Drug Monograph

A - Drug Name

romidepsin

COMMON TRADE NAME(S): Istodax®

DO NOT initiate romidepsin treatment in new patients. It is only available through the Restricted Access Program to registered patients currently receiving treatment with this drug.

Refer to Health Canada's health professional risk communication.

Contact Bristol-Myers Squibb's medical information at 1-866-463-6267 or medical.canada@bms.com for more information on the Restricted Access Program.

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B - Mechanism of Action and Pharmacokinetics

Romidepsin, initially isolated from Chromobacterium violaceum, is a bicyclic peptide inhibitor of Class I histone deacetylases. Accumulation of acetylated histones induces cell cycle arrest and apoptosis in some cancer cell lines, although the exact mechanism of its anticancer effect is not clear. Romidepsin is a prodrug and requires reduction of disulfide bonds for activation.

Distribution	Rapid distribution into many tissue and organ systems. Accumulates into human hepatocytes via an unknown uptake mechanism.	
	PPB	92-94%, mainly to alpha-1 acid glycoprotein
	Cross blood brain barrier?	Very low
Metabolism	Active metabolites	Yes

Elimination	Multiphasic elimination; mainly eliminated through bile with excretion into feces. No accumulation was observed after repeat dosing.	
	Half-life	3.7 hours
	Feces	96% (animal studies)
	Urine	< 20%, with < 5% parent drug (animal studies)

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C - Indications and Status

DO NOT initiate romidepsin treatment in new patients. It is only available through the Restricted Access Program to registered patients currently receiving treatment with this drug. Romidepsin will be withdrawn from the Canadian market once the last patient completes treatment.

The Phase 3 confirmatory study failed to demonstrate romidepsin, in combination with chemotherapy, was more effective than chemotherapy alone at delaying the progression of peripheral T-cell lymphoma (PTCL). However, there is no evidence of new safety issues with romidepsin monotherapy.

Refer to Health Canada's health professional risk communication.

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Health Canada Conditional Approvals
(pending the result of studies to verify the drug's clinical benefit. Patients should be advised of the nature of the marketing authorization granted.)

- peripheral T-cell lymphoma (PTCL)

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

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Minimal

The following adverse effects were reported in ≥ 5% of patients with PTCL treated with romidepsin in the pivotal single-arm clinical trial. Severe, life-threatening and post-marketing adverse effects are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (4%)	E
	Hypotension (8%)	I E
	QT interval prolonged (rare)	E
	Tachycardia (10%)	E
Dermatological	Rash (9%)	E
Gastrointestinal	Abdominal pain (14%)	E
	Anorexia, weight loss (28%)	E
	Constipation (30%)	E
	Diarrhea (36%)	E
	Dyspepsia (8%)	E
	Mucositis (11%)	E
	Nausea, vomiting (59%)	I
General	Edema (10%)	E
	Fatigue (55%) (8% severe)	E
Hematological	Myelosuppression ± infection, bleeding (41%) (including opportunistic infections/viral reactivation; 24% severe)	E
Hepatobiliary	↑ LFTs (29%) (2% severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (11%) (↓ K, ↓ Mg)	E
	Tumor lysis syndrome (2%)	I
Musculoskeletal	Musculoskeletal pain (9%)	E
Nervous System	Anxiety (7%)	E
	Depression (5%)	D
	Dizziness (8%)	E

	Dysgeusia (21%)	E
	Headache (15%)	E
	Insomnia (7%)	E
Respiratory	Cough, dyspnea (18%)	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 romidepsin include nausea/vomiting , fatigue, myelosuppression ± infection/bleeding, diarrhea, constipation, ↑ LFTs, anorexia/weight loss, dysgeusia, cough/dyspnea and headache.

Gastrointestinal adverse effects such as nausea, vomiting, constipation and diarrhea were generally mild to moderate.

Serious or fatal **infections** (including opportunistic infections) have been observed during treatment and within 30 days after treatment. Patients with a history of bone marrow involvement or prior treatment with monoclonal antibodies directed against lymphocyte antigens may have high risk of infections. Viral reactivation (hepatitis B, CMV, EBV) has been described.

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E - Dosing

Refer to protocol by which patient is being treated.

Plasma potassium and magnesium levels should be within normal range before each romidepsin administration.

Do not treat if QTc > 480 ms.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Consider prophylaxis in patients at increased risk for opportunistic infections or reactivation of hepatitis B, cytomegalovirus and Epstein-Barr virus infections.

Adults:

Q 28 day cycle:

Intravenous: 14 mg/m² Days 1, 8, 15

Dosage with Toxicity:

Dose Level	Romidepsin Dose* (mg/m^2)
0	14
-1	10
-2	Discontinue

*Do not re-escalate reduced doses.

Toxicity	Action
Grade 2 or 3 non-hematological/organ	Hold*; Restart at same dose level. If grade 3 toxicity recurs, hold* then ↓ 1 dose level. If grade 3 toxicity recurs after dose reduction, discontinue.
Grade 4 non-hematological/organ	Hold*; Restart by ↓ 1 dose level. If grade 4 toxicity recurs after dose reduction, discontinue.
Grade 3 or 4 ANC or platelets	Hold*; Restart at same dose level.
Grade 4 febrile neutropenia or thrombocytopenia requiring platelet transfusion	Hold*; Restart by ↓ 1 dose level.

*Do not retreat until platelets ≥ 75 x 10^9/L, ANC ≥ 1.5 x 10^9/L, non-hematological/organ toxicities recover to ≤ grade 1 or baseline.

Dosage with Hepatic Impairment:

Patients with hepatic impairment have a higher risk of adverse effects. Romidepsin clearance decreases with severity of hepatic impairment.

Bilirubin		AST	Romidepsin Starting Dose
≤ ULN	and	> ULN	No dose adjustment required
1 to 1.5 x ULN	and	any	No dose adjustment required
> 1.5 to 3 x ULN	and	any	↓ by 50%
> 3 x ULN	and	any	Not recommended for use

Dosage with Renal Impairment:

Not formally studied. Population pharmacokinetic analysis suggested that renal impairment was not expected to affect drug exposure significantly.

Creatinine Clearance (mL/min)	Romidepsin Dose
> 50-80	No change
30-50	No change
< 30	No change
ESRD	Caution (no data)

Dosage in the elderly:

No overall differences in safety or efficacy were observed between elderly and younger patients; however, elderly patients are at higher risk of toxicity and may require dose modifications.

Dosage based on ethnicity:

Race did not appear to affect romidepsin pharmacokinetics.

Children:

Safety and efficacy have not been established in patients < 18 years of age.

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F - Administration Guidelines

- Reconstitute romidepsin using the supplied diluent. Refer to the product monograph for instructions.
- Add the required dose into 500 mL 0.9% Sodium Chloride (NS).
- Infuse IV over 4 hours.
- Missed doses should be administered as soon as possible, unless it is within 5 days of the next scheduled dose.
- Diluted solution is compatible with PVC, ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles.
- Store unopened vial and diluent together at room temperature (15 to 30^{o}C).

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G - Special Precautions

Contraindications:

- Patients who have hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Patients with a significant cardiac history were excluded from clinical trials; exercise extreme caution in these patients
- Use with caution in patients who are at risk of experiencing torsade de points or QT prolongation, including female patients, age ≥ 65 years, congenital long QT syndrome, cardiac disease, history of arrhythmias, electrolyte disturbances, bradycardia, acute neurological events, diabetes, on concomitant antiarrhythmics or drugs that prolong QT, or autonomic neuropathy.
- Use with caution in patients with advanced stage disease and/or high tumour burden due to the risk of tumour lysis syndrome.

- Use with caution in patients with compromised bone marrow (disease, or heavily pretreated) due to the risk of infection.
- Patients should avoid driving, operating dangerous machinery or performing tasks that require alertness if experiencing fatigue and dizziness.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Fetotoxicity: Yes
  Romidepsin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **8 weeks** after the last dose (in females) and for at least **1 month** after the last dose (in males). Estrogen-containing contraceptives should not be used (refer to interactions).
- Embryotoxicity: Yes
- Teratogenicity: Yes
- Mutagenicity: No
- Clastogenicity: No
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment.
- Fertility effects: Yes
  These effects may be irreversible.

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H - Interactions

Romidepsin is metabolized by CYP3A4; it does not significantly inhibit or induce CYP450 substrates, but is susceptible to drug interactions from CYP3A4 inhibitors/inducers. Minor metabolism occurs via CYP3A5, 1A1, 2B6, and 2C19, but substrates of these enzymes are unlikely to affect romidepsin.

Romidepsin is a substrate of Pgp and MRP1.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ romidepsin concentration and/or toxicity	↓ metabolism of romidepsin	Avoid use with strong inhibitors. Caution with moderate inhibitors; monitor for toxicity.

CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ romidepsin concentration/efficacy (theoretical), ↑ romidepsin exposure observed with rifampin	↑ metabolism of romidepsin; rifampin may inhibit hepatic uptake that limits romidepsin access to induced CYP3A4	Avoid strong CYP3A4 inducers.
Coumarin derivatives	↑ PT and INR observed	Unknown	Caution; monitor PT and INR closely.
Estrogen containing contraceptives	↓ effectiveness of estrogen-containing contraceptives	Competition with binding to the estrogen receptors	Caution; use alternate non-estrogen contraception (e.g. condoms, IUD); monitor for estrogen deficiency in patients on hormone replacement therapy.
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine)	↑ Romidepsin concentration and/or toxicity	↓ Romidepsin elimination	Caution.
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ QT prolongation effect	Additive	Caution; monitor patient closely.
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose	↑ risk of QT prolongation	Electrolyte disturbance	Avoid if possible.

corticosteroids)

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each treatment
Electrolytes, including potassium and magnesium	Baseline, before each treatment and as clinically indicated
ECG	Baseline and as clinically indicated (for all patients); baseline and periodic (for patients at risk of QT prolongation)
Liver function tests	Baseline and as clinically indicated
INR and PT (for patients taking warfarin or its derivatives)	Baseline and as clinically indicated
Clinical toxicity assessment for infection (including opportunistic infections/viral reactivation), bleeding, thromboembolism, fatigue, GI effects, hypersensitivity, tumour lysis syndrome	At each visit

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

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Romidepsin - Relapsed or Refractory Peripheral T-Cell Lymphoma

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K - References

Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 2012 Feb 20;30(6):631-6.

Health Canada's health professional risk communication (Istodax: Restricted access program). March 20, 2023.

Product Monograph: Istodax® (romidepsin). Celgene Inc. July 25, 2019 and March 8, 2023.

Yang LPH. Romidepsin: in the treatment of T-cell lymphoma. Drugs 2011;71(11):1469-80.

March 2023 Updated Drug name and Indications sections with info on the Restricted Access Program

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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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