DRUG NAME: Selinexor

SYNONYM(S): KPT-330[1]

COMMON TRADE NAME(S): XPOVIO®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Selinexor is an orally administered Selective Inhibitor of Nuclear Export (SINE). Selinexor reversibly binds and inhibits the nuclear exporter protein exportin 1 (XPO1) which is overexpressed in certain tumour cells. XPO1 facilitates transport of macromolecules from the nucleus to the cytoplasm. By inhibiting XPO1, selinexor causes accumulation of tumour suppressor proteins in the nucleus, inhibition of oncogenic mRNA translation, and reduction of oncoprotein synthesis which results in cell cycle arrest and apoptosis of tumour cells.[2-4]

PHARMACOKINETICS:

Oral absorption	T_{max} = 2 to 4 h; high fat meal increases AUC by 16% (not considered clinically significant)[2]	
Distribution	highly bound to plasma proteins	
	cross blood brain barrier?	yes[5]
	volume of distribution	133 L
	plasma protein binding	95%
Metabolism	undergoes oxidation by CYP 3A4, followed by glucuronidation by UGTs and glutathione conjugation by GSTs	
	active metabolite(s)	KPT-375 (minimally active)[1]
	inactive metabolite(s)	KPT-452, KPT-5000[6]
Excretion	primarily by fecal elimination	
	urine	<1%[6]
	feces	approximately 75%[6]
	terminal half life	6 to 8 h
	clearance	18.6 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[2-4] unless specified otherwise.

USES:

Primary uses:
*Multiple myeloma

Other uses:
Lymphoma, non-Hodgkin[2]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***cataract*** formation may occur with selinexor; patients with pre-existing cataracts may experience a worsening of their symptoms[3]

Carcinogenicity: Carcinogenicity studies have not been conducted.[3]

Mutagenicity: Not mutagenic in Ames test. Selinexor was not clastogenic in the mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: In animal studies, findings included: reduced numbers of ovarian follicles, reduced sperm/spermatid count, testicular germ cell depletion, and single cell necrosis of testes. Effects were observed at exposures less than those seen following human clinical exposure.[3]

Pregnancy: In animal studies, selinexor was teratogenic and caused embryo-fetal toxicity. Structural malformations (microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus) and growth alterations (incomplete or delayed ossification, skeletal variations, and decreased fetal weight) were observed at exposures less than those seen following human clinical exposure. Pregnancy tests are recommended prior to starting treatment for female patients of childbearing potential. Contraception is recommended during treatment and for at least 1 week after the last dose of selinexor for female patients of childbearing potential and for male patients with female partners of reproductive potential.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least 1 week after the last dose of selinexor.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (43%, severe 22%)
	febrile neutropenia (3%)
	lymphopenia (63%, severe 37%)
	neutropenia (58%, severe 31%); consider G-CSF if indicated
	thrombocytopenia (86%, severe 49%); see paragraph following **Side Effects** table
cardiac	cardiac failure (3%)
eye	***blurred vision*** (11%, severe 1%)
	cataract (4%); incidence is 22% in combination regimens including dexamethasone; see paragraph following **Side Effects** table
gastrointestinal (see paragraph following **Side Effects** table)	*emetogenic potential:* high[8-11]
	abdominal pain (10%)
	constipation (29%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (37%, severe 3%)
	nausea (57%, severe 6%)
	vomiting (30%, severe 2%)
general disorders and administration site conditions	asthenia (22%, severe 5%)
	edema (17%, severe 2%)
	fatigue (47%, severe 15%)
	pyrexia (22%, severe 5%)
infections and infestations (see paragraph following **Side Effects** table)	herpes virus infection (3%)
	pneumonia (10%, severe 6%)
	sepsis (6%, severe 5%)
	upper respiratory tract infection (17%, severe 2%)
	urinary tract infection (10%, severe 3%)
injury, poisoning, and procedural complications	fall (8%)
investigations	albumin decrease (25%)
	ALT increase (29%, severe 1%)
	AST increase (24%, severe 3%)
	bilirubin increase (16%, severe 2%)
	calcium decrease (30%, severe 1%)
	creatine kinase increase (21%, severe 2%)
	creatinine increase (47%, severe 4%)
	glucose increase (57%, severe 5%)
	magnesium decrease (30%, severe 3%)
	sodium decrease (62%, severe 16%); see paragraph following **Side Effects** table
	phosphate decrease (34%, severe 11%)
	potassium decrease (23%, severe 7%)
	potassium increase (26%, severe 4%)
	weight loss (30%); see paragraph following **Side Effects** table
metabolism and nutrition	***anorexia*** (37%, severe 4%); see paragraph following **Side Effects** table
	appetite decrease (37%, severe 4%)
	dehydration (7%)
musculoskeletal and connective tissue	back pain (5%)
	musculoskeletal pain (15%, severe 2%)
nervous system	confusion (9%)
	dizziness (16%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	headache (5%)
	peripheral neuropathy (10%)
	syncope (2%)
	taste disorder (13%)
psychiatric	***mental status changes*** (11%, severe 4%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (18%)
	dyspnea (10%, severe 2%)
	epistaxis (20%)
vascular	hypotension (13%, severe 3%)
	hemorrhage (10%, severe <1%)

Adapted from standard reference[2,11] unless specified otherwise.

New or worsening ***cataract*** may occur with selinexor. The incidence of cataract is higher when selinexor is used in combination regimens with bortezomib and dexamethasone compared to selinexor alone (22% vs 4%).[2,3] Steroids are known to increase the risk of cataract formation; therefore, it is proposed that dexamethasone used in combination with selinexor may explain the amplified risk.[12] Signs and symptoms of cataract may include blurred vision, double vision, and sensitivity to light. Symptoms that are grade 2 or higher may require ophthalmologic evaluation and dose modification. Treatment of cataract usually requires surgical removal. If cataract surgery is warranted, withhold selinexor 24 hours prior to the procedure and for 72 hours after.[3]

Gastrointestinal toxicities such as nausea, vomiting, and diarrhea are frequently reported with selinexor. Despite the use of antiemetic prophylaxis, nausea occurs in approximately 50% of patients.[2,3] ***Anorexia*** is reported in 37% of patients and can lead to ***weight loss*** or malnutrition. If weight loss is greater than 10% of baseline, dose interruption may be considered. Once recovered, selinexor may be restarted at a reduced dose. Patients are advised to maintain adequate caloric and fluid intake throughout treatment. For patients at risk of dehydration, intravenous fluids may be required.[3]

Infections are reported in approximately 50% of patients, with 25% reported as grade 3 or higher events. Events are sometimes fatal. Most infections are *not* associated with severe neutropenia.[3] Most frequently reported serious infections include lower respiratory tract infections (including pneumonia) and sepsis.[2,3]

Neurological toxicities are reported in 25% of patients and can be severe. Symptoms may include dizziness, drowsiness, confusion, syncope, delirium, hallucination, amnesia, depressed level of consciousness, and mental status changes. The median time to onset is 4 weeks and the median time to recovery is 2 weeks. Low hemoglobin level, dehydration, or concomitant medication may exacerbate dizziness or mental status changes. Patients are advised to avoid driving or operating heavy machinery if experiencing neurologic symptoms. Fall precautions may be implemented as indicated.[3]

Severe ***thrombocytopenia*** can occur with selinexor. Median time to onset of thrombocytopenia is approximately 28 days. In patients who receive selinexor in combination with bortezomib and dexamethasone, approximately 40% of patients experience grade 3 or 4 thrombocytopenia and commonly require dose modification. Bleeding events have been reported in 16% of patients. Management of thrombocytopenia may include dose modification, dose interruption, or platelet transfusion based on severity of the event.[2,3]

Hyponatremia has been reported in 62% of patients and may occur in the context of gastrointestinal toxicities such as nausea, vomiting, diarrhea, dehydration, and anorexia. The mechanism of selinexor-associated hyponatremia is

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not well understood.[13] Sodium may appear lower in the context of elevated serum paraprotein or glucose levels. Use corrected sodium level in patients with high serum paraprotein levels or concurrent hyperglycemia (serum glucose greater than 8.3 mmol/L). Management of hyponatremia may include dose interruption, dose reduction, and supportive care.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acetaminophen[2]	no significant changes in selinexor AUC and C_{max}	glutathione depletion by acetaminophen	not considered clinically significant; no adjustment required
clarithromycin[2]	no significant changes in selinexor AUC and C_{max}	strong inhibition of CYP 3A4 by clarithromycin	not considered clinically significant; no adjustment required

Selinexor is a substrate of CYP3A4, UDP-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs); clinical significance is unknown.[3]

In vitro, selinexor is an inhibitor of OATP1B3; clinical significance is unknown.[3]

SUPPLY AND STORAGE:

Oral: Forus Therapeutics Inc. supplies selinexor as 20 mg film-coated tablets. Store at room temperature.[3]

Additional information: Selinexor tablets are packaged in blister cards containing 5 tablets per card. Each carton contains 4 blister cards (total 20 tablets).[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:

100 mg (range 40-120 mg) ***PO for one dose on day 1 of each week***
(total dose per week 40-120 mg)[3,14,15]

60-80 mg PO for one dose on day 1 and 3 of each week
(range 40 mg PO once weekly to 80 mg twice weekly)
(total dose per week 40-160 mg)[2]

Administer with food or on an empty stomach

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

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BC Cancer usual dose noted in ***bold, italics***

Dosage in renal failure:	no adjustment required[3]
Dosage in hepatic failure:	mild impairment (bilirubin ≤1.5 x ULN): no adjustment required[3] moderate to severe impairment (bilirubin >1.5 x ULN): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

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