DRUG NAME: Romidepsin

SYNONYMS: FK228, NSC 630176, FR901228, Depsipeptide[1-3]

COMMON TRADE NAME(S): ISTODAX®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Romidepsin is a bicyclic depsipeptide and a potent inhibitor of class 1 histone deacetylase (HDAC). Inhibition of HDAC results in the accumulation of acetylated histones, leading to changes in chromatin structure and transcription factor activation. Induction of cell cycle arrest and apoptosis occurs in the G_1 and G_2/M phases.[2,4-6]

PHARMACOKINETICS:

Distribution	highly protein bound to α_1-acid glycoprotein[5,7]	
	cross blood brain barrier?	low concentration reaches the brain in animal studies
	volume of distribution	no information found
	plasma protein binding[7]	92-94%
Metabolism	extensive CYP3A4 metabolism[7]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	no accumulation after repeat dosing	
	urine	no information found
	feces	no information found
	terminal half life	3.7 h
	clearance	8.4 L/h

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:
*Lymphoma, peripheral T-cell

Other uses:
Lymphoma, cutaneous T-cell[7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- Transient ***ECG changes*** have been reported but are not associated with functional cardiovascular changes or symptoms; clinical significance is unknown.[4]
- ***QT interval prolongation*** has been associated with romidepsin; monitor ECG and electrolytes. Correct preexisting electrolyte disturbances prior to treatment. Use with caution in patients with known risk factors for torsade de points or those also taking other QT-prolonging agents.[2,4,5]
- ***Hyperuricemia*** and ***tumour lysis syndrome*** have been reported; patients with advanced stage disease and/or high tumour burden are most at risk.[4]

- ***Reactivation*** of hepatitis B, cytomegalovirus, and Epstein-Barr infections have been reported; consider antiviral prophylaxis.[4,5]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Romidepsin is weakly mutagenic in a mammalian *in vitro* mutation test but this is considered unlikely to be biologically significant. Romidepsin is not clastogenic in mammalian *in vivo* chromosome tests.[4]

Fertility: Animal studies have demonstrated morphological changes in the testes and mammary glands of males and in the ovaries, uterus, vagina and mammary glands in females. Changes may be irreversible.[4]

Pregnancy: FDA Pregnancy Category D.[7] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
In animal studies, romidepsin was embryocidal and teratogenic; fetal effects included rotated limbs, folded retina, and incomplete sternal ossification. Females of childbearing potential should use appropriate contraception during treatment and for 8 weeks after discontinuation of therapy. Romidepsin may reduce the effectiveness of estrogen-containing contraceptives; consider alternate methods of contraception. Condoms with spermicide are recommended for male patients, even after a vasectomy.[4,7]

Breastfeeding is not recommended due to the potential secretion into breast milk.

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.[8,9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (19-72%, severe 3-28%)[4,7]
	febrile neutropenia (severe 3%)
	leucopenia (4-55%, severe 6-45%)[4,7]
	lymphopenia (4-57%, severe 37%)[7]
	neutropenia (11-66%, severe 4-47%)[4,7]
	thrombocytopenia (17-72%, severe 14-36%)[4,7]
cardiac	atrial fibrillation, cardiogenic shock, cardiopulmonary failure, myocardial ischemia (<1%)[5]
	supraventricular arrhythmia, syncope, ventricular arrhythmia (1-10%)[5]
	tachycardia (10%)
gastrointestinal	*emetogenic potential: low-moderate*[10]
	abdominal pain (7-14%, severe 1-2%)
	constipation (12-40%, severe 1-2%)[4,7]
	diarrhea (20-36%, severe 1-2%)[4,7]
	dyspepsia (8%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nausea (56-86%, severe 2-6%)[4,7]
	stomatitis (6-11%)[4,7]
	vomiting (34-52%, severe 1-10%)[4,7]
general disorders and administration site conditions	*extravasation hazard: none*[11]
	asthenia/fatigue (53-77%, severe 8-19%)[4,7]
	chest pain (8%, severe 3%)
	chills (11-17%, severe <1%)[4,7]
	pain (8%, severe <1%)
	peripheral edema (6-10%, severe <1%)[4,7]
	pyrexia (20-47%, severe 1-17%)[4,7]
immune system	hypersensitivity (1-2%)[5]
infections and infestations	cellulitis (5%, severe 4%)
	Epstein-Barr virus reactivation (<1%)[5]
	infections (46-54%, severe 11-33%)[7]; see paragraph following **Side Effects** table
	nasopharyngitis (5%)
	oral candidiasis (6%, severe <1%)
	pneumonia (7%, severe 5%)
	sepsis (5%, severe 5%)
	upper respiratory tract infection (9%, severe 2%)
	urinary tract infection (7%, severe <1%)
investigations	ALT increase (3-22%, severe 2%)[7]
	AST increase (3-28%, severe 4%)[7]
	ECG ST-T wave changes (2-63%)[7]
	hyperbilirubinemia (1-10%)[5]
	QT prolongation (1-10%)[5]
	weight decrease (10-15%)[4,5,7]
metabolism and nutrition	anorexia (23-54%, severe 1-4%)[4,7]
	appetite decrease (9%, severe <1%)
	dehydration (severe 2%)
	hyperglycemia (2-51%, severe 1-2%)[7]
	hypermagnesemia (27%, severe 8%)[7]
	hyperuricemia (33%, severe 8%)[7]; see paragraph following **Side Effects** table
	hypoalbuminemia (3-48%, severe1-4%)[7]
	hypocalcemia (4-52%, severe 6%)[7]
	hypokalemia (6-20%, severe 2%)[4,7]
	hypomagnesemia (7-28%, severe <1%)[4,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyponatremia (1-20%, severe 1-2%)[7]
	hypophosphatemia (27%, severe 10%)[7]
	tumour lysis syndrome (2%); see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (5%, severe 2 %)
	back pain (7%, severe <1%)
	muscle spasms (9%)
	myalgia (6%, severe <1%)
	pain in extremity (5%)
nervous system	dizziness (8%)
	dysgeusia (15-40%)[4,7]
	headache (15-34%, severe 2%)[4,7]
	lethargy (6%, severe <1%)
psychiatric	anxiety (7%)
	depression (5%)
	insomnia (7%)
renal and urinary	acute renal failure (<1%)
respiratory, thoracic and mediastinal	acute respiratory distress syndrome (<1%)
	cough (18-21%)[4,7]
	dyspnea (13-21%, severe 2-4%)[4,7]
	oropharyngeal pain (6%)
	rhinorrhea (6%)
skin and subcutaneous tissue	dermatitis (4-27%, severe 1-8%)[7]
	dry skin (6%)
	night sweats (7%)
	pruritis (7-31%, severe 6%)[4,7]
	rash (8%, severe <1%)
	skin lesion (8%)
vascular	***deep vein thrombosis*** (severe 4%)
	hypotension (7-23%, severe 2-4%)[4,7]
	pulmonary embolism (severe 2%)

Adapted from standard reference[4] unless specified otherwise.

Serious and sometimes fatal ***infections*** have been reported, including the reactivation of hepatitis B, cytomegalovirus, and Epstein-Barr infections. Infections may occur during treatment and have been reported within 30 days after treatment. Patients who have received prior treatment with anti-lymphocytic monoclonal antibodies or those with bone marrow involvement may be at higher risk. Consider antiviral prophylaxis if indicated.[4,5]

Hyperuricemia may result from cell lysis by romidepsin and may lead to electrolyte disturbances or acute renal failure.[12] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients [13]:

- aggressive hydration: 3 L/m^2/24 hours with target urine output >100 mL/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg PO initially, then 300 mg PO q6h x 6 doses, then 300 mg PO daily x 5-7 days.

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[14] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[15]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[4,7]	romidepsin AUC increased by 25% and C_{max} increased by 10%	inhibition of CYP 3A4 by ketoconazole	monitor for increased romidepsin toxicity; may require romidepsin dose reduction
rifampin[4,7]	romidepsin AUC increased by 80% and C_{max} increased by 60%	possible inhibition of hepatic uptake process by rifampin	avoid concurrent therapy
warfarin[4]	prolonged prothrombin time and elevation of INR	unknown	monitor PT/PTT and INR; adjust warfarin dose as needed

Romidepsin is a substrate of CYP 3A4. Strong **CYP 3A4 inhibitors** may increase romidepsin concentration; monitor for toxicity related to increased romidepsin exposure. The effect of **CYP 3A4 inducers** on romidepsin is unknown.[4,5].

Romidepsin competes with β-estradiol for binding to estrogen receptors and may reduce the effectiveness of **estrogen-containing contraceptives** may be reduced.[4]

Drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes may be required.[4]

Romidepsin is a substrate of P-glycoprotein; clinical significance is unknown.[4]

SUPPLY AND STORAGE:

Injection**:** Celgene Inc. supplies romidepsin as a 10 mg* single-use vial of sterile lyophilized powder. Vials contain povidone as a bulking agent. Use supplied single-use vial of diluent (propylene glycol and dehydrated alcohol) for reconstitution. Store at room temperature in original carton.[16]

Additional information: Drug and diluent vials contain overfill to facilitate consistent delivery of recommended volume needed for product preparation. Each **10 mg*** vial of romidepsin contains 11 mg. Each vial of supplied diluent contains 2.4 mL (includes an overfill of 0.2 mL).[16,17]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not recommended[4]
Intermittent infusion	***over 4 hours***[4,18]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous[4,6,18-20]*:*	***4 weeks***:	***14 mg/m²*** (range 8-17.5 mg/m^2) ***IV for one dose on days 1, 8 and 15*** (total dose per cycle 42 mg/m^2 [range 24-52.5 mg/m^2])
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[2,4,5]*:*	renal impairment does not affect romidepsin pharmacokinetics; no information found for end-stage renal disease	
Dosage in hepatic failure[2,4,5]*:*	mild hepatic impairment does not affect romidepsin pharmacokinetics; no information found for moderate or severe hepatic impairment	
Dosage in dialysis:	no information found	

Children: no information found

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