Drug Monograph

A - Drug Name

vismodegib

COMMON TRADE NAME(S): Erivedge®

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B - Mechanism of Action and Pharmacokinetics

The Hedgehog pathway is a key regulator of cell differentiation and growth during embryogenesis. This pathway is normally inactive in adults; mutations resulting in a constitutive active status are implicated in the development and progression of a number of cancers, including basal cell carcinoma and medulloblastoma. The Hedgehog pathway signals through the transmembrane Smoothened (SMO) protein, inducing the Hedgehog target genes involved in cell proliferation, survival and differentiation. The patch homologue 1 transmembrane receptor (PTCH1) normally has inhibitive effects on SMO signalling. Vismodegib inhibits the SMO protein, preventing Hedgehog signal transduction from a mutated overactive SMO or mutated inactive PTCH1.

Absorption	Absorption is saturable as exposure did not increase above the recommended dose (up to 540 mg daily). Weight, age (range 26-89), creatinine clearance (range 30-80 mL/min) and sex do not have significant effects on exposure.	
	Bioavailability	31.8%
	Effects with food	None
	Time to reach steady state	Within ~7 days
Distribution	Vismodegib binds to serum albumin and alpha-1-acid glycoprotein.	
	PPB	>99%

	Cross blood brain barrier?	Unknown
Metabolism	Metabolized primarily by the liver and metabolic pathways including oxidation and glucuronidation, etc. Several minor metabolites are produced by multiple CYP450 enzymes.	
	Main enzymes involved	CYP2C9, CYP3A4, CYP3A5
	Inhibitor of	CYP2C8, CYP2C9, CYP2C19, BCRP
Elimination	Slowly eliminated by a combination of metabolism (main route) and excretion of parent drug.	
	Half-life	12 days (single dose), 4 days (steady state)
	Feces	82% of dose
	Urine	4% of dose

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C - Indications and Status

Health Canada Approvals:

- Basal cell carcinoma (BCC)

Refer to the product monograph for a full list and details of approved indications.

Vismodegib may only be prescribed and dispensed by physicians and pharmacists registered with the Erivedge® Pregnancy Prevention Program (EPPP). Patients must also be registered and meet all conditions of the program. Call 1-888-748-8926 or log onto www.erivedge.ca

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects were reported in ≥ 5% of advanced BCC patients in clinical trials. Severe, life-threatening or post-marketing adverse events are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	E D
	Hypertension (≥5%)	E
	Hypotension (orthostatic; rare)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (64%)	E D
	Other - Acute generalized exanthematous pustulosis (rare)	E
	Rash (9%) (may be severe)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Abdominal pain (6%)	E
	Anorexia, weight loss (45%)	E
	Constipation (21%)	E
	Diarrhea (29%)	E
	Dyspepsia (9%)	I E
	Dysphagia (5%)	E
	Flatulence (7%)	E
	GI hemorrhage (rare)	E
	GI obstruction (rare)	E
	Nausea, vomiting (30%)	I
General	Edema (7%)	E
	Fatigue (40%)	E
Hematological	Anemia (7%) , lymphopenia (mild to moderate)	E
Hepatobiliary	↑ LFTs (25%) (severe <1%)	E

	Pancreatitis (rare, may be severe)	E
Hypersensitivity	DRESS syndrome (rare)	E
	Hypersensitivity (mild)	I
Infection	Infection (10%) (UTI, URTI)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (29%) (severe 4%, decreased Na, K, Mg)	E
Musculoskeletal	Fracture (rare)	D
	Musculoskeletal pain (72%)	E
	Rhabdomyolysis (also increased CPK; rare)	E
Neoplastic	Secondary malignancy (9%) (squamous cell carcinoma)	E D
Nervous System	Anxiety (8%)	E
	Depression (7%)	E
	Dizziness (6%)	E
	Dysgeusia (55%)	E
	Headache (13%)	E
	Insomnia (11%)	E
	Other (paranoia - rare)	E
	Paresthesia (6%)	E
	Syncope (may be severe)	E
Renal	Creatinine increased (13%) (may rarely be severe)	E D
Reproductive and breast disorders	Irregular menstruation (30%) (amenorrhea)	E
Respiratory	Cough, dyspnea (19%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for vismodegib include musculoskeletal pain, alopecia, dysgeusia, anorexia, weight loss, fatigue, irregular menstruation, nausea, vomiting, abnormal electrolyte(s), diarrhea and ↑ LFTs.

Elevations in liver enzymes are mainly grades 1 and 2 in severity. Severe increases have been transient and have not led to treatment interruption or discontinuation in the majority of the cases. However, some serious cases of hepatotoxicity necessitating dose interruption or discontinuation have been observed, including cholestasis, hepatitis, and hepatocellular injury. Risk factors may

include pre-existing liver disease, underlying malignancy and its complications, concomitant hepatotoxic medications, and systemic infections.

Pancreatitis (including one fatal case) has been reported.

Syncope may be severe in some cases where vismodegib was held and then restarted after symptom resolution.

Thromboembolic events, such as deep vein thrombosis and pulmonary embolism (including one fatal case) have been reported.

Prolonged symptoms (persisting at least 12 months post-treatment discontinuation) of weight loss, muscle spasm, dysgeusia and ageusia have been reported.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Vismodegib may only be prescribed and dispensed by physicians and pharmacists registered with the EPPP. Patients must also be registered and meet all conditions of the program. Call 1-888-748-8926 or log onto www.erivedge.ca

Women of child-bearing potential must have a negative pregnancy test within 7 days before starting treatment.

Adults:

Oral: 150 mg once daily

Dosage with Toxicity:

There are no dose reductions for vismodegib. Interruptions up to 8 weeks are allowed for intolerable side effects* or for a planned surgical procedure. New onset of cutaneous squamous cell carcinoma should be managed according to the standard of care.

*intolerable side effects: Grade 3 or 4 related toxicities that are likely to be clinically significant, life-threatening or irreversible

The following were excluded in the phase II clinical trial:

- Hematologic or metabolic/chemistry abnormalities not considered clinically significant
- Nausea, vomiting, or diarrhea that are adequately controlled after optimization of medical management.
- Transient and manageable grade 3 infection
- Asymptomatic thromboembolism found incidentally on imaging and managed with anti-coagulation therapy

Toxicity	Action
Pancreatitis	Consider hold or discontinuation
Grade 3 or 4 treatment-related	Hold up to 8 weeks
Planned surgery	Hold up to 8 weeks
Grade 3 or 4 hepatotoxicity	Hold or discontinue
Severe cutaneous adverse reactions (SCARs) (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, acute generalized exanthematous pustulosis)	Discontinue

Dosage with Hepatic Impairment:

Hepatic Impairment	Total bilirubin / AST		AST	Vismodegib dose
Mild	≤ ULN	And	>ULN	No change; exercise caution
	>ULN to 1.5x ULN	And	any	No change; exercise caution
Moderate	>1.5 to < 3x ULN	And	any	No change; exercise caution
Severe	3 to <10x ULN	And	any	Not recommended for use

Dosage with Renal Impairment:

The safety and efficacy of vismodegib have not been established in patients with severe renal impairment.

Creatinine clearance (ml/min)	Vismodegib dose
≥ 50	No change
30 to 49	No change
< 30	No data

Dosage in the elderly:

No specific dose adjustment is necessary. However, monitor with caution.

Children:

CONTRAINDICATED in patients aged below 18 years as efficacy and safety have not been established. Precocious puberty, severe irreversible changes in reproductive (male), dental and bone growth were observed in pediatric or post-natal animal studies.

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F - Administration Guidelines

Vismodegib may only be prescribed and dispensed by physicians and pharmacists registered with the EPPP. Patients must also be registered and meet all conditions of the program. Call 1-888-748-8926 or log onto www.erivedge.ca

- Capsules must be swallowed whole with a glass of water and not crushed or opened; can be taken with or without food.
- If dose is missed, skip this dose and give the next scheduled dose. Do not double the dose to make up for the missed one.
- Store at room temperature (15 - 30°C), in original package away from moisture and heat.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- In patients aged below 18 years
- Females patients of childbearing potential and male patients who do not comply with the EPPP requirements
- Breastfeeding female patients

Other Warnings/Precautions:

- Vismodegib is not recommended for use in patients with severe hepatic impairment. Use with caution in patients with mild to moderate hepatic impairment.
- Use with caution in patients with a history of pancreatitis and gallbladder disease.
- Patients should not donate blood or semen while taking vismodegib, during dose interruptions and for 24 months (2 months for semen) after stopping therapy.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- Patients with history of significant cardiovascular disease or risk factors for syncope: Severe related adverse events have been reported in these patients groups. There was no effect of vismodegib on the QT interval.

Other Drug Properties:

- Carcinogenicity: Probable
  Cases of cutaneous squamous cell carcinoma have been reported in advanced BCC patients.

Pregnancy and Lactation:

- Genotoxicity: No
  Clastogenicity: No
- Embryotoxicity: Yes
  Fetotoxicity: Yes
- Teratogenicity: Yes
  Vismodegib is **contraindicated in pregnancy and in males and females of childbearing potential who do not comply with the EPPP**.

  REFER TO THE EPPP FOR COMPLETE DETAILS. Vismodegib can cross the placenta and cause fetal malformations. **Females of childbearing potential** as defined by EPPP (including those who are either menstruating, amenorrheic but have not entered menopause or are perimenopausal) must be capable of understanding and complying with the patient registration, education, and safety requirements of the ERIVEDGE® program, **regular pregnancy testing** (7 days prior to initiating vismodegib treatment, monthly during treatment and interruptions and for 24 months after the last dose) and the use of **two simultaneous contraception methods** (including 1 acceptable barrier method with spermicide) for at least one month prior to starting treatment, during treatment, during dose interruptions, and for **24 months** following the last dose of vismodegib. If pregnancy occurs or is suspected during treatment, vismodegib must be discontinued and patients referred to a gynaecologist/obstetrician for evaluation and counselling.

  Male patients must be capable of understanding and complying with the patient registration, education, and safety requirements of the EPPP, including **mandatory contraceptive measures for men** (condoms with spermicide should be used even with vasectomized males) while taking vismodegib, during dose interruptions and for **2 months** after stopping therapy. Also, male patients should not donate semen during the above period of time. If the female sexual partner becomes pregnant, the female partner should be referred to a gynecologist/obstetrician for evaluation and counselling.

  Any suspected exposure to vismodegib during pregnancy must be reported immediately to the EPPP at 1-888-748-8926 or through forms available for healthcare professionals on www.erivedge.ca

- Breastfeeding:
  Breastfeeding is **contraindicated** during treatment and dose interruptions, and for **24 months** after the last dose.
- Fertility effects: Yes
  These effects may be irreversible. Amenorrhea occurred in 30% of females of childbearing potential in clinical trials, and animal studies indicate decreased male fertility. Fertility preservation strategies should be discussed prior to starting treatment.

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H - Interactions

Vismodegib is a substrate of CYP3A4, CYP2C9 and P-gp in vitro.

Concurrent use of vismodegib with oral contraceptives (ethinyl estradiol and norethindrone) did not alter oral contraceptive levels.

CYP3A4 induction is not predicted to significantly change vismodegib exposure. Although administration with a fluconazole (a moderate CYP3A4 and CYP2C9 inhibitor) increased mean vismodegib AUC and steady-state concentrations by 1.3-fold, no dose adjustment for vismodegib is required.

Administration of vismodegib with a proton pump inhibitor (e.g. rabeprazole) or strong inhibitor of CYP3A4 and P-gp (e.g. itraconazole) had no effect on steady state exposure of vismodegib. Dose adjustment for vismodegib is not required.

Vismodegib does not significantly alter the exposure of CYP2C8 or CYP3A4 substrates (e.g. rosiglitazone). Dose adjustment is not required.

Vismodegib is a possible inhibitor of BCRP, CYP2C9 and CYP2C19. Use caution when administering vismodegib and these respective substrates with a narrow therapeutic range.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline, before each cycle, and as clinically indicated
Renal function tests	Baseline and before each cycle
Lipase, amylase	Baseline and as clinically indicated
Controlled distribution program requirements regarding pregnancy tests for women of child-bearing potential	As per the EPPP

Clinical toxicity assessment for musculoskeletal pain, fatigue, syncope, hypersensitivity, diarrhea, anorexia and other GI, cardiovascular effects, thromboembolism and psychiatric effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Electrolytes, including magnesium	baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- vismodegib - Treatment for metastatic basal cell carcinoma (BCC) or with locally advanced BCC (including patients with basal cell nevus syndrome, i.e. Gorlin syndrome), according to specific criteria ()

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K - References

Keating GM. Vismodegib in locally advanced or metastatic basal cell carcinoma. Drugs 2012;72(11):1535-41.

Poggi L, Kolesar JM. Vismodegib for the treatment of basal cell skin cancer. Am J Health-Syst Pharm 2013;70:1033-8.

Prescribing Information: Erivedge® (vismodegib). Genentech USA Inc., January 2012.

Product Monograph: Erivedge® (vismodegib). Hoffmann-La Roche Ltd., May 2020.

Summary of Product Characteristics: Erivedge® (vismodegib). Roche Products Ltd. (UK), July 12, 2013.

August 2023 Modified Adverse Effects, Dosage with toxicity, Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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