

STARTING YOUR CLL PATIENTS ON VENCLEXTA®

MANAGING THE RISK OF TUMOUR LYSIS
SYNDROME (TLS)



VENCLEXTA can cause rapid tumour reduction and thus poses a risk for TLS in the initial 5-week dose titration phase.¹

The rapid breakdown of CLL cells can cause the release of intracellular metabolites (proteins, nucleic acids etc.) into the bloodstream that can lead to:^{2,3}



Hyperkalaemia

Can cause cardiac arrhythmias and sudden death



Hyperuricaemia

Can cause urate crystal build up in the kidneys, leading to acute renal failure



Hyperphosphataemia

Can cause secondary hypocalcaemia



Hypocalcaemia

Can lead to life-threatening dysrhythmias, cause neuromuscular irritability and precipitation of calcium phosphate crystals in the kidney and heart

Clinical symptoms associated with TLS include:⁴

FEVER OR CHILLS	NAUSEA OR VOMITING	CONFUSION
SHORTNESS OF BREATH	IRREGULAR HEARTBEAT	FITS OR SEIZURES
DARK OR CLOUDY URINE	UNUSUAL TIREDNESS	MUSCLE OR JOINT PAIN

TLS can occur as early as 6–8 hours following the first dose and at each dose increase of VENCLEXTA, and can be life-threatening or fatal.¹

CLL: chronic lymphocytic leukaemia; TLS: tumour lysis syndrome.




Before starting on VENCLEXTA, a patient's level of TLS risk needs to be established.^{1,5}

Defining level of risk for TLS based on tumour burden

- LOW RISK** All lymph nodes <5 cm **and** ALC <25 x 10⁹/L
- MEDIUM RISK** Any lymph node ≥5 cm to <10 cm **or** ALC ≥25 x 10⁹/L
- HIGH RISK** Any lymph node ≥10 cm **or** ALC ≥25 x 10⁹/L & any lymph node ≥5 cm

Consider patients' renal clearance and any co-morbidities before the final determination of the prophylaxis and monitoring schedule for TLS.

TLS prophylaxis should take place 48 hours prior to initiating VENCLEXTA therapy.^{1,4}

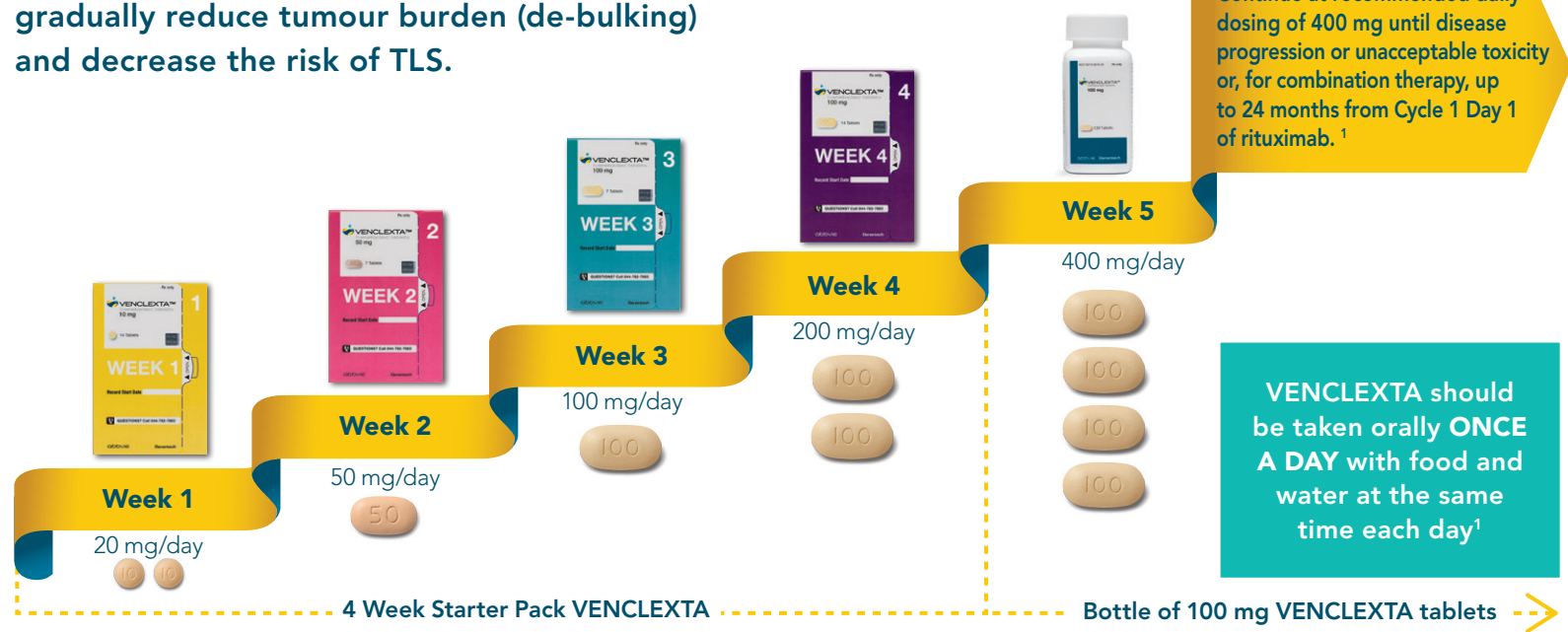
	LOW RISK	MEDIUM RISK	HIGH RISK
 <p>Adequate hydration from 2 days before and for 2 days after the first dose and each dose increase during the dose titration phase (IV fluids for patients who can't tolerate oral hydration).</p>	1.5–2 litres orally (~6–8 glasses of water)	1.5–2 litres orally (consider additional IV if tolerated)	1.5–2 litres and IV 150–200 mL/hour (as tolerated)
 <p>Anti-hyperuricaemics should be started 2–3 days before treatment, and can be continued throughout the 5-week dose titration phase. Hydration is important throughout treatment.</p>	Allopurinol	Allopurinol	Allopurinol or consider rasburicase if baseline uric acid is elevated
 <p>Blood chemistry (potassium, uric acid, phosphorus, calcium and creatinine) should be reviewed in real time, pre-dose, at 6–8 hours and 24 hours after the first doses of 20 mg and 50 mg (for low/medium risk), and pre-dose at each step of the 5-week dose titration phase. Further blood tests may be required throughout the dose titration phase depending on the patient's TLS risk level.</p>	Assess blood chemistry as an outpatient	Assess blood chemistry as an outpatient, but consider hospitalisation if creatinine clearance <80 mL/min at first dose of 20 mg and 50 mg	In hospital at first dose of 20 mg and 50 mg · Pre-dose, 4, 8, 12 and 24 hours Outpatients at subsequent titration doses · Pre-dose, 6 to 8 hours, 24 hours

Prophylaxis, monitoring and the 5-week dose titration phase reduce the risk of TLS.¹

ALC: absolute lymphocyte count; IV: intravenous; TLS: tumour lysis syndrome.

Patients must follow a 5-week dose titration phase when starting on VENCLEXTA.¹

The 5-week dose titration phase is designed to gradually reduce tumour burden (de-bulking) and decrease the risk of TLS.



Tablets shown are not actual size. TLS: tumour lysis syndrome.

A typical first week for a patient starting on VENCLEXTA.^{1,2}

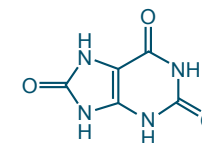
6–8 hours	Day 2	Day 3–7	Day 8
<p>First post-dose pathology assessment for the presence of TLS after taking the first dose of medication with food and water (tablets should be swallowed whole – no chewing or crushing)</p> <ul style="list-style-type: none"> Assess pathology results and consult with the patient For patients with a high risk of TLS, more frequent monitoring is required at 4, 8 and 12 hours after the first doses of 20 mg and 50 mg 	<p>Second post-dose pathology assessment – the patient cannot take second dose until assessment complete</p> <ul style="list-style-type: none"> Assess pathology results and consult with the patient 	<p>Patient continues daily medication at the same time with food and water</p>	<p>Pre-dose pathology assessment & step up to higher dose</p> <ul style="list-style-type: none"> Repeat this process for the first 2 weeks of the dose titration phase for low and medium risk patients and at each subsequent dose increase for high risk patients If clinical symptoms appear, expedite the pathology assessment

*Clinical TLS defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias,

or seizures and/or sudden death. TLS: tumour lysis syndrome.

Assessing blood chemistry

If the following metabolic abnormalities are present, withhold the next day's dose. If the abnormalities are corrected within 24–48 hours, resume at the same dose. If the abnormalities take longer than 48 hours to correct, resume VENCLEXTA treatment at a reduced dose (dose modification table below).



• **Uric acid**
>0.476 mmol/L

¹⁹
K
Potassium
39.0983

• **Potassium**
>6 mmol/L

¹⁵
P
Phosphorus
30.974

• **Phosphorus**
>1.5 mmol/L

²⁰
Ca
Calcium
40.08

• **Calcium**
<1.75 mmol/L

DOSE MODIFICATION FOR TOXICITY

Dose at interruption, mg	Restart dose, mg (During the 5-week dose titration phase, continue the reduced dose for 1 week before increasing the dose)
400	300
300	200
200	100
100	50
50	20
20	10

For any events of clinical TLS*, resume at reduced dose following resolution

Find out more at venclexta.co.nz

Log in to the Healthcare Professional portal by typing CLL for both the username and password.

References: 1. VENCLEXTA Approved Data Sheet. 2. Howard SC et al. N Engl J Med 2011;364(19):1844–54. 3. Jones GL et al. Br J Haematol 2015;169(5):661–71. 4. VENCLEXTA Consumer Medicine Information. 5. Coutre S et al. Blood 2018; pii: blood-2017-06-788133.

VENCLEXTA in combination with rituximab is fully funded for relapsed refractory chronic lymphocytic leukaemia (CLL). Special authority criteria apply. Refer to the PHARMAC website, www.pharmac.govt.nz, for full authority information.

Please review full Data Sheet before prescribing. Full Data Sheet is available on request from AbbVie Limited by calling 0800 900 030, or on the Medsafe website. <http://www.medsafe.govt.nz/profs/Datasheet/v/venclextatab.pdf> VENCLEXTA is a Prescription Medicine containing venetoclax 10 mg, 50 mg or 100 mg for oral use. THERAPEUTIC INDICATIONS: VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). **DOSE AND METHOD OF ADMINISTRATION:** VENCLEXTA should be taken orally once daily, with a meal and water. The starting dose (week 1) is 20 mg once daily for 7 days. Dose must be administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks. Week 2 daily dose is 50 mg, week 3 daily dose is 100 mg, week 4 daily dose is 200 mg, week 5 daily dose is 400 mg. The 5-week dose titration schedule is designed to gradually reduce tumour burden and decrease risk of Tumour Lysis Syndrome (TLS). **First line CLL/SLL Combination Therapy with obinutuzumab** When VENCLEXTA is used in combination with obinutuzumab it should be given for a total of 12 cycles (28 days in each cycle): 6 cycles in combination with obinutuzumab, followed by 6 cycles of VENCLEXTA as a single agent. On Cycle 1 Day 1, start obinutuzumab administration at 1000 mg (dose may be split as 100 mg and 900 mg on Days 1 and 2, respectively). Administer 1000 mg on Days 8 and 15 of Cycle 1, and on Day 1 of five subsequent cycles (total of 6 cycles, 28 days each). On Cycle 1 Day 22, start VENCLEXTA according to the 5-week dose titration schedule, continuing through Cycle 2 Day 28. After completing the dose titration schedule, patients should continue VENCLEXTA 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the end of Cycle 12. **Previously treated CLL/SLL Combination Therapy with rituximab** When VENCLEXTA is used in combination with rituximab, start rituximab administration after the 5-week dose titration schedule has been completed and the patient has received the 400 mg dose of VENCLEXTA for 7 days. The daily dose of 400 mg is to continue for up to 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. **Monotherapy** When VENCLEXTA is used as a single agent, the recommended dose is 400 mg once daily after patient has completed the 5-week dose titration schedule. Treatment is to continue until disease progression or no longer tolerated by patient. See full DS for additional information on duration of treatment, risk assessment and prophylaxis for TLS as well as dose modifications based on toxicities, use with CYP3A and P-gp inhibitors and use in patients with severe hepatic impairment. **CONTRAINDICATIONS:** Hypersensitivity to venetoclax, or to any of the excipients. In patients with CLL or SLL, concomitant use with strong CYP3A inhibitors (i.e. itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin and ritonavir) at initiation and dose titration is contraindicated. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Life-threatening tumour lysis syndrome (TLS): risk of TLS is highest at initiation and during the dose titration phase; changes in electrolytes consistent with TLS can occur 6–8 hours following first dose and at each dose increase; monitor blood chemistries and promptly manage abnormalities; increased TLS risk with reduced renal function (CrCl < 80 mL/min); assess patients for risk and provide appropriate prophylaxis, including hydration and anti-hyperuricaemics. Neutropenia: monitor complete blood counts; recommend dose interruptions and reductions if severe; consider administration of granulocyte-colony stimulating factor (G-CSF) for neutropenia if clinically indicated. Serious infection: monitor for fever and symptoms of infection and treat promptly; interrupt dosing as appropriate. Live attenuated vaccines should not be administered before, during or after treatment until B-cell recovery occurs. No dose adjustment recommended for mild or moderate hepatic or renal impairment. Not recommended during pregnancy, lactation, in children and adolescents less than 18 years of age. See full DS for details. **INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION:** Potential for significant drug interactions requiring dose-adjustment or appropriate clinical monitoring with various agents, incl. ciprofloxacin, diltiazem, erythromycin, dronedarone, fluconazole, verapamil, amiodarone, captopril, carvedilol, ciclosporin, felodipine, quercetin, quinidine, ranolazine, ticagrelor, azithromycin, warfarin, digoxin, everolimus, and sirolimus. Avoid carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, and nafcillin. Avoid grapefruit products, Seville oranges, starfruit. **UNDESIRABLE EFFECTS:** Upper respiratory tract infection, pneumonia, neutropenia, anaemia, lymphopenia, hyperkalaemia, hyperphosphataemia, hypocalcaemia, diarrhoea, nausea, vomiting, constipation, fatigue, urinary tract infection, sepsis, febrile neutropenia, TLS, hyperuricaemia, blood creatinine increased. Version 06 **Date of Preparation:** November 2019, based on Data Sheet last updated 7 November 2019. AbbVie Limited, PO Box 11437, Manners Street, Wellington 6142, New Zealand. NZ-VENC-190007. TAPS PP4816. ONO0010. November 2019.