DRUG NAME: Vismodegib

SYNONYM(S):

COMMON TRADE NAME(S): ERIVEDGE®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Vismodegib is an oral, low molecular weight 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, but patients with basal cell carcinoma (BCC) have gene mutations that activate the Hh pathway. This activation leads to uncontrolled proliferation of basal skin cells and overexpression of glioma-associated protein 1 (GLI1).[1-3] Vismodegib selectively binds to the transmembrane protein smoothened homolog (SMO), thereby preventing Hh signal transduction, resulting in tumour regression and stable disease.[1,4] Vismodegib also targets patched homolog 1 (PTCH1) mutations and expression changes in GLI1.[3]

PHARMACOKINETICS:

Oral Absorption	time to peak[2] 2.4 days; bioavailability 32%; pH dependent solubility (reduced solubility with increasing pH)	
Distribution	non-linear pharmacokinetics	
	cross blood brain barrier?	no information found
	volume of distribution	16-27 L
	plasma protein binding	greater than 99%; primarily to albumin and alpha1 acid glycoprotein
Metabolism	via oxidation, glucuronidation, and pyridine ring cleavage in liver; unchanged drug accounts for greater than 98% of circulating component	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	slow elimination	
	urine	4%
	feces	82% (primarily as unchanged drug)
	terminal half life	4 days
	clearance[3]	79 mL/h

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:

*Skin cancer, non-melanoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to vismodegib[4]
- children and adolescents less than 18 years[4]
- pregnant or breastfeeding women[4]
- females of childbearing potential (FCBP) or males, unless they can comply with the criteria of the controlled distribution program, ERIVEDGE® Pregnancy Prevention Program[4]

Caution:

- Patients ***should not donate blood*** while taking vismodegib, including during dose interruptions, and for 24 months after discontinuation of therapy.[4]
- Vismodegib distributes into ***semen***; male patients should ***not donate semen*** while taking vismodegib, including during dose interruptions, and for 2 months after discontinuation of therapy.[4]
- Pre-existing ***liver disease and concomitant hepatotoxic medications*** may be risk factors for the development of hepatotoxicity (e.g., cholestasis, hepatitis, and hepatocellular injury) associated with vismodegib use.[5]

Special populations:

- ***Females of childbearing potential*** (FCBP) may be treated provided that they comply with the conditions of the ERIVEDGE® Pregnancy Prevention Program (EPPP), including using adequate contraception or abstinence. Contraceptive measures are indicated even in females with a history of infertility, and those who have amenorrhea and are not menopausal, and must be in practice for at least 4 weeks before starting treatment, during dose interruptions, continually during treatment, and for 24 months after discontinuation of therapy.
- ***Male*** patients must comply with the conditions of the EPPP, 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, dose interruptions, and for 2 months after discontinuation of therapy.[4]
- Vismodegib should not be used in ***children*** (i.e., less than 18 years). Irreversible premature fusion of the epiphyses and precocious puberty have been reported in pediatric patients exposed to vismodegib**.** In some cases, fusion progressed after drug discontinuation.[5]

Carcinogenicity: No carcinogenicity studies have been conducted. Pilomatricoma has been reported in animal studies but relevance to humans is unknown. Cases of cutaneous squamous cell carcinoma (cuSCC) have been reported with vismodegib usage in advanced basal cell carcinoma patients who already have an increased risk of developing cuSCC.[4]

Mutagenicity: Not mutagenic in Ames test. Vismodegib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: In clinical trials, amenorrhea has been reported in females of childbearing potential. Reversibility of fertility impairment is unknown. In animal studies, the following have been reported: increased number of degenerating germ cells, decreased number of spermatozoa, abnormal accumulation of cell debris in epididymides, decreased sperm motility, and decreased number of corpora lutea.[4]

Pregnancy: In animal embryo-fetal development studies, vismodegib crossed the placenta, resulting in delays in development and fetal malformations which included craniofacial anomalies, open perineum and absent and/or fused digits.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Due to the potential to cause serious developmental defects, patients should not breastfeed during treatment with vismodegib, including during dose interruptions, and for 24 months after discontinuation of therapy.[4]

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].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (7%)
cardiac	***cardiac-related events***, including atrial fibrillation, cardiac flutter, cardiac failure, restrictive cardiomyopathy, angina, myocardial infarction, and left ventricular dysfunction (1-3%)[4,8]
endocrine	precocious puberty[5]
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (6%)
	constipation (21%)
	diarrhea (29%, severe 1%)
	dyspepsia (9%)
	dysphagia (5%)
	flatulence (7%)
	nausea (30%, severe 1%)
	vomiting (14%)
	gastrointestinal hemorrhage, small intestinal obstruction (1%)
general disorders and administration site conditions	asthenia (8%, severe 1%)
	chest pain (5%)
	fatigue (40%, severe 6%)
	peripheral edema (7%, severe 1%)
	pain (9%, severe 1%)
hepatobiliary	cholestasis[5]
	hepatitis[5]
	hepatocellular injury[5]
infections and infestations	nasopharyngitis (9%)
	rhinitis (5%)
	upper respiratory tract infection (10%)
	urinary tract infection (5%, severe 1%)
investigations	alkaline phosphatase increase (15%, severe 1%)
	ALT increase (18%, severe 1%)
	AST increase (25%)
	bilirubin increase (8%, severe 1%)
	BUN increase (25%, severe 2%)
	creatinine increase (13%)
	weight decrease (45%, severe 7%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolism and nutrition	***appetite decrease*** (25%, severe 2%)
	hypokalemia (5-14%, severe 1-2%)
	hypomagnesia (12%)
	hyponatremia (29%, severe 4%)
musculoskeletal and connective tissue	arthralgia (16%, severe 1%)
	back pain (8%)
	limb pain (9%, severe 1%)
	muscle spasms (72%, severe 4%)
	musculoskeletal chest pain (7%)
	myalgia (6%)
	premature epiphyses fusion[5]
	rhabdomyolysis[5]
neoplasms	squamous cell carcinoma (9%, severe 1%)
nervous system	***ageusia/dysgeusia*** (11-56%)
	dizziness (6%)
	hypoaesthesia (5%)
	paraesthesia (6%)
psychiatric	anxiety (8%)
	depression (7%)
	insomnia (11%)
reproductive system and breast disorders	amenorrhea (30%)[1,2]
respiratory, thoracic and mediastinal	cough (19%)
	dyspnea (9%, severe 2%)
	rhinorrhea (7%)
skin and subcutaneous tissue	***alopecia*** (64%)
	dry skin (7%)
	erythema (8%)
	pruritus (9%)
	rash (8%)

Adapted from standard reference[4] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ethinyl estradiol and norethindrone oral contraceptive[4]	no effect on systemic exposure of oral contraceptive	unknown; possible induction of CYP 3A4 by vismodegib[5]	none required[5]
fluconazole[5]	1.3 fold increase in vismodegib exposure	moderate inhibition of CYP 2C9 and CYP 3A4 by fluconazole	none required[5]
itraconazole[5]	no effect on systemic exposure of vismodegib	strong inhibition of CYP 3A4 and P-glycoprotein by itraconazole	none required[5]
rabeprazole[5]	no effect on systemic exposure of vismodegib	pH dependent solubility	none required[5]
rosiglitazone[4]	no effect on systemic exposure of rosiglitazone	possible inhibition of CYP 2C8 by vismodegib[5]	none required[5]

Vismodegib is a substrate of CYP 2C9 and CYP 3A4 and P-glycoprotein and an inhibitor of CYP 2C8, CYP 2C9, CYP 2C19, and BCRP *in vitro*. No vismodegib dose adjustments are required.[5]

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies vismodegib as 150 mg capsules. Capsules contain lactose monohydrate. Store at room temperature in original package.[4]

Additional information[4]: Vismodegib is only available through a controlled distribution program called the ERIVEDGE® Pregnancy Prevention Program (EPPP). Further information is available at www.erivedge.ca.

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***

Cycle Length:

Oral[4,10]: ***150 mg PO once daily***.

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; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: mild to moderate impairment: no adjustment required[5]
severe impairment: no information found

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

	Cycle Length:
Dosage in hepatic failure:	mild to moderate impairment: no adjustment required[5] severe impairment: no information found
Dosage in dialysis:	no information found
Children:	contraindicated in children and adolescents less than 18 years[4]

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