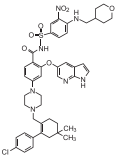
VENETIZ 10/100
Venetoclax Tablets 10 mg/100 mg

Rx only



COMPOSITION

VENETIZ 10

Venetoclax Tablets	10 mg
Venetoclax	10 mg
Excipients:	q.s.

Colours: Ferric oxide red, Ferric oxide yellow & Titanium dioxide

VENETIZ 100

Venetoclax Tablets	100 mg
Venetoclax	100 mg
Excipients:	q.s.

Colours: Ferric oxide red, Ferric oxide yellow & Titanium dioxide

DESCRIPTION

VENETIZ is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. VENETIZ has very low aqueous solubility. VENETIZ is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4–dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4–ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

CLINICAL PHARMACOLOGY

Mechanism of Action: VENETIZ is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. VENETIZ helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, VENETIZ has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

Pharmacodynamics:

Cardiac Electrophysiology:The effect of multiple doses of VENETIZ up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated hematologic malignancies. VENETIZ had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

Pharmacokinetics:

Absorption: Following multiple oral administrations under fed conditions, maximum plasma concentration of VENETIZ was reached 5-8 hours after dose. VENETIZ steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, VENETIZ mean (± standard deviation) steady state Cmax was 2.1 ± 1.1 µg/mL and AUC0-24 was32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Distribution: VENETIZ is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 µM (0.87-26 µg/mL). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution (Vdss/F) of VENETIZ ranged from 256-321 L in patients.

Metabolism: *In vitro* studies demonstrated that VENETIZ is predominantly metabolized by CYP3A4/5. M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than VENETIZ in vitro.

Excretion: After single oral administration of 200 mg radiolabeled [14C]-venetoclax dose to healthy subjects, >99.9% of the dose was recovered in feces and <0.1% of the dose was excreted in urine within 9 days, indicating that hepatic elimination is responsible for the clearance of VENETIZ from the systemic circulation. Unchanged VENETIZ accounted for 20.8% of the administered radioactive dose excreted in feces.

DRUG INTERACTIONS

Ketoconazole: Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 previously treated NHL patients increased VENETIZ C_{max} by 2.3-fold and AUC_∞ by 6.4-fold.

Ritonavir: Co-administration of 50 mg once daily ritonavir, a strong CYP3A, P-gp and OATP1B1/B3 inhibitor, for 14 days in 6 healthy subjects increased VENETIZ Cmax by 2.4-fold and AUC by 7.9-fold.

Rifampin multiple doses: Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased VENETIZ Cmax by 42% and AUC_∞ by 71%.

Rifampin single dose: Co-administration of a 600 mg single dose of rifampin, an OATP1B1/B3 and P-gp inhibitor, in 11 healthy subjects increased VENETIZ Cmax by 106% and AUC_∞ by 78%.

Azithromycin: In a drug-drug interaction study in 12 healthy subjects, co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days decreased VENETIZ C_{max} by 25% and AUC_∞ by 35%. No dose adjustment is needed when VENETIZ is co-administered with azithromycin.

Gastric Acid Reducing Agents: Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect VENETIZ bioavailability.

Warfarin: In a drug-drug interaction study in three healthy subjects, administration of a single 400 mg dose of VENETIZ with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_∞ of R-warfarin and S-warfarin.

Digoxin: In a drug-drug interaction study in 10 healthy subjects, administration of a single 100 mg dose of VENETIZ with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin C_{max} and a 9% increase in AUC_τ.

INDICATIONS

VENETIZ is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA-approved test, who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

Patient Selection: Select patients for the treatment of relapsed or refractory CLL with VENETIZ based on the presence of 17p deletions in blood specimens. Patients without 17p deletion at diagnosis should be retested at relapse because acquisition of 17p deletion can occur.

Recommended Dosage: Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENETIZ to reduce risk of TLS. Administer the VENETIZ dose according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

Instruct patients to take VENETIZ tablets with a meal and water at approximately the same time each day. VENETIZ tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Table 1. Dosing Schedule for Ramp-Up Phase

Week	VENETIZ Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

The Starting Pack provides the first 4 weeks of VENETIZ according to the ramp-up schedule. Once the ramp-up phase is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles.

VENETIZ should be taken orally once daily until disease progression or unacceptable toxicity is observed.

Risk Assessment and Prophylaxis for Tumor Lysis Syndrome: VENETIZ can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENETIZ and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Perform tumor burden assessments, including radiographic evaluation, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENETIZ. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases.

Table 2. Recommended TLS Prophylaxis Based on Tumor Burden From Clinical Trial Data.

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics[b]	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x109/L	Oral (1.5-2 L)	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x109/L	Oral (1.5-2 L)and consider additional intravenous	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital.
High	Any LN ≥10 cm OR ALC ≥25 x109/L AND any LN ≥5 cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8, 12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.

aAdminister intravenous hydration for any patient who cannot tolerate oral hydration.

bStart allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENETIZ.

cEvaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

dFor patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Dose Modifications Based on Toxicities: Interrupt dosing or reduce dose for toxicities. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if re initiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule).

Consider discontinuing VENETIZ for patients who require dose reductions to less than 100 mg for more than 2 weeks.

[a]Adverse reactions were graded using NCI CTCAE.

[b]Clinical TLS was defined as laboratory TLS with clinical consequences

Table 3. Recommended Dose Modifications for Toxicities[a]

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose.
		For any events of clinical TLS,[b] resume at a reduced dose following resolution.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt VENETIZ. Once the toxicity has resolved to Grade 1 or baseline level, VENETIZ therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt VENETIZ. Follow dose reduction guidelines in when resuming treatment with VENETIZ after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt VENETIZ. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENETIZ if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, VENETIZ therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt VENETIZ. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines when resuming treatment with VENETIZ after resolution. A larger dose reduction may occur at the discretion of the physician.

such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

Table 4. Dose Modification for Toxicity During VENETIZ Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

Dose Modifications for Use with CYP3A and P-gp Inhibitors

Concomitant use of VENETIZ with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of VENETIZ with strong CYP3A inhibitors increases VENETIZ exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of VENETIZ, reduce the VENETIZ dose by at least 75% when *strong* CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of VENETIZ with *moderate* CYP3A inhibitors or P-gp inhibitors. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENETIZ dose by at least 50%. Monitor these patients more closely for signs of toxicities.

Resume the VENETIZ dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

Table 5. Management of Potential VENETIZ Interactions with CYP3A and P-gp Inhibitors.

Inhibitors	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the venetoclax dose by at least 75%
Moderate CYP3A inhibitor	Avoid inhibitor use or reduce the venetoclax dose by at least 50%	
P-gp inhibitor		

Missed Dose: If the patient misses a dose of VENETIZwithin 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. 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 next day.

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

CONTRAINDICATIONS

Concomitant use of VENETIZ with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.

ADVERSE REACTIONS:

The following serious adverse events are discussed in greater detail in other sections of the labeling:

- Tumor Lysis Syndrome
- Neutropenia

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENETIZ. In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures. Patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 109/L and any measurable lymph node ≥5 cm were hospitalized to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the ramp-up phase.

In 66 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 μmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events. The events occurred in patients who had a lymph node(s) ≥5 cm or ALC ≥25 x 109/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

Adverse Reactions of TLS and Relevant Laboratory Abnormalities Reported in Patients with CLL

Parameter	All Grades (%) N=66	Grade ≥3 (%) N=66
Laboratory TLS[a]	6	6
Hyperkalemia[b]	20	2
Hyperphosphatemia[c]	15	3
Hypocalcemia[d]	9	3
Hyperuricemia[e]	6	2

[a]Laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 μmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L; or were reported as TLS events.
[b]Hyperkalemia/blood potassium increased.
[c]Hyperphosphatemia/blood phosphorus increased.
[d]Hypocalcemia/blood calcium decreased.
[e]Hyperuricemia/blood uric acid increased.

WARNINGS AND PRECAUTIONS

Tumor Lysis Syndrome: Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with previously treated CLL with high tumor burden when treated with VENETIZ.

VENETIZ can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENETIZ and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burdenand comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases.

Concomitant use of VENETIZ with strong or moderate CYP3A inhibitors and P-gp inhibitors increases VENETIZ exposure, may increase the risk of TLS at initiation and during ramp-up phase, and may require VENETIZ dose adjustment.

Neutropenia: Grade 3 or 4 neutropenia occurred in 41% of patients treated with VENETIZ. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including anti microbials for signs of infection and use of growth factors (e.g., G-CSF).

Immunization: Do not administer live attenuated vaccines prior to, during, or after treatment with VENETIZ until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENETIZ therapy have not been studied. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, VENETIZ may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of VENETIZ to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant women using VENETIZ. Advise females of reproductive potential to avoid pregnancy during treatment. If VENETIZ is used during pregnancy or if the patient becomes pregnant while taking VENETIZ, the patient should be apprised of the potential hazard to the fetus.

OVERDOSAGE

There is no specific antidote for VENETIZ. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt VENETIZ and monitor carefully for signs and symptoms of TLS along with other toxicities. Based on VENETIZ large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of VENETIZ.

HOW SUPPLIED

VENETIZ tablets10 mg supplied as 14 tablets packed in a HDPE container.

VENETIZ tablets 100 mg supplied as 28 tablets packed in a HDPE container.

STORAGE

Store at or below 30°C (86°F).

SHELF LIFE

24 months

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited
Factory: Tukucha, Nala-1, Banepa, Nepal.
Regd. Office: Maligaun-5, Kathmandu, Nepal.