Venetoclax

Indication

Treatment of chronic lymphocytic leukaemia (CLL) in patients:
- with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor.

or

- without a 17p deletion or TP53 mutation and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

(NICE TA796)

ICD-10 codes

Codes with a prefix C91.10

Regimen details

Venetoclax dose is titrated weekly as below to reduce tumour burden and decrease the risk of tumour lysis syndrome (TLS):

Day	Drug	Dose	Route
1-7	Venetoclax	20mg OD	PO
8-14	Venetoclax	50mg OD	PO
15-21	Venetoclax	100mg OD	PO
22-28	Venetoclax	200mg OD	PO
29 onwards	Venetoclax	400mg OD	PO

Cycle frequency

See above

Number of cycles

Continuous as above until disease progression or unacceptable toxicity.

Administration

Venetoclax is available as 10mg, 50mg and 100mg tablets. The tablets should be swallowed whole with water at approximately the same time each day. Tablets should be taken with a meal, ideally breakfast.

Grapefruit products, Seville oranges and starfruit should be avoided during treatment with venetoclax.

If a patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

If a patient vomits following a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time on the following day.

Some patients especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours.

Pre-medication

Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should drink at least 1.5 to 2.0 L of water daily starting 2 days before the first dose and throughout the dose-titration phase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and may be continued through the titration phase.

Emetogenicity

This regimen has low emetic potential.

Additional supportive medication

Anti emetics if required.
Anti viral and PCP prophylaxis as per local policy.
Anti-hyperuricaemic agents – see below

Investigations – prior to commencing venetoclax and before each dose increase

Investigation	Validity period
FBC	24 hours
U+Es (including creatinine)	24 hours
Urate	24 hours
LFTs	24 hours
Calcium	24 hours
Magnesium	24 hours
Phosphate	24 hours

Other investigations:
Hepatitis B core antibody and hepatitis BsAg, Hepatitis C antibody
HIV 1+2 serology
Urine pregnancy test (women of child bearing potential)
CT scan (neck, chest, abdomen, pelvis) – must be performed prior to commencing treatment to confirm disease bulk and TLS risk factor category.

Investigations – during dose titration phase

The following should be assessed within 24 hour prior to the first dose and 6-8 hours and 24 hours post first dose. The second dose should not be administered until these results are reviewed. The same monitoring schedule should be followed at the start of the 50 mg dose and then, for patients who continue to be at risk, at subsequent dose increases during titration period. All patients should have blood monitoring within 24 hours of each dose increase.

See sections below for action required in the event of abnormal results.

Investigation	Validity period
FBC	As above
U+Es (including creatinine)	As above
Urate	As above
LFTs	As above
Calcium	As above
Magnesium	As above
Phosphate	As above

Any electrolyte abnormalities should be corrected prior to commencing treatment. The next dose of venetoclax should not be administered until the 24-hour blood chemistry results have been evaluated.

Investigations – following dose titration phase

Investigation	Validity period
FBC	Monthly or as clinically indicated
U+Es (including creatinine)	Monthly or as clinically indicated
Urate	Monthly or as clinically indicated
LFTs	Monthly or as clinically indicated
Calcium	Monthly or as clinically indicated
Magnesium	Monthly or as clinically indicated
Phosphate	Monthly or as clinically indicated

Standard limits for go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	> 25 x 10^9/L
CrCl	> 80 mL/min
Potassium	Within normal limits
Calcium	Within normal limits
Phosphate	Within normal limits
Bilirubin	See below
AST/ALT	See below

Dose modifications

Any dose reductions should be as follows:

Dose at interruption	Dose to restart
400mg	300mg
300mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	10mg

Once a dose has been reduced it should be continued for 1 week before increasing.

- **Haematological toxicity**

If grade 3 or 4 neutropenia (neutrophils < 1.0 x10^9/L) with infection or fever or any grade 4 haematological toxicity (except lymphopenia) (neutrophils < 1.0 x10^9/L and/or platelets < 25 x10^9/L):

Withhold venetoclax. Consider GCSF as per local policy. Once resolved to ≤ Grade 1 (or baseline) resume at the same dose.

If second or subsequent occurrence, withhold venetoclax. Consider GCSF as per local policy. Once resolved to ≤ Grade 1 (or baseline) resume at reduced dose (as per table above).

- **Renal impairment**

Renal function should be evaluated prior to commencing treatment.

Patients with CrCl <80 mL/min are at increased risk of TLS and may require more intensive prophylaxis and monitoring to reduce the risk of TLS during the initiation and titration phase.

CrCl ≥30 mL/min- No venetoclax dose modification required.

CrCl <30 mL/min or dialysis- No information available. Administer only if the benefit outweighs the risk. Patients should be monitored closely for signs of toxicity.

- **Hepatic impairment**

No dose adjustment required in mild or moderate hepatic impairment.

Severe hepatic impairment- No information available. It is not recommended to administer venetoclax to patients with severe hepatic impairment.

- **Other toxicities**

Biochemistry results:
If any of the following occur withhold venetoclax until resolved:

Potassium > 0.5mmol/L increase from prior value or >ULN
Urate > 476 umol/l (8.0mg/dL)
Corrected Calcium <1.75 mmol/L
Phosphate > 1.615 mmol/l
Creatinine >25% increase from baseline

Tumour Lysis Syndrome (TLS):
Venetoclax can cause rapid reduction in tumour load and there is a risk of TLS, particularly during the titration period. Fatal cases of TLS have been observed even in patients receiving the lowest dose of venetoclax so dose escalation and TLS risk minimisation measures must be strictly adhered to and all patients should receive a patient alert card. Changes in electrolytes consistent with TLS can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase. Prompt management is required.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors is contraindicated as this may increase venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities.

<u>Risk Assessment for TLS</u>
The risk of TLS is based on multiple factors, including comorbidities. Patients with high/medium tumour burden (e.g., any lymph node with a diameter > 5 cm or high absolute lymphocyte count [ALC > 25 × 10^9/L]) have a greater risk of TLS. Reduced renal function (creatinine clearance CrCl < 80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment. Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g., CT scan) should be performed for all patients.
In addition, blood chemistry (creatinine, uric acid, potassium, phosphate, magnesium and calcium) should be carried out for all patients prior to starting treatment with correction of pre-existing abnormalities corrected.

<u>Prevention of TLS</u>
Hydration: Patients should be adequately hydrated, as described above.
For patients at risk of volume overload consider admission to hospital.

Recommended prophylaxis based on tumour burden (consider all patient co-morbidities and creatinine clearance before final determination of prophylaxis and monitoring schedule):

Tumour Burden		**Prophylaxis**		**Setting and Biochemistry Monitoring**
		Hydration	Anti-hyperuricaemics	
Low	All lymph nodes < 5cm **and** ALC <25 x 10^9/L	Oral (1.5-2L)	Allopurinol	Outpatient Monitoring as above.
Medium	Any lymph node 5 - <10cm **or** ALC >25 x 10^9/L	Oral (1.5-2L) Consider additional IV if required.	Allopurinol	Outpatient Monitoring as above.
High	Any lymph node >10cm **or** ALC >25 x 10^9/L **and** any lymph node > 5 cm **or** ALC >100 x10^9/L	Oral (1.5-2L) and IV (150-200mL/hr as tolerated)	Allopurinol Consider rasburicase if baseline uric acid is elevated	Inpatient at first dose of 20 mg and 50 mg As above and 4, 8,12 and 24 hours post dose Outpatient at subsequent doses: Monitoring as above.

Treatment of TLS:
During treatment if biochemistry or symptoms suggest TLS:
- Withhold venetoclax.
- If resolved within 24-48 hours of last dose continue with same dose on resolution.
- If takes more than 48 hours continue with reduced dose on resolution. Discuss with consultant. If rapid dose escalation required due to progressive disease consider admission for IV hydration.

Other toxicities:
For any other grade 3-4 toxicity:
- Withhold venetoclax.
- Once resolved to grade 1 or baseline resume with same dose.
- If recurs once resolved continue with dose reduction.

If dose reductions to <100mg for more than 2 weeks are required consider discontinuing treatment.

Adverse effects

Myelosuppression
Tumour lysis syndrome
Diarrhoea, constipation
Nausea and vomiting
Upper respiratory tract infection
Fatigue
Electrolyte abnormalities

Significant drug interactions

Note this list is not exhaustive. Always refer to the product SPC and consult with a pharmacist.

Strong CYP3A inhibitors: (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) Concomitant use is contraindicated during initiation and the dose-titration phase. If the patient requires use of these medications after titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Patients must not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Moderate CYP3A inhibitors and P-gp and BCRP inhibitors:
Avoid concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) and P-gp and BCRP inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor or P-gp inhibitor must be used, reduce the initiation and titration doses of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

CYP3A inducers:
Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

Bile acid sequestrants:
Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the summary of product characteristics for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

Warfain:
If concomitant use is necessary the INR should be closely monitored.

Substrates of P-gp, BCRP, and OATP1B1:
Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g. digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

Additional comments

References

- National Institute for Health and Clinical Excellence. NICE TA796. Accessed 29 June 2022 via www.nice.org.uk
- Summary of Product Characteristics Venetoclax (AbbVie) accessed 21 November 2018 via www.medicines.org.uk
- Roberts AW, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311–322.
- Stilgenbauer S, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17:768–778.

Written/reviewed by: Dr B Austen (Consultant Haematologist, Taunton and Somerset NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network), Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: January 2019