L prior to initiation of VENCLYXTO • Cytoreduction prior to treatment may be required • All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of VENCLYXTO • Monitor blood chemistries for TLS at pre-dose • Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLYXTO	• Monitor blood chemistries for TLS at 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose • All patients should be adequately hydrated and receive anti-hyperuricaemic agents during the dose titration phase • Consider additional measures, including increasing laboratory monitoring and reducing VENCLYXTO starting dose for patients with risk factors for TLS, eg: – Circulating blasts – High burden of leukaemia involvement in bone marrow – Elevated pretreatment LDH levels – Reduced renal function

In the AML trials, the rates of reported events of laboratory or clinical TLS were low (<6%)[1,2]

TLS RATES

LDH=lactate dehydrogenase; WBC=white blood cell.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020. **3.** Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood.* 2020;135(24):2137-2145.

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MANAGEMENT OF TLS IN PATIENTS TREATED WITH VENCLYXTO

TLS RATES[1-3]

VEN+AZA (VIALE-A) (n=283)	VEN+LDAC (VIALE-C) (n=142)	VEN+DEC (M14-358) (n=31)
3 patients (1.1%)	8 patients (6%)	0 patients
1 clinical TLS	4 clinical TLS (2 reported as serious AEs) 4 laboratory TLS	

- All cases of TLS occurred during the dose ramp-up period

VEN=VENCLYXTO.

TLS RATES

LDH=lactate dehydrogenase.

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DOSING RECOMMENDATIONS FOR PATIENTS WITH AML

Rapid dose ramp-up safely attains the recommended daily dose[1,2]

VENCLYXTO is administered orally once daily with the dose increasing per the titration schedule, which depends on the combination agent

- Start VENCLYXTO and the combination agent on the same first day of the treatment cycle

VEN+AZA | VEN+LDAC | VEN+DEC

Recommendations for starting VENCLYXTO in special populations

SPECIAL POPULATIONS

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020.

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DOSING RECOMMENDATIONS FOR PATIENTS WITH AML

DOSING SCHEDULE: VEN+AZA[1]

	DAY 1	DAY 2	DAY 3	DAYS 4-7	DAYS 8-28	SUBSEQUENT CYCLES
	3-Day Dose Titration Phase					
VENCLYXTO oral tablet (mg/day)	100	200	400	400	400	**400**
AZA IV or SC (mg/m²/day)	75	75	75	75	——	**Days 1-7**

- VENCLYXTO should be taken whole with a meal and water at approximately the same time each day
- VENCLYXTO is available in 10 mg, 50 mg, and 100 mg film-coated tablets

IV=intravenous; SC=subcutaneous.

Please see section 4.2 of the VENCLYXTO SmPC for additional information.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020

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DOSING SCHEDULE: VEN+LDAC[1,2]

	DAY 1	DAY 2	DAY 3	DAY 4	DAYS 5-10	DAYS 11-28	SUBSEQUENT CYCLES
	4-Day Dose Titration Phase						
VENCLYXTO oral tablet (mg/day)	100	200	400	600	600	600	**600**
LDAC SC (mg/m^2/day)	20	20	20	20	20	——	**Days 1-10**

- VENCLYXTO should be taken whole with a meal and water at approximately the same time each day
- VENCLYXTO is available in 10 mg, 50 mg, and 100 mg film-coated tablets

SC=subcutaneous.

Please see section 2.3 of the VENCLEXTA Prescribing Information for additional information.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020

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DOSING RECOMMENDATIONS FOR PATIENTS WITH AML

DOSING SCHEDULE: VEN+DEC[1]

	DAY 1	DAY 2	DAY 3	DAYS 4-5	DAYS 6-28	SUBSEQUENT CYCLES
	3-Day Dose Titration Phase					
VENCLYXTO oral tablet (mg/day)	100	200	400	400	400	**400**
DEC IV (mg/m^2/day)	20	20	20	20	——	**Days 1-5**

- VENCLYXTO should be taken whole with a meal and water at approximately the same time each day
- VENCLYXTO is available in 10 mg, 50 mg, and 100 mg film-coated tablets

IV=intravenous.

Please see section 4.2 of the VENCLYXTO SmPC for additional information.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020

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RECOMMENDATIONS FOR STARTING VENCLYXTO IN SPECIAL POPULATIONS[1]

Patients with hepatic impairment: Dosing considerations

- For severe hepatic impairment, reduce the dose of VENCLYXTO by at least 50% throughout treatment
- These patients should be monitored more closely for signs of toxicity

Patients with renal impairment: Dosing considerations

SEVERE RENAL IMPAIRMENT (CrCl ≥15 mL/min and <30 mL/min)	**REDUCED RENAL FUNCTION** (CrCl <80 mL/min)
Only administer VENCLYXTO if the benefit outweighs the risk. Monitor patients closely.	More intensive prophylaxis and monitoring may be required to reduce the risk of TLS at initiation and during the dose titration phase.

- No dose adjustment is needed for patients with mild or moderate renal impairment

CrCl=creatinine clearance.

REFERENCES: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021. **2.** VENCLEXTA. Prescribing information. AbbVie Inc; 2020

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RECOMMENDATIONS FOR THE MANAGEMENT OF CONCOMITANT DRUG INTERACTIONS

CYP3A INHIBITORS

If a CYP3A inhibitor, such as an antifungal, must be used, follow the recommended dosing modifications

- If given concomitantly with a CYP3A inhibitor, the VENCLYXTO dose must be modified at initiation, and during or after the dose-titration phase. Refer to the SmPC for more information
- Concomitant use with strong or moderate CYP3A inhibitors increases VENCLYXTO exposure and may increase the risk for TLS at initiation and during the dose titration phase and for other toxicities
- Resume the VENCLYXTO dose used prior to initiating the CYP3A inhibitor 2-3 days after discontinuation of the inhibitor
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment, as they contain inhibitors of CYP3A

CYP3A AND P-GP INDUCERS

When using VENCLYXTO, avoid strong or moderate CYP3A and P-gp inducers

- Strong or moderate CYP3A inducers may decrease VENCLYXTO efficacy. Refer to the SmPC for more information
- If concomitant use of P-gp substrates is unavoidable, patients should be monitored closely for signs of toxicities

WARFARIN

Concomitant use of warfarin:

- Closely monitor international normalised ratio (INR) in patients taking warfarin

P-gp=permeability glycoprotein.

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GUIDELINES FOR THE MANAGEMENT OF CONCOMITANT USE WITH CYP3A, P-GP, AND BCRP INHIBITORS AND CYP3A INDUCERS

INHIBITOR/INDUCER	INITIATION AND DOSE-TITRATION PHASE		STEADY DAILY DOSE (AFTER DOSE-TITRATION PHASE)
Strong CYP3A inhibitor (itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir)	Day 1: 10 mg Day 2: 20 mg	Day 3: 50 mg Day 4: 100 mg or less	Reduce VENCLYXTO dose to 100 mg or less
Moderate CYP3A inhibitor (ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil)	Reduce VENCLYXTO dose by at least 50%		
P-gp (rifampin) and BCRP inhibitor	Should be avoided; however, if must be used, patients should be monitored closely for signs of toxicities		
Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin) and moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	Should be avoided		

CONSIDERATIONS FOR USE WITH CYP3A INHIBITORS

BCRP=breast cancer resistance protein.

REFERENCE: VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. 2021.

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GUIDELINES FOR THE MANAGEMENT OF CONCOMITANT USE WITH CYP3A AND P-GP INHIBITORS AND CYP3A INDUCERS[1,2]

INHIBITOR/INDUCER	INITIATION AND DOSE-TITRATION PHASE		STEADY DAILY DOSE (AFTER DOSE-TITRATION PHASE)
Posaconazole	Day 1: 10 mg Day 2: 20 mg	Day 3: 50 mg Day 4: 70 mg	Reduce VENCLYXTO dose to 70 mg
Strong CYP3A inhibitor (eg, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir)	Day 1: 10 mg Day 2: 20 mg	Day 3: 50 mg Day 4: 100 mg	Reduce VENCLYXTO dose to 100 mg or less
Moderate CYP3A inhibitor (eg, ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil)	Reduce VENCLYXTO dose by at least 50%		
P-gp (eg, rifampin)	Should be avoided; however, if must be used, patients should be monitored closely for signs of toxicities		
Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin)	Should be avoided		
Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	Should be avoided		

CONSIDERATIONS FOR USE WITH CYP3A INHIBITORS

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GUIDELINES FOR THE MANAGEMENT OF CONCOMITANT USE WITH CYP3A AND P-GP INH

CONSIDERATIONS FOR USE WITH CYP3A INHIBITORS

- Concomitant use with strong or moderate CYP3A inhibitors increases VENCLYXTO exposure
- Monitor patients closely for signs of toxicities that may require further dose adjustments
- Resume the VENCLYXTO dose used prior to initiating the CYP3A inhibitor 2-3 days after discontinuation of the inhibitor

Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)

Should be avoided

CONSIDERATIONS FOR USE WITH CYP3A INHIBITORS

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GUIDELINES FOR THE MANAGEMENT OF HAEMATOLOGIC TOXICITIES

Management of some adverse reactions may require dose interruptions or permanent discontinuation of VENCLYXTO[1,2]

MANAGING GRADE 4 NEUTROPAENIA OR THROMBOCYTOPAENIA*

BEFORE REMISSION IS ACHIEVED	AFTER REMISSION IS ACHIEVED
In most instances, VENCLYXTO and AZA, LDAC, or DEC cycles should not be interrupted due to cytopaenias prior to achieving remission.	Delay subsequent treatment cycle of VENCLYXTO and AZA, LDAC, or DEC and monitor blood counts. Administer granulocyte colony stimulating factor (G-CSF) if clinically indicated for neutropenia.
	FOR FIRST OCCURRENCE Delay subsequent cycle of VENCLYXTO in combination with AZA, LDAC, or DEC and monitor blood counts. Administer G-CSF if clinically indicated for neutropaenia. Upon resolution to grade 1 or 2, resume VENCLYXTO at the same dose in combination with AZA, LDAC, or DEC.
	FOR SUBSEQUENT OCCURRENCES LASTING 7 DAYS OR LONGER Delay subsequent cycle of VENCLYXTO in combination with AZA, LDAC, or DEC and monitor blood counts. Administer G-CSF if clinically indicated for neutropaenia. Upon resolution to grade 1 or 2, resume VENCLYXTO at the same dose in combination with AZA, LDAC, or DEC, and reduce VENCLYXTO duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days. Refer to the AZA, LDAC, or DEC prescribing information for additional information.

Patients were assessed for remission by conducting a bone marrow test at the end of Cycle 1 and during treatment as needed

*Grade 4 neutropaenia (ANC <500/µL) with or without fever or infection; or Grade 4 thrombocytopaenia (platelet count <25,000/µL).

ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor.

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SAMPLE TREATMENT PLAN

An example of what the treatment journey might look like for you and your patient

1 PREPARE

A treatment decision is made for a newly diagnosed, adult patient with AML who is ineligible for intensive chemotherapy. VENCLYXTO is started immediately after the following is done:

- Patient risk factor assessments for TLS and additional measures, if needed
- Blood chemistry tests for potassium, uric acid, phosphorus, calcium, and creatinine
- WBC count evaluations
- Adequate hydration and initiation of anti-hyperuricaemic agents, which should be continued during the dose-titration period

2 INITIATE

After the patient is adequately hydrated for 2 days, initiation of the dose ramp-up begins on the same first day as the combination agent.

- Dose modifications are made for concomitant drug interactions
- The patient has a full understanding of how to take the medication
- Blood chemistries are monitored for TLS 6-8 hours after each dose and 24 hours after reaching the recommended dose

3 ADJUST

Maintain monitoring of blood chemistries and clinical management that began prior to VENCLYXTO and perform bone marrow assessments at the end of Cycle 1 and during treatment as needed.

- Patient risk factors for TLS are monitored per label recommendations
- If any haematologic toxicities arise, the proper dose modifications take place

The assessment of remission is done by conducting a bone marrow test at the end of Cycle 1 and during treatment as needed if the VENCLYXTO combination regimen dosing schedule or dose is adjusted.

4 CONTINUE

Treatment is continued until disease progression or unacceptable toxicity.

See this treatment plan in action. View VENCLYXTO patient profiles.

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SAMPLE TREATMENT PLAN

[Placeholder for indication statement, as per local regulation, and placeholder for safety statement, as per local regulation.]

See this treatment plan in action. View VENCLYXTO patient profiles.

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