DRUG NAME: Sonidegib

SYNONYM(S): LDE225[1]

COMMON TRADE NAME(S): ODOMZO®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Sonidegib is an orally administered, small molecule, selective inhibitor of the Hedgehog (Hh) signalling pathway. In embryogenesis, the Hh signalling pathway regulates cell growth and differentiation. This pathway is usually dormant in adult tissues through suppression of the transmembrane protein Smoothened (SMO) by transmembrane receptor protein patched homolog 1 (PTCH1). Patients with basal cell carcinoma have gene mutations in PTCH1 or SMO that activate the pathway, leading to activation of glioma-associated oncogene (Gli) transcription factors and proliferation of basal skin cells. Sonidegib selectively binds to SMO, preventing signal transduction, which results in tumour regression.[1-4]

PHARMACOKINETICS:

Oral Absorption	<10% of oral dose is absorbed; exposure increased 1.8- to 2.5-fold with a light meal and 7.4- to 7.8-fold with a high-fat meal	
Distribution	primarily bound to human plasma proteins (serum albumin and alpha-1 acid glycoprotein)	
	cross blood brain barrier?	yes[2]
	volume of distribution	9166 L
	plasma protein binding	>97% (concentration independent)
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	LGE899, LNC110
Excretion	elimination of absorbed drug primarily via metabolism	
	urine	<5%
	feces	93% (primarily as unchanged drug)
	terminal half life	28 days
	clearance	no information found
Elderly	no clinically relevant difference	
Ethnicity	1.7-fold increase in AUC and 1.6-fold increase in C_{max} in Japanese patients compared to Western patients	

Adapted from standard reference[2,4,5] unless specified otherwise.

USES:

Primary uses:

*Skin cancer, non-melanoma

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Contraindications:
- pregnant or breastfeeding women[4]
- females of childbearing potential (FCBP) or males, unless they can comply with the criteria of the controlled distribution program, ODOMZO® Pregnancy Prevention Program[4]

Caution:
- patients ***should not donate blood*** while taking sonidegib (including during dose interruptions) and for 20 months after treatment has ended[4,5]
- sonidegib distributes into ***semen***; male patients should ***not donate semen*** while taking sonidegib (including during dose interruptions) and for at least 6 months after treatment has ended[4,5]

Special populations:
- ***females of childbearing potential*** (FCBP) may be treated provided that they comply with the conditions of the ODOMZO® Pregnancy Prevention Program (OPPP), including using adequate contraception or abstinence; contraceptive measures must be in practice for at least 4 weeks before starting treatment, during dose interruptions, continually during treatment, and for 20 months after discontinuation of therapy[4,5]
- ***male*** patients must comply with the conditions of the OPPP, and use a condom with spermicide during any sexual contact with FCBP, even if they have undergone a vasectomy; condoms must be used during treatment, including during dose interruptions, and for at least 6 months after discontinuation of therapy[4,5]
- ***children*** (i.e., less than 18 years of age) should not take sonidegib; epiphyseal disorders (e.g., premature fusion of the epiphyses) have been reported in pediatric patients exposed to sonidegib[4,5]
- ***patients aged 65 years or older*** may experience more serious adverse events and grade 3 or 4 reactions compared to younger patients; older patients are also more likely to require dose interruption or discontinuation[4,5]

Carcinogenicity: No carcinogenicity studies have been conducted. Cases of cutaneous squamous cell carcinoma (cuSCC) have been reported following sonidegib usage in advanced basal cell carcinoma; however, as these patients already have an increased risk of developing cuSCC, it has not been determined whether cuSCC is related to sonidegib treatment.[4]

Mutagenicity: Sonidegib is not mutagenic in Ames test. Sonidegib is not clastogenic or aneugenic in mammalian *in vitro* and *in vivo* chromosome tests.[4,5]

Fertility: Sonidegib has been reported to cause amenorrhea lasting for at least 18 months in human females of childbearing potential. It is not known if fertility impairment is reversible. In animal studies, at exposures below those expected with human clinical exposure, there were fewer pregnant females on treatment, an increased number of early resorptions, and a reduced number of viable fetuses. At exposures approximately equal to those seen following human clinical exposure, a lack of fertility was reported in female test subjects. Atrophy of the uterus and ovaries was observed at exposures higher than those seen following human clinical exposure. No effects on male fertility were observed in animal studies.[4,5]

Pregnancy: In animal studies, sonidegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures below the recommended human dose. Following administration to pregnant animal test subjects, complete resorption of fetuses and abortion were observed. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure was below the limit of detection.[4,5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Due to the potential to cause serious developmental defects, breastfeeding is not recommended at any time during treatment with sonidegib (including during dose interruptions) and for 20 months after treatment has ended.[4,5]

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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.[6,7] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (32%)
	lymphopenia (28%, severe 3%)
eye	dry eye (<5%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (18-19%)
	constipation (8%, severe 1%)
	diarrhea (32%, severe 1%)
	dry mouth (5%)
	dyspepsia (9%, severe 1%)
	gastrointestinal reflux disease (<5%)
	nausea (39%, severe 1%)
	vomiting (11%, severe 1%)
general disorders and administration site conditions	***fatigue*** (41-49%, severe 4-5%)
	pain (14-15%, severe 1%)
infections and infestations	***pneumonia*** (8%, severe 1-3%)[9]
	urinary tract infection (9%)[9]
investigations	ALT increase (19-20%, severe 4%)
	amylase increase (16-17%, severe 1%)
	AST increase (19-20%, severe 4%)
	blood glucose increase (51%, severe 4%)
	hyperkalemia (18%, severe 4%)
	lipase increase (43-44%, severe 13%)
	serum creatinine increase (92%); remained within normal range in 76% of patients
	serum creatine phosphokinase increase (61%, severe 8%); median time to onset = 13 weeks, median time to resolution = 12 days
	weight decrease (30%, severe 3-5%)
metabolism and nutrition	appetite decrease (23%, severe 1%)
	dehydration (<5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
musculoskeletal and connective tissue see paragraph following **Side Effects** table	***muscle spasms*** (54-56%, severe 3%)
	musculoskeletal pain (32-39%, severe 1%)
	myalgia (19%)
	myopathy (5%)
	rhabdomyolysis (severe 1%)
	trigger finger (<5%)
neoplasms	cutaneous squamous cell carcinoma
nervous system	dizziness (9%, severe 1%)
	dysgeusia (44-46%)
	headache (15%, severe 1%)
	paresthesia (5%)
	peripheral neuropathy (<5%)
psychiatric	depression (6%)
reproductive system and breast disorders	***amenorrhea*** (14%)
skin and subcutaneous tissue	***alopecia*** (49-53%)
	hair growth abnormality (<5%)
	pruritus (10-11%)
	rash (9%)
vascular	hypotension (5%, severe 3%)

Adapted from standard reference[4,5,9] unless specified otherwise.

Musculoskeletal adverse reactions, including muscle spasms, musculoskeletal pain, and myalgia, are frequently reported and may be accompanied by serum creatine phosphokinase (CPK) elevations and rhabdomyolysis. In the majority of patients, muscle symptoms developed prior to the elevation of CPK. Advise patients to maintain adequate hydration during treatment with sonidegib and promptly report any new or unexplained muscle pain, tenderness, or weakness. Manage symptoms with medical intervention (such as magnesium supplementation, muscle relaxants, or analgesics), dose interruption, or treatment discontinuation as clinically appropriate. Monitor CPK levels and renal function throughout treatment.[4,5,10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
bupropion[4]	no effect on systemic exposure of bupropion	inhibition of CYP 2B6 by sonidegib	none required
esomeprazole[4]	32-38% decrease in sonidegib exposure	pH dependent solubility of sonidegib (i.e., reduced sonidegib solubility with increasing pH)	may be administered concurrently; reduced efficacy of sonidegib is possible

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AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[4]	may increase plasma level of sonidegib	may inhibit CYP 3A4 metabolism of sonidegib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of sonidegib therapy
ketoconazole[4,5]	2.2-fold increase in AUC and 1.5-fold increase in C_{max} of sonidegib	strong inhibition of CYP 3A4 by ketoconazole	avoid concurrent use
rifampin[4,5]	72% decrease in AUC and 54% decrease in C_{max} of sonidegib	strong induction of CYP 3A4 by rifampin	avoid concurrent use
warfarin[4]	1-2 hour delay in peak concentration of S- and R-warfarin	inhibition of CYP 2C9 by sonidegib	dose adjustment is not expected; monitor PT and INR regularly

Sonidegib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentrations of sonidegib. Avoid concurrent use with *moderate* and *strong* CYP 3A4 inhibitors. If concurrent use with *moderate* CYP 3A4 inhibitors cannot be avoided, limit coadministration to 14 days or less and monitor closely for adverse reactions. CYP 3A4 ***inducers*** may decrease the plasma concentrations of sonidegib. Avoid concurrent use with *moderate* and *strong* CYP 3A4 inducers.[4,5,10]

Sonidegib is an inhibitor of breast cancer resistance protein (BCRP) *in vitro*; clinical significance is unknown.[4,5]

SUPPLY AND STORAGE:

Oral: Sun Pharma Global FZE supplies sonidegib as 200 mg capsules. Capsules contain lactose. Store at room temperature.[4]

Additional information: Sonidegib is only available through a controlled distribution program called the ODOMZO® Pregnancy Prevention Program (OPPP). Further information is available at 1-844-266-2974 or www.odomzo.ca.[4]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

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

Oral:[4,5]

200 mg PO once daily

Administer on an empty stomach, one hour before or two hours after a meal. Do not take with grapefruit or grapefruit juice.

Concurrent radiation:

no information found

Dosage in myelosuppression:

modify according to protocol by which patient is being treated

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[4]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

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Dosage in hepatic failure: no initial adjustment required; monitor for toxicity[4]

Dosage in dialysis: no information found

Children: contraindicated in children and adolescents less than 18 years[4]

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