Ventax

Venetoclax INN

Composition:
Ventax 100 Tablet: Each film coated tablet contains Venetoclax INN 100mg.

Pharmacology:
Pharmacodynamics: Cardiac Electrophysiology: The effect of multiple doses of Venetoclax up to 1200 mg once daily (2 times the maximum approved recommended dosage) on the QTc interval was evaluated in an open-label, single-arm trial in 176 patients with previously treated hematologic malignancies. Venetoclax 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: Maximum plasma concentration was reached 5 to 8 hours following multiple oral administration under fed conditions. **Effect of Food:** Administration with a low-fat meal (approximately 512 kilocalories, 25% fat calories, 60% carbohydrate calories, and 15% protein calories) increased Venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal (approximately 753 kilocalories, 55% fat calories, 28% carbohydrate calories, and 17% protein calories) increased Venetoclax exposure by 5.1-to 5.3-fold compared with fasting conditions. **Distribution:** Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 micromolar (0.87-26 mcg/mL). The mean blood-to-plasma ratio was 0.57. The apparent volume of distribution (Vdss/F) of Venetoclax ranged from 256-321 L in patients. **Elimination:** The terminal elimination half-life was approximately 26 hours. **Metabolism:** Venetoclax is predominantly metabolized by CYP3A in vitro. The major metabolite identified in plasma, M27, has an inhibitory activity against BCL-2 that is at least 58-fold lower than Venetoclax in vitro and its AUC represented 80% of the parent AUC. **Excretion:** After single oral dose of radiolabeled [14C]-Venetoclax 200 mg to healthy subjects, >99.9% of the dose was recovered in feces (21% as unchanged) and <0.1% in urine within 9 days.

Indications:
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Venetoclax is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). **Acute Myeloid Leukemia:** Venetoclax is indicated in combination with Azacitidine, or Decitabine, or low-dose Cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Dosage & administration:
Important Safety Information: 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 Venetoclax to reduce risk of TLS.
Venetoclax 5-week Dose Ramp-Up Schedule: Administer Venetoclax according to the 5-week ramp-up dosing schedule to the recommended dosage of 400 mg orally once daily as shown in table below:
Table 1: Dosing Schedule for 5-Week Ramp-Up Phase for Patients with CLL/SLL

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

In Combination with Obinutuzumab: Start Obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for a total of 6 cycles. Refer to the Obinutuzumab prescribing information for additional dosing information. On Cycle 1 Day 22, start Venetoclax according to the 5-week ramp-up dosing schedule (see Table 1). After completing the ramp-up phase on Cycle 2 Day 28, continue Venetoclax at a dose of 400 mg orally once daily from Cycle 3 Day 1 until the last day of Cycle 12.
In Combination with Rituximab: Start Rituximab administration after the patient has completed the 5-week ramp-up dosing schedule for Venetoclax (see Table 1) and has received Venetoclax at the recommended dosage of 400 mg orally once daily for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, at a dose of 375 mg/m² intravenously for Cycle 1 and 500 mg/m² intravenously for Cycles 2-6. Continue Venetoclax 400 mg orally once daily for 24 months from Cycle 1 Day 1 of Rituximab.
Monotherapy: The recommended dosage of Venetoclax is 400 mg once daily after completion of the 5-week ramp-up dosing schedule (see Table 1). Continue Venetoclax until disease progression or unacceptable toxicity.
Recommended Dosage for Acute Myeloid Leukemia: The recommended dosage and ramp-up of Venetoclax depends upon the combination agent. Follow the dosing schedule, including the 3-day or 4-day dose ramp-up, as shown in Table 2. Start Venetoclax administration on Cycle 1 Day 1 in combination with:
• Azacitidine 75 mg/m² intravenously or subcutaneously once daily on Days 1-7 of each 28day cycle; or
• Decitabine 20 mg/m² intravenously once daily on Days 1-5 of each 28-day cycle; or
• Cytarabine 20 mg/m² subcutaneously once daily on Days 1-10 of each 28-day cycle.
Table 2: Dosing Schedule for 3-or 4-Day Ramp-up Phase in Patients with AML

Day	Venetoclax	
	Oral Daily Dose	
Day 1	100mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg orally once daily of each 28-day cycle in combination with **Azacitidine or Decitabine**	600 mg orally once daily of each 28-day cycle in combination with **low-dose Cytarabine**

Continue Venetoclax, in combination with Azacitidine or Decitabine or low-dose Cytarabine, until disease progression or unacceptable toxicity.
Administration: Instruct patients of the following:
• Take Venetoclax with a meal and water.
• Take Venetoclax at approximately the same time each day.
• Swallow Venetoclax tablets whole. Do not chew, crush, or break tablets prior to swallowing.If the patient misses a dose of Venetoclax within 8 hours of the time it is usually taken, instruct the patient to 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, instruct the patient to take the missed dose and resume the usual dosing schedule the next day. If the patient vomits following dosing, instruct the patient to not take an additional dose that day and to take the next prescribed dose at the usual time. Or, as directed by the registered physicians.

Contraindications:
Concomitant use of Venetoclax with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome.

Side Effects:
• Tumor Lysis Syndrome • Neutropenia Infections

Precautions:
Tumor Lysis Syndrome: Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with Venetoclax. In patients with CLL who followed the current 5-week ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the Venetoclax CLL monotherapy trials. The rate of TLS remained consistent with Venetoclax in combination with Obinutuzumab or Rituximab. In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received Venetoclax in combination with Azacitidine. In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received Venetoclax in combination with low-dose Cytarabine. Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the 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 Venetoclax and at each dose increase. Concomitant use of Venetoclax with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during ramp-up phase of Venetoclax. For patients with CLL/SLL, coadministration of Venetoclax with strong CYP3A inhibitors at initiation and during the 5-week ramp-up phase is contraindicated. For patients with AML, reduce the dose of Venetoclax when coadministered with strong CYP3A inhibitors at initiation and during the 3-or 4-day ramp-up phase. For patients with CLL/SLL or AML, reduce the dose of Venetoclax when coadministered with moderate CYP3A4 inhibitors or P-gp inhibitors.

Neutropenia: In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with Venetoclax in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients. In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with Venetoclax in combination with azacitidine, decitabine or low-dose Cytarabine. Neutropenia can recur with subsequent cycles. Monitor complete blood counts throughout the treatment period. For interruption and dose resumption of Venetoclax for severe neutropenia, see Table 4 for CLL and Table 6 for AML. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF).

Infections: Fatal and serious infections, such as pneumonia and sepsis, have occurred in patients treated with Venetoclax. Monitor patients for signs and symptoms of infection and treat promptly. Withhold Venetoclax for Grade 3 and 4 infection until resolution. For dose resumptions, see Table 4 for CLL and Table 6 for AML.

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

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, Venetoclax may cause embryo-fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Venetoclax and for at least 30 days after the last dose.

Pregnancy & lactation:
Venetoclax may cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Venetoclax use in pregnant women to inform a drug-associated risk. Administration of Venetoclax to pregnant mice during the period of organogenesis was fetotoxic at exposures 1.2 times the human exposure at the recommended dose of 400 mg daily based on AUC. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Lactation: There are no data on the presence of Venetoclax in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed, advise women not to breastfeed during treatment with Venetoclax and for 1 week after the last dose.

Females and Males of Reproductive Potential: Venetoclax may cause fetal harm when administered to pregnant women. Verify pregnancy status in females of reproductive potential prior to initiating Venetoclax.

Contraception: Advise females of reproductive potential to use effective contraception during treatment with Venetoclax and for at least 30 days after the last dose.

Pediatric Use:
The safety and effectiveness of Venetoclax have not been established in pediatric patients.

Drug Interactions: Effects of Other Drugs on Venetoclax: Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors: Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases Venetoclax Cmax and AUC0-INF, which may increase Venetoclax toxicities, including the risk of TLS. Concomitant use with a strong CYP3A inhibitor at initiation and during the ramp-up phase in patients with CLL/SLL is contraindicated. In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust Venetoclax dosage and monitor more frequently for adverse reactions. In patients with AML, adjust Venetoclax dosage and monitor more frequently for adverse reactions. Resume the Venetoclax dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor. Avoid grapefruit products, Seville oranges, and starfruit during treatment with Venetoclax, as they contain inhibitors of CYP3A.
Strong or Moderate CYP3A Inducers: Concomitant use with a strong CYP3A inducer decreases Venetoclax Cmax and AUC0-INF, which may decrease Venetoclax efficacy. Avoid concomitant use of Venetoclax with strong CYP3A inducers or moderate CYP3A inducers.
Effect of Venetoclax on Other Drugs: Warfarin: Concomitant use of Venetoclax increases Warfarin Cmax and AUC0-INF, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using Warfarin concomitantly with Venetoclax.
P-gp Substrates: Concomitant use of Venetoclax increases Cmax and AUC0-INF of P-gp substrates, which may increase toxicities of these substrates. Avoid concomitant use of Venetoclax with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before Venetoclax.

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

Storage:
Do not store above 25°C. Protect from light. Keep out of the reach of children.

Packaging:
Ventax 100 Tablet: Each HDPE container of Ventax 100 contains 60 tablets, a silica gel desiccant and polyester coil with a child resistent closure.

Manufactured by:
ZISKA PHARMA **Ziska Pharmaceuticals Ltd.**
Kaliakoir, Gazipur, Bangladesh
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