VENCLYXTO INITIATION GUIDE IN CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

[Placeholder for indication statement, based on affiliate local label]

▼ 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.

Please see the VENCLYXTO (venetoclax) Summary of Product Characteristics for full product information.

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Using this guide

This guide provides the recommendations for TLS assessment, prophylaxis, laboratory monitoring, and dosing for VENCLYXTO in patients with CLL based on information from the approved SmPC.

Tumour lysis syndrome[1]

- TLS, including fatal events and renal failure requiring dialysis, has occurred in patients with CLL, including after a single 20-mg dose of VENCLYXTO in the post-marketing setting
- VENCLYXTO can cause rapid tumour reduction, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLYXTO and at each dose increase
- To prevent and reduce the risk of TLS, follow the recommendations for risk assessment, prophylactic measures, dose-titration schedule, laboratory monitoring, and drug interactions*

TLS risk assessment and prevention[1]

1. Assess TLS risk

- Perform tumour burden assessment, including radiographic evaluation (eg, CT scan), for all patients
- Assess patient-specific factors

LOW TUMOUR BURDEN	MEDIUM TUMOUR BURDEN	HIGH TUMOUR BURDEN
All LN <5 cm **AND** ALC <25 × 10^9/L	Any LN 5 cm to <10 cm **OR** ALC ≥25 × 10^9/L	Any LN ≥10 cm **OR** Any LN ≥5 cm and ALC ≥25 × 10^9/L

The risk of TLS is a continuum based on multiple factors and comorbidities, particularly including:
- **Reduced renal function (CrCl <80 mL/min)**
- **Tumour burden, including radiographic evaluation (eg, CT scan)**
- **Splenomegaly**

- All patient comorbidities should be considered for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital

2. Administer prophylaxis

Administer hydration: Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase and at each subsequent dose increase.

Administer anti-hyperuricaemics: Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLYXTO. For patients with high tumour burden, consider rasburicase if baseline uric acid levels are elevated.

3. Assess blood chemistry labs per monitoring schedule

- **Assess pre-dose blood chemistry labs**
  - Potassium
  - Uric acid
  - Phosphorous
  - Calcium
  - Creatinine
- **Correct pre-existing abnormalities prior to initiating VENCLYXTO**
- **Assess labs as scheduled; promptly review results and manage abnormalities**

*More intensive measures (IV hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases.

SmPC=Summary of Product Characteristics; CT=computed tomography; LN=lymph node; ALC=absolute lymphocyte count; CrCl=creatinine clearance; IV=intravenous.

See prophylaxis and monitoring calendar for low and medium tumour burden patients on page 3 and for high tumour burden patients on pages 4-5.

Please see the VENCLYXTO (venetoclax) Summary of Product Characteristics for full product information.

Low or *Medium* tumour burden* patients with CLL

5-week venetoclax initiation calendar[1]

Instruct patients to DRINK WATER DAILY starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase.†

Consider additional IV hydration for patients with medium tumour burden.

Assess blood chemistry labs per monitoring schedule.

Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLYXTO.

	Outpatient						
WEEK 1 20 mg (10 10)	**DAY 1†‡** Labs • Pre-dose • Post-dose: ◦ 6-8h ◦ 24h; Dose 20 mg	**DAY 2** Dose 20 mg	**DAY 3** Dose 20 mg	**DAY 4** Dose 20 mg	**DAY 5** Dose 20 mg	**DAY 6** Dose 20 mg	**DAY 7** Dose 20 mg
WEEK 2 50 mg (50)	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 6-8h ◦ 24h; Dose 50 mg	**DAY 2** Dose 50 mg	**DAY 3** Dose 50 mg	**DAY 4** Dose 50 mg	**DAY 5** Dose 50 mg	**DAY 6** Dose 50 mg	**DAY 7** Dose 50 mg
WEEK 3 100 mg (100)	**DAY 1†** Labs§ • Pre-dose; Dose 100 mg	**DAY 2** Dose 100 mg	**DAY 3** Dose 100 mg	**DAY 4** Dose 100 mg	**DAY 5** Dose 100 mg	**DAY 6** Dose 100 mg	**DAY 7** Dose 100 mg
WEEK 4 200 mg (100 100)	**DAY 1†** Labs§ • Pre-dose; Dose 200 mg	**DAY 2** Dose 200 mg	**DAY 3** Dose 200 mg	**DAY 4** Dose 200 mg	**DAY 5** Dose 200 mg	**DAY 6** Dose 200 mg	**DAY 7** Dose 200 mg
WEEK 5 400 mg (100 100 100 100)	**DAY 1†** Labs§ • Pre-dose; Dose 400 mg	**DAY 2** Dose 400 mg	**DAY 3** Dose 400 mg	**DAY 4** Dose 400 mg	**DAY 5** Dose 400 mg	**DAY 6** Dose 400 mg	**DAY 7** Dose 400 mg

*In patients with medium tumour burden, for first doses of 20 mg and 50 mg, consider hospitalisation for patients with CrCl <80 mL/min; see high-risk guidance for monitoring in hospital.
†Administer intravenous hydration for any patient who cannot tolerate oral hydration.
‡Consider additional IV hydration for patients with medium tumour burden.
§For patients at risk of TLS at weeks 3, 4, and 5, monitor blood chemistries at 6–8 hours and at 24 hours at each dose increase.

High tumour burden* patients with CLL

5-week venetoclax initiation calendar[1]

Instruct patients to DRINK WATER DAILY starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase.†

Intravenous hydration should also be administered at 150 mL to 200 mL per hour as tolerated.

Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLYXTO.

Consider rasburicase if baseline uric acid is elevated.

		Hospital						
WEEK 1 20 mg 10 10	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 4h ◦ 8h ◦ 12h ◦ 24h Dose 20 mg	**DAY 2** Dose 20 mg	**DAY 3** Dose 20 mg	**DAY 4** Dose 20 mg	**DAY 5** Dose 20 mg	**DAY 6** Dose 20 mg	**DAY 7** Dose 20 mg
WEEK 2 50 mg 50	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 4h ◦ 8h ◦ 12h ◦ 24h Dose 50 mg	**DAY 2** Dose 50 mg	**DAY 3** Dose 50 mg	**DAY 4** Dose 50 mg	**DAY 5** Dose 50 mg	**DAY 6** Dose 50 mg	**DAY 7** Dose 50 mg
	Outpatient						
WEEK 3 100 mg 100	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 6-8h ◦ 24h Dose 100 mg	**DAY 2** Dose 100 mg	**DAY 3** Dose 100 mg	**DAY 4** Dose 100 mg	**DAY 5** Dose 100 mg	**DAY 6** Dose 100 mg	**DAY 7** Dose 100 mg
WEEK 4 200 mg 100 100	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 6-8h ◦ 24h Dose 200 mg	**DAY 2** Dose 200 mg	**DAY 3** Dose 200 mg	**DAY 4** Dose 200 mg	**DAY 5** Dose 200 mg	**DAY 6** Dose 200 mg	**DAY 7** Dose 200 mg
WEEK 5 400 mg 100 100 100 100	**DAY 1†** Labs • Pre-dose • Post-dose: ◦ 6-8h ◦ 24h Dose 400 mg	**DAY 2** Dose 400 mg	**DAY 3** Dose 400 mg	**DAY 4** Dose 400 mg	**DAY 5** Dose 400 mg	**DAY 6** Dose 400 mg	**DAY 7** Dose 400 mg

*In patients with medium tumour burden, for first doses of 20 mg and 50 mg, consider hospitalisation for patients with CrCl <80 mL/min

†Administer intravenous hydration for any patient who cannot tolerate oral hydration.

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MANAGEMENT OF POTENTIAL VENCLYXTO INTERACTIONS WITH CYP3A INHIBITORS IN CLL[1]

- Assess patient's medication profile for drug interactions prior to initiation of VENCLYXTO
- Concomitant use of VENCLYXTO with strong or moderate CYP3A inhibitors increases VENCLYXTO exposure and may increase the risk for TLS at initiation and during the dose-titration phase
- Avoid concomitant use of VENCLYXTO with strong or moderate CYP3A inhibitors. Consider alternative medications or reduce the VENCLYXTO dose as described in this table

	Strong CYP3A inhibitors	Moderate CYP3A inhibitors
Initiation and dose-titration phase	Contraindicated	Should be avoided (Alternative treatments should be considered)
		If used, reduce VENCLYXTO dose by **at least 50%** Week 1: 10 mg; Week 2: ≤20 mg; Week 3: ≤50 mg; Week 4: ≤100 mg; Week 5: ≤200 mg
Steady daily dose (after dose titration)	Reduce VENCLYXTO by **at least 75%** to 100 mg or less	Reduce VENCLYXTO dose by **at least 50%**

EXAMPLES OF CYP3A INHIBITORS[1]

STRONG CYP3A inhibitors

- Clarithromycin
- Itraconazole
- Ketoconazole
- Posaconazole
- Ritonavir
- Voriconazole

MODERATE CYP3A inhibitors

- Ciprofloxacin
- Diltiazem
- Erythromycin
- Fluconazole
- Verapamil

FOOD CYP3A inhibitors*

- Grapefruit products
- Seville orange
- Starfruit (carambola)

- Patients should be monitored closely for signs of toxicities and the dose may need to be further adjusted
- Resume the VENCLYXTO dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor
- Preparations containing St. John's wort are contraindicated during treatment with VENCLYXTO, as efficacy may be reduced

*These foods should be avoided during treatment with VENCLYXTO as they contain inhibitors of CYP3A.

CYP3A=cytochrome P450 3A.

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RECOMMENDED VENCLYXTO DOSE MODIFICATIONS[1]

- Patients treated with VENCLYXTO may develop TLS. Risk assessment, prophylactic measures, dose-titration schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS
- Dose interruption and/or dose reduction for TLS and/or other toxicities may be required

TLS

- **Blood chemistry changes or symptoms suggestive of TLS**

→ Withhold the next day's dose → Resolved within 24 to 48 hours of last dose?

- Y → Resume VENCLYXTO at same dose.
- N → For any blood chemistry changes requiring more than 48 hours to resolve or any events of clinical TLS, resume VENCLYXTO at reduced dose **(see table below)**.

NONHAEMATOLOGIC TOXICITIES

- **Grade 3 or 4 nonhaematologic toxicities**

→ Interrupt VENCLYXTO **(see table below)** → First occurrence?

- Y → Once the toxicity has resolved to Grade 1 or baseline level, resume VENCLYXTO at the same dose.
- N → After resolution of the toxicity, resume VENCLYXTO at reduced dose **(see table below)**. A larger dose reduction may occur at the discretion of the physician.

HAEMATOLOGIC TOXICITIES

- **Grade 3 neutropaenia with infection or fever; or**
- **Grade 4 haematologic toxicities (except lymphopaenia)**

→ Interrupt VENCLYXTO **(see table below)** → First occurrence?

- Y → To reduce the infection risks associated with neutropaenia, G-CSF may be administered with VENCLYXTO if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, therapy may be resumed at the same dose.
- N → Consider using G-CSF as clinically indicated. After resolution of the toxicity, resume VENCLYXTO at reduced dose **(see table below)**. A larger dose reduction may occur at the discretion of the physician.

Dose modification for TLS and other toxicities

Dose at interruption	400 mg	300 mg	200 mg	100 mg	50 mg	20 mg
Restart dose*†	300 mg	200 mg	100 mg	50 mg	20 mg	10 mg

*The modified dose should be continued for 1 week before increasing the dose.

†Consider discontinuation in patients who require dose reductions to <100 mg for more than 2 weeks.

Reassessing TLS risk after dose interruption

When did the dosing interruption occur?

- During first 5 weeks of dose titration phase → If the dose interruption lasted **longer than 1 week** → Reassess TLS risk to determine if restarting at a reduced dose is necessary (eg, all or some levels of the dose titration) **(see dose modification table above)**.
- After completing dose titration phase → If the dose interruption lasted **longer than 2 weeks** → Reassess TLS risk to determine if restarting at a reduced dose is necessary (eg, all or some levels of the dose titration) **(see dose modification table above)**.

G-CSF=granulocyte-colony stimulating factor.

Important treatment considerations

[Placeholder for important treatment considerations and additional safety information, based on affiliate local label]

[Placeholder for affiliate to add local adverse event reporting instructions]

Reference: 1. VENCLYXTO Summary of Product Characteristics. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG. <Current SmPC.>

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