Venetoclax and azaCITIDine Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Venetoclax in combination with azaCITIDine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.	C92	00852	Venetoclax: CDS 01/06/2024 azaCITIDine: N/A

* This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Venetoclax is administered orally, once daily, commencing on Day 1 of Cycle 1 with a starting dose of 100mg. This is increased to 200mg on Day 2 and 400mg on Day 3 and thereafter. The 3-day dose-titration schedule is designed to decrease the risk of tumour lysis syndrome (TLS). The recommended venetoclax dosing schedule (including dose-titration) is shown in Table 1 below.

azaCITIDine, commencing on Day 1 of Cycle 1, is administered at dose of 75mg/m^2 daily for 5 days (Monday-Friday), followed by a rest period of 2 days and then administered again on Day 8 & 9 (Monday and Tuesday) followed by a rest period of 19 days, as detailed in Table 2. Alternatively, azaCITIDine may be administered at a dose of 100mg/m^2 daily for 5 days (Monday–Friday), followed by a rest period of 23 days, as detailed in Table 3.

Each cycle is 28 days. Treatment with both venetoclax and azaCITIDine should be continued until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) is administered.

Table 1: Dose increase schedule for venetoclax*

*If azole antifungal prophylaxis is required venetoclax dose should be dose adjusted (please refer to table 8)

Day	Venetoclax daily dose*
1	100mg
2	200mg
3 and beyond	400mg

Table 2: Treatment schedule for venetoclax and azaCITIDine 75mg/m² Days 1-5 and 8-9

Day	Drug	Dose	Route	Cycle
1-28	Venetoclax[a, b, c, d]	See Table 1	PO, once daily	Cycle 1 only
1-5, 8-9	azaCITIDine	75mg/m²	SC using a 25-gauge needle into upper arm, thigh or abdomen [e, f, g]	All cycles
1-28	Venetoclax[a, b, c, d]	400mg[h]	PO, once daily	Cycle 2 onwards
[a] Swallow tablets whole with water and with a meal, at approximately the same time each day.				
[b] During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.				
[c] Missed doses: If a patient misses a dose of venetoclax 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. Vomiting: If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.				
[d] Tablets should not be chewed, crushed, or broken before swallowing.				
[e] Doses > 4ml should be equally divided into 2 syringes and injected into two separate sites.				
[f] Injection sites should be rotated. New injections should be given at least 2.5cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.				
[g] Note: In individual cases where approved by Consultant, azaCITIDine may be administered as IV Infusion in 100ml NaCl 0.9% over 10 minutes. Note that this is an unlicensed method of administration.				
[h] If azole antifungal prophylaxis is required venetoclax dose should be dose adjusted (See table 8)				

Table 3: Alternate Treatment schedule for venetoclax and azaCITIDine 100mg/m² Days 1-5 only

Day	Drug	Dose	Route	Cycle
1-28	Venetoclax[a, b, c, d]	See Table 1	PO, once daily	Cycle 1 only
1-5	azaCITIDine	100mg/m²	SC using a 25-gauge needle into upper arm, thigh or abdomen [e, f, g]	All cycles
1-28	Venetoclax[a, b, c, d]	400mg[h]	PO, once daily	Cycle 2 onwards
[a] Swallow tablets whole with water and with a meal, at approximately the same time each day.				
[b] During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.				
[c] Missed doses: If a patient misses a dose of venetoclax 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. Vomiting: If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.				
[d] Tablets should not be chewed, crushed, or broken before swallowing.				
[e] Doses > 4ml should be equally divided into 2 syringes and injected into two separate sites.				
[f] Injection sites should be rotated. New injections should be given at least 2.5cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.				
[g] Note: In individual cases where approved by Consultant, azaCITIDine may be administered as IV Infusion in 100ml NaCl 0.9% over 10 minutes. Note that this is an unlicensed method of administration.				
[h] If azole antifungal prophylaxis is required venetoclax dose should be dose adjusted (See table 8)				

ELIGIBILITY:

- Indication as above
- ≥ 18 years
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to venetoclax, azaCITIDine, or to any of the excipients
- Advanced malignant hepatic tumours
- Acute promyelocytic leukaemia
- Pregnancy/breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
  - Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected
- Tumour burden assessment
  - Please refer to the Supportive Care section for recommended TLS prophylaxis and monitoring, based on tumour burden, during venetoclax treatment
- Coagulation screen
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), C and HIV
  *Hepatitis B reactivation: Regimen specific complications

Regular tests:

- For patients with full count recovery
  - FBC prior to each cycle
- For patients without full count recovery
  - FBC weekly or as clinically indicated

<u>Pre-dose of venetoclax</u>:

- FBC, renal and liver profile
- Uric acid
- These should be checked prior to each subsequent dose increase during the venetoclax titration phase
- For patients at risk of TLS during the 3-day titration schedule, the following post dose monitoring should be considered:

Post-dose of venetoclax (For patients at risk of TLS during the 3-day titration schedule):

- FBC, renal and liver profile 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose

For azaCITIDine:

- FBC at a minimum prior to each treatment cycle or more frequently as clinically indicated depending on level of cytopenia or haematological toxicity experienced
- Renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Dose modifications for adverse reactions are provided in Tables 4 - 8

Venetoclax:

- Venetoclax dosing may be interrupted as needed for management of hematologic toxicities and blood count recovery (see Tables 4 and 5 below)
  - Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status
- It is strongly recommended that patients should have a bone marrow response assessment after Cycle 1, between Day 21-28 (regardless of blood counts) which will guide the dosing for Cycle 2
  - In most instances, venetoclax or azacitidine should not be interrupted for haematological toxicity during Cycle 1 prior to documentation of bone marrow response
- Dose modifications of venetoclax for adverse reactions are provided in Table 8

Haematological:

Following Cycle 1, before complete remission has been achieved:

Table 4: Dose modification of venetoclax in combination with azaCITIDine in haematological toxicity (following Cycle 1, before complete remission)

ANC ($x10^9$ /L)		Platelets ($x10^9$ /L)	Dosage Modification
<1 prior to start of next cycle	Or	<75 prior to start of next cycle	If blast clearance confirmed then GCSF may be commenced until neutrophil recovery. If not, continue treatment without reduction in dose / cycle length.

After complete remission has been achieved:

Table 5: Dose modification of venetoclax in combination with azaCITIDine in haematological toxicity (after complete remission)

ANC (x10^9 /L)		Platelets (x10^9 /L)	Occurrence	Dosage Modification
≥0.5	and	≥25	n/a	No dosage modification
<0.5 With / without infection or fever	Or	<25	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of treatment and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azaCITIDine.
			Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of treatment and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azaCITIDine, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.

Renal and Hepatic Impairment:

Table 6: Dose modification of venetoclax and azaCITIDine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Venetoclax[a]	**CrCl (ml/min)**	**Dose**	**Level**	**Dose**
	≥ 15 ml/min	No dose adjustment is needed.	Child-Pugh A/B and mild/moderate	No dose adjustment is needed
	< 15 ml/min	No need for dose adjustment is expected. Monitor closely due to increased risk of TLS	Child-Pugh C and severe	50% of the original dose
	Haemodialysis	No need for dose adjustment is expected. Monitor closely due to increased risk of TLS		
azaCITIDine[b]	Any renal impairment	No dose adjustment is needed	Mild or moderate	No need for dose adjustment is expected
	Haemodialysis	No dose adjustment is needed	If albumin <30 g/L/or advanced malignant hepatic tumours: not recommended	

[a] Venetoclax (renal and hepatic - Giraud et al 2023)
[b] azaCITIDine (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 7: Dose modification of venetoclax for adverse effects

Adverse reaction	Recommended dose modification
Grade 3 or 4 Non-haematological toxicities	Interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose.
Any occurrence	

Dose modifications for use with CYP3A inhibitors:

- Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose titration phase and for other toxicities
- If a CYP3A inhibitor must be used, refer to Table 8 for recommendations for managing venetoclax interactions with CYP3A inhibitors
- Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted
- The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor

Table 8: Management of potential venetoclax interactions with CYP3A inhibitors

Inhibitors	Initiation and titration phase	Steady daily dose (After titration phase)
Strong CYP3A inhibitor	Day 1 – 10mg Day 2 – 20mg Day 3 – 50mg Day 4 – 100mg or less	Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%	
Note: Azole antifungal agents are CYP3A inhibitors. Consult the relevant SPC for further details.		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

Venetoclax: Minimal to low **(Refer to local policy)**
azaCITIDine: Moderate **(Refer to local policy)**

PREMEDICATIONS:

No specific recommendations

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome (TLS) prophylaxis:
  - All patients should have white blood cell count <25 × 10^9/l prior to initiation of venetoclax and 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 venetoclax and during dose-titration phase
  - Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax
  - Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose
  - For patients with risk factors for TLS (e.g. circulating blasts, high burden of leukaemia 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 venetoclax starting dose
- Antiviral prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Antifungal prophylaxis (if tolerated), for patients with baseline cytopenia or persistent neutropenia, continued until haematological improvement **(Refer to local policy)**
  - Moderate and strong CYP3A4 inhibitors (e.g. posaconazole) can increase venetoclax exposure. Refer to Table 8 for the management of potential venetoclax interactions with CYP3A inhibitors
- Pregnancy: Women of childbearing potential must use a highly effective method of contraception while taking venetoclax and azaCITIDine. Women should avoid becoming pregnant for at least 30 days after ending treatment with venetoclax and for at least 6 months after ending treatment with azaCITIDine. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. Men should be advised not to father a child while receiving treatment and must use effective contraception during and for at least 3 months after treatment with azaCITIDine
- Both diarrhoea and constipation are common side effects associated with azaCITIDine treatment Patients may require either laxatives or anti-diarrhoeals
- Consider topical hydrocortisone 1% for treatment of local allergic skin reactions

ADVERSE EFFECTS:

Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information

REFERENCES:

1. DiNardo CD et al. AzaCITIDine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13; 383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Venetoclax (Venclyxto®) Summary of Product Characteristics. Last updated 17/04/2024. Accessed 09/04/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf
5. azaCITIDine (VIDAZA®) Summary of Product Characteristics. Last updated 07/12/2023. Accessed 09/04/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/vidaza-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	04/06/2024		Dr Vitaliy Mykytiv
2	12/06/2024	Addition of Regimen Specific Complication section and inclusion of hepatitis B reactivation therein.	Dr Vitaliy Mykytiv

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.