Drug Monograph

A - Drug Name

vorinostat

COMMON TRADE NAME(S): Zolinza®

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B - Mechanism of Action and Pharmacokinetics

Accumulation of acetylated histones results in transcriptional activation of genes, including tumour suppression genes. HDACs catalyze the removal of the acetyl group from lysine residues of proteins, including histones. Inhibition of HDACs may result in anti-tumour effects. Vorinostat is a histone deacetylase (HDAC) inhibitor, which has effects on HDAC1, HDAC2, HDAC3, and HDAC6. Marketing approval was based on response rates in phase 2 studies.

Absorption	(Oral absorption) Bioavailability	43% (fasting). A high fat meal increases AUC by 38% and a 2.5 h delay in absorption rate. Peak level is reached in 4 hours. There is no significant accumulation with multiple doses. Pharmacokinetics are linear and dose proportional.
Distribution	Cross blood brain barrier?	yes
	PPB	71 %
Metabolism	Major pathways include glucuronidation or hydrolysis followed by oxidation. Negligible biotransformation by CYP 450 and not a substrate for PGP. Vorinostat has not been shown to inhibit CYP enzymes at pharmacologically relevant concentrations.	

	Active metabolites	none
	Inactive metabolites	o-glucuronide vorinostat, 4-anilino-4-oxobutanoic acid
Elimination	Primarily eliminated through metabolism	
	Urine	< 1 % (unchanged) 52 % (metabolites)
	Half-life	2 hours (vorinostat and o-glucuronide vorinostat) 11 hours (4-anilino-4-oxobutanoic acid)

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C - Indications and Status

Health Canada Approvals:

Treatment of cutaneous manifestations in patients with advanced cutaneous T-cell lymphoma (CTCL) who have progressive persistent or recurrent disease subsequent to prior systemic therapies

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported mainly as monotherapy in CTCL patients.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Hypertension (rare; reported in non-CTCL patients)	E
	QT interval prolonged	E
	Tachycardia	E
	Venous thromboembolism (7%)	E
Dermatological	Alopecia (16%)	E

Gastrointestinal	Abdominal pain (8%)	E
	Anorexia (23%)	E
	Constipation (11%)	E
	Dehydration	E
	Diarrhea (47%)	E
	Dry mouth (16%)	E
	GI hemorrhage (rare, in combination with other HDAC inhibitors)	E
	GI perforation (or fistula; rare)	E
	Nausea, vomiting (38%)	E
	Weight loss (20%)	E
General	Delayed wound healing	E
	Fatigue (45%)	E
Hematological	Anemia (2%) (severe)	E
	Hemorrhage (tumour; rare; reported in non-CTCL patients)	E
	Thrombocytopenia (6%) (severe)	E
Hypersensitivity	Angioedema (rare)	I
	Hypersensitivity (drug eruption - rare)	E
Metabolic / Endocrine	Hyperglycemia (5%) (severe <1%)	E
	↓ K	E
	↓ Na (reported in non-CTCL patients)	E
Musculoskeletal	Myalgia (16%) (spasms)	E
Neoplastic	Secondary malignancy (NSCLC; rare; reported in non-CTCL patients)	D L
Nervous System	Dizziness (7%)	E
	Dysgeusia (23%)	E
	Guillain-Barre syndrome (rare; reported in non-CTCL patients)	E
	Headache (7%)	E
Renal	Creatinine increased (13%)	E
	Proteinuria (8%)	E
Respiratory	Dyspnea (7%)	E
Vascular	Vasculitis (rare; reported in non-CTCL patients)	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 adverse effects in CTCL patients include **fatigue, nausea/vomiting, diarrhea, taste disturbances, dry mouth, anorexia, and thrombocytopenia.** Frequencies of adverse effects were higher in non-CTCL patients; however, the types of adverse effects reported were generally similar to those in CTCL patients.

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, occurs with an increased incidence. Patients with a prior history or at risk of thromboembolic events should be closely monitored. Vorinostat is associated with **QT interval prolongation**. It should be used with caution in patients with risk factors for QT prolongation or torsade de pointes, such as female gender, age 65 or older, congenital long QT syndrome, cardiac disease, history of arrhythmia, and concomitant medications that prolong QT interval, etc. In the CTCL clinical trial leading to vorinostat approval, there were no grade 3 or higher ECG adverse effects. **Increases in heart rate** have been described; exercise caution in patients with a history of ischemic heart disease or tachyarrhythmias.

Gastrointestinal effects, such as nausea, vomiting, and diarrhea are usually mild to moderate in severity; some cases may require treatment with antiemetics and antidiarrheals. Women may experience more nausea, diarrhea and dysgeusia than men. Fluid (at least 2 L/day) and/or electrolyte replacement should be administered to prevent dehydration (may be severe) in patients taking vorinostat.

Impaired wound healing has been reported, with fistulas, perforations, and abscess formation.

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E - Dosing

Refer to protocol by which patient is being treated. Patients must be adequately hydrated.

Adults:

Dose: 400mg orally once daily with food
Treatment may be continued until disease progression or unacceptable toxicity occurs.

Suggested dose levels are 400 mg daily, 300 mg daily, and 300 mg daily for 5 consecutive days per week.

Dosage with Toxicity:

Toxicity	Action	Dose
Grade 3	Hold #*	↓ 1 dose level

Grade 4	Hold #; or discontinue	If re-start, ↓ 1 dose level
* consider hold for Platelets 10-25 x 10^9/L and/or Hemoglobin 65-80 g/L if considered related to vorinostat # until recovery to ≤ grade 1		

Dosage with Hepatic Impairment:

Although hepatic impairment did not produce statistically significant differences in pharmacokinetics, tolerability decreased with increasing severity of hepatic impairment.

Bilirubin		**AST**	**Action**
1 to 1.5 x ULN			Caution; reduce dose to 300 mg daily
≤ ULN	and	> ULN	Caution; reduce dose to 300 mg daily
1.5 to ≤ 3 x ULN	and	any	Not recommended for use
> 3 x ULN	and	any	Contraindicated

Dosage with Renal Impairment:

No data available. Treat with caution in renal impairment as the 2 major metabolites are excreted in urine.

Dosage in the elderly:

No dosage adjustment is necessary. No overall differences in safety or effectiveness as compared to younger patients. Limited data suggest that age has no meaningful effects on vorinostat pharmacokinetics.

Dosage based on gender:

Limited data suggest that gender has no meaningful effects on vorinostat pharmacokinetics.

Dosage based on ethnicity:

Limited data suggest that ethnicity has no meaningful effects on vorinostat pharmacokinetics.

Children:

Safety and effectiveness have not been established.

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F - Administration Guidelines

- Outpatient prescription for home administration.
- Capsules should not be opened or crushed.
- Patients should be instructed to drink at least 2 L/day of fluids for adequate hydration.

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G - Special Precautions

Other:

Vorinostat is **contraindicated** in patients who are hypersensitive to the drug or any component in the formulation, and in patients with severe hepatic impairment (total bilirubin > 3 x ULN). Electrolyte abnormalities, pre-existing nausea, vomiting and diarrhea should be controlled prior to vorinostat initiation. Use with caution in diabetics, patients with cardiac risk factors and in patients taking medications which prolong QTc or the PR interval, or mild hepatic impairment (total bilirubin > 1 to 1.5× ULN or total bilirubin ≤ ULN and AST > ULN). Dizziness and syncope have been reported; exercise caution when driving or operating machinery. Exercise caution in patients undergoing bowel surgery or other surgery due to impaired wound healing.

No carcinogenic tests have been conducted. In vitro and animal studies suggest that vorinostat has **clastogenic, mutagenic, embryotoxic, fetotoxic** effects, and can cross the placenta. It in unknown whether vorinostat is excreted in human milk. Therefore, its use is not recommended in **pregnancy** and **lactation**. Adequate contraception should be used by both sexes during vorinostat treatment, and for at least 6 months after treatment cessation.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Warfarin or other coumarin-derivative	Prolonged PT and INR	Unknown	Monitor PT and INR closely

anticoagulants			
HDAC inhibitors (ie: valproic acid)	Grade 4 thrombocytopenia with GI bleeding and anemia	Additive	Avoid concomitant use
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT interval prolongation	Additive	Avoid concomitant use
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxative, enemas, amphotericin B, high dose corticosteroids)	↑ risk of QT prolongation		Caution; monitor

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver and renal function tests	Baseline and regular
ECG	Baseline and periodic
CBC, electrolytes (including Ca, Mg, K) and blood glucose	Baseline, then every 2 weeks during the first 2 months, then monthly thereafter
Clinical toxicity assessment of dehydration, hyperglycemia, fatigue, gastrointestinal, and	Routine

cardiovascular toxicities	

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Monitor blood glucose closely in diabetic or potentially diabetic patients.	

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K - References

Galanis E, Jaeckle KA, Maurer MJ, et al. Phase II Trial of vorinostat in recurrent glioblastoma multiforme: a north central cancer treatment group study. J Clin Oncol 2009; 27:2052-2058.

Kelly WK, O'Connor OA, Krug LM, et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. JCO 2005; 23: 3923-31.

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1287-8.

Product Monograph: Zolinza® (vorinostat). Merck Canada Inc., October 18, 2013.

Yin D, Ong JM, Hu J, et al: Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor: effects on gene expression and growth of glioma cells in vitro and in vivo. Clin Cancer Res 2007; 13:1045-52.

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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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