Selinex

Selinexor 20 mg tablets

Everest

COMPOSITION

Selinex tablet: Each film coated tablet contains Selinexor INN 20 mg.

PHARMACOLOGY

Mechanism of Action

In nonclinical studies, Selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by Selinexor leads to accumulation of TSPs in the nucleus, reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. Selinexor demonstrated pro-apoptotic activity in vitro in multiple myeloma cell lines and patient tumor samples, and in murine xenograft models.

Pharmacokinetic properties

Following a single-dose administration of Selinexor 80 mg, the mean (standard deviation) peak plasma concentration (Cmax) was 680 (124) ng/mL and the mean AUC was 5386 (1116) ng h/mL. Selinexor Cmax and AUC increased proportionally over doses from 3 mg/m2 to 85 mg/m2 (0.06 to 1.8 times the approved recommended dose based on 1.7 m2 body surface area). No clinically relevant accumulation at steady state was observed.

Absorption

The Cmax is reached within 4 hours following oral administration of Selinexor.

Effect of food

Concomitant administration of a high-fat meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) did not affect the pharmacokinetics of Selinexor to a clinically significant extent.

Distribution

The apparent volume of distribution of Selinexor is 125 L in patients with cancer. The protein binding of Selinexor is 95%.

Elimination

following a single dose of SELINEXOR, the mean half-life is 6 to 8 hours. The apparent total clearance of Selinexor is 17.9 L/h in patients with cancer.

Metabolism

Selinexor is metabolized by CYP3A4, multiple UDP- glucuronosyltransferases (UGTs) and glutathione S- transferases (GSTs).

Specific Populations

No clinically significant differences in the pharmacokinetics of Selinexor were observed based on age (18 to 94 years old), sex, ethnicity, mild to severe renal impairment (CLCR: 15 to 89 mL/min, estimated by the Cockcroft- Gault equation). The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on Selinexor pharmacokinetics is unknown. Mild hepatic impairment had no clinically significant effect on the pharmacokinetics of Selinexor. The effect of moderate and severe hepatic impairment on Selinexor pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

No dedicated drug interaction studies have been performed with Selinexor.

In vitro Studies

CYP Enzymes: Selinexor does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Selinexor is not a CYP3A4, CYP1A2, or CYP2B6 inducer. Selinexor is a substrate of CYP3A4. Non-CYP Enzyme Systems: Selinexor is a substrate of UGTs and GSTs. Transporter Systems: Selinexor inhibits OATP1B3 but does not inhibit other solute carrier (SLC) transporters. Selinexor is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.

INDICATIONS AND USAGE

Selinexor is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended starting dosage of Selinexor is 80 mg (four 20 mg tablets) taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity. The recommended starting dosage of dexamethasone is 20 mg taken orally with each dose of Selinexor on Days 1 and 3 of each week. For additional information regarding the administration of dexamethasone, refer to its prescribing information. Each Selinexor dose should be taken at approximately the same time of day, and each tablet should be swallowed whole with water. Do not break, chew, crush, or divide the tablets. If a dose of Selinexor is missed or delayed, instruct patients to take their next dose at the next regularly scheduled time. If a patient vomits a dose of Selinexor, the patient should not repeat the dose and the patient should take the next dose on the next regularly scheduled day.

Recommended Monitoring for Safety

Monitor complete blood count (CBC), standard blood chemistry, and body weight at baseline and during treatment as clinically indicated. Monitor more frequently during the first two months of treatment.

Recommended Concomitant Treatments

Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration. Provide prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents prior to and during treatment with Selinexor.

Dosage Modification for Adverse Reactions

Recommended Selinexor dosage reductions and dosage modifications for adverse reactions are presented in Table 1 and Table 2, respectively.

Refer to the dexamethasone prescribing information for dexamethasone dosage modifications due to adverse reactions.

Table 1: Selinexor Dosage Reduction Steps for Adverse Reactions

Recommended Starting Dosage	First Reduction	Second Reduction	Third Reduction	
80 mg Days 1 and 3 of each week (160 mg total per week)	100 mg once weekly	80 mg once weekly	60 mg once weekly	Discontinue

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Thrombocytopenia

Selinexor can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with Selinexor. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia and fatal hemorrhage occurred in <1% of patients. Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia

Selinexor can cause neutropenia, potentially increasing the risk of infection. Neutropenia was reported as an adverse reaction in 34% of patients, and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with Selinexor. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients. Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity

Gastrointestinal toxicities occurred in patients treated with Selinexor.

Nausea/Vomiting

Nausea was reported as an adverse reaction in 72% of patients, and Grade 3 nausea occurred in 9% of patients treated with Selinexor. The median time to onset of the first nausea event was 3 days. Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with Selinexor. The median time to onset of the first vomiting event was 5 days. Provide prophylactic 5-HT3 antagonists and/or other anti-nausea agents, prior to

and during treatment with Selinexor. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti- nausea medications as clinically indicated.

Diarrhea
Diarrhea was reported as an adverse reaction in 44% of patients, and Grade 3 diarrhea occurred in 6% of patients treated with Selinexor. The median time to onset of diarrhea was 15 days. Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk.

Anorexia/Weight Loss
Anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with Selinexor. The median time to onset of anorexia was 8 days. Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with Selinexor. The median time to onset of weight loss was 15 days. Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

Hyponatremia
Selinexor can cause hyponatremia; 39% of patients treated with Selinexor experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days. Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose>150 mg/dL) and high serum paraprotein levels. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Infections
In patients receiving Selinexor, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly reported Grade ≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms.

Neurological Toxicity
Neurological toxicities occurred in patients treated with Selinexor. Neurological adverse reactions including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients, and severe events (Grade 3-4) occurred in 9% of patients treated with Selinexor. Median time to the first event was 15 days. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes.

Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, Selinexor can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with Selinexor and for 1 week after the last dose.

SIDE EFFECTS
The following adverse drug reactions are described elsewhere in the labeling:
- Dermatologic Adverse Reactions
- Tiredness
- Low red blood cell count (anemia). Symptoms may include tiredness and shortness of breath.
- Constipation
- Shortness of breath

Drug Interaction
Studies Clinical Studies No dedicated drug interaction studies have been performed with Selinexor.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on findings in animal studies and its mechanism of action. Selinexor can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose. Advise pregnant women of the risks 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal data
In an embryo-fetal development study in pregnant rats, daily oral administration of Selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

Lactation
Risk Summary
There is no information regarding the presence of Selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Selinexor and for 1 week after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating Selinexor.

Contraception
Selinexor can cause fetal harm when administered to a pregnant woman. Females Advise females of reproductive potential to use effective contraception during treatment with Selinexor and for 1 week after the last dose.

Males
Advise males with a female partner of reproductive potential to use effective contraception during treatment with Selinexor and for 1 week after the last dose.

Infertility Females and Males
Based on findings in animals, Selinexor may impair fertility in females and males of reproductive potential.

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

Geriatric Use
Of the 202 patients with RRMM who received Selinexor, 49% were 65 years of age and over, while 11% were 75 years of age and over. No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients. When comparing patients 75 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (44% vs 27%), higher incidence of serious adverse reactions (70% vs 58%), and higher incidence of fatal adverse reactions (17% vs 9%).

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
Selinex tablet: Each HDPE container contains 16 tablets (each tablet contains 20 mg Selinexor) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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