DRUG NAME: Dactinomycin

SYNONYM(S)[1]: actinomycin D, actinomycin C1

COMMON TRADE NAME(S): COSMEGEN®

CLASSIFICATION: antitumour antibiotic

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

MECHANISM OF ACTION:

Dactinomycin is an antineoplastic antibiotic derived from *Streptomyces parvullus.*[2] Stable complexes are formed with DNA through intercalation and DNA-dependent RNA synthesis is selectively inhibited.[1-3] Protein and DNA synthesis are inhibited to a lesser extent.[3] Dactinomycin is cell cycle phase-nonspecific[1]. Dactinomycin is an immunosuppressive agent.[3]

PHARMACOKINETICS:

Oral Absorption	poor[3]	
Distribution	rapid; high concentrations in bone marrow and nucleated cells[3]; extensively bound to body tissues	
	cross blood brain barrier?	<10%
	volume of distribution	no information found
	plasma protein binding	not highly protein bound
Metabolism	minimal	
	active metabolite(s)	none
	inactive metabolite(s)[3]	small amounts of monolactones have been recovered in urine
Excretion	rapidly cleared from plasma (85% within 2 min)	
	urine	12-20% of dose recovered within 24 h, 15% of dose recovered unchanged after 1 week
	feces	50-90% of dose excreted in bile within 24 h, 15% of dose recovered after 1 week
	terminal half life	36 hours, possibly prolonged with hepatic dysfunction
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Gestational trophoblastic tumour
*Rhabdomyosarcoma
*Wilms' tumour

Other uses:
*Ewing's sarcoma
Ovarian germ cell tumour[3]
Kaposi's sarcoma[4]
Malignant melanoma[5]
Testicular cancer[3,6]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- recent or current infection with chicken pox or herpes zoster[2]

Caution:
- ***concurrent dactinomycin with radiation therapy*** has been associated with severe reactions, including increased side effects, potentiation of radiation, and reactivation reactions[3];
- hepatomegaly, ascites, and elevated AST levels have been noted in combination therapy of ***right-sided Wilms' tumour***; avoid using dactinomycin concurrently with radiation for Wilms' tumour, particularly within the first two months after irradiation.[2]

Special populations:
- not recommended in children ***under 6 months of age*** due to an increased frequency of toxic effects[2]
- ***elderly*** patients may experience an increased risk of myelosuppression, and consideration should be given to initiating therapy at the lower end of the dose range[2]

Carcinogenicity: Secondary malignancies, including leukemia, have been reported in patients treated with concurrent radiation and other agents.[2,3,7,8] In animal studies, local sarcomas and mesenchymal tumours were reported after repeated injections. The International Agency on Research on Cancer (IARC) has judged dactinomycin as a carcinogen in animals.[9]

Mutagenicity: Mutagenic in various *in vitro* and *in vivo* test systems, including human fibroblasts and leukocytes, and HELA cells. Clastogenic in mammalian *in vivo* chromosome tests.[2]

Fertility: Dactinomycin has been associated with an increased incidence of infertility when administered in combination with other antineoplastic agents.[9]

Pregnancy: In animal studies, dactinomycin has been shown to cause malformations and embryotoxicity in multiple species.[9]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

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.[10,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions (<1%)
	anaphylactoid reactions
blood/bone marrow/ febrile neutropenia	agranulocytosis
	anemia, including aplastic anemia (>10%)
	febrile neutropenia
	leukopenia; nadir at 14-21 days, recovery within 21-25 days[3]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neutropenia (>10%); dose limiting[12,13]
	pancytopenia
	reticulopenia
	thrombocytopenia (>10%); may be the first manifestation of myelosuppression, occurring 1-7 days after treatment; nadir at 12-21 days, recovery within 21-25 days[3,5]
constitutional symptoms	fatigue (>10%)
	fever
	lethargy
	malaise
dermatology/skin	*extravasation hazard:* vesicant[2,3]
	acne, acneiform eruptions
	alopecia (11%)[5]; usually begins after 7-10 days, reversible; may involve the scalp and eyebrows[3]
	erythema; occurs early at site of irradiation, may be followed rapidly by hyperpigmentation, and/or edema, desquamation, vesiculation, and rarely necrosis [3]
	folliculitis; may extend down back, including buttocks[14]
	pruritic maculopapular rash
	rash (37%, severe 26%); exacerbated by radiation or sun exposure (16%)[5]
endocrine	growth retardation
gastrointestinal	*emetogenic potential:* moderate to high-moderate[12,13]
	abdominal pain
	anorexia
	cheilitis (inflammation of the lips)
	diarrhea (1-29%)[2,5]; hold treatment until recovery[2,3]
	dysphagia (11%)[5]
	esophagitis
	gastrointestinal ulceration
	glossitis
	mucositis (29-47%, severe 11%)[5]; more severe with high doses combined with high doses of radiation therapy[3]
	nausea and vomiting (29-79%)[5]; usually occurs during the first few hours,[2] and can last up to 24 hours[3]; sometimes lasts up to 3 days and requires hospitalization[5]
	pharyngitis
	proctitis
	stomatitis; dose limiting[2,12,13]
hepatobiliary/pancreas	ascites

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hepatic failure, usually reversible, sometimes fatal[2-4]; see paragraph following **Side Effects** table
	hepatic veno-occlusive disease[2]; sometimes fatal (particularly in children <4 years); may be associated with intravascular clotting disorder and multiorgan failure[3,6]
	hepatitis
	hepatomegaly
infection	infection, unspecified (1-10%)
metabolic/laboratory	hypocalcemia
	liver function test abnormalities, unspecified
	renal function test abnormalities, unspecified
musculoskeletal	myalgia
pulmonary	pneumonitis
secondary malignancy	leukemia[2,3,7]
syndromes	flu-like syndrome; may occur 1 week after infusion and persist 1-3 weeks[6]

Adapted from standard reference[2] unless specified otherwise.

Hepatotoxicity: Ascites, hepatomegaly, hepatic veno-occlusive disease, hepatitis, and liver function test abnormalities have been reported, sometimes with fatal outcomes.[2,4] Usual doses are more likely to produce hepatotoxicity in situations where additional stressors are placed on the liver (e.g., concomitant radiation).[4]

Severe reactions, including increased side effects, potentiation of radiation, and reactivation reactions have been reported ***with concurrent radiation therapy***. Gastrointestinal toxicity and marrow suppression can occur more frequently, especially with higher doses. Radiation myelitis has been reported.[3] Severe oropharyngeal mucositis has been associated with concurrent therapy when radiation is directed towards the nasopharynx.[2,3] Potentiation effects of radiation therapy include smaller radiation doses causing erythema and vesiculation,[2] and rarely necrosis.[3] Skin sequelae may progress more rapidly through the stages of tanning and desquamation with healing occurring in 4-6 weeks (compared to 2-3 months).[2] Reactivation erythema has been reported in previously irradiated tissues, especially if the treatment interval is brief, but has also been described in therapy occurring months after radiation.[3] Reactivation of radiation enteritis has also been described.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
halogenated inhalation anesthetics (enflurane, halothane)[2]	increased hepatoxicity	not specified	monitor liver function tests; use with caution
vaccines, live[2]	increased risk of infection	decreased immune response may allow vaccine to produce infection	avoid vaccination with live vaccines

Bioassay procedures for the determination of antibacterial drug levels may be affected by dactinomycin.[2]

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SUPPLY AND STORAGE:

***Injection*:** Recordati Rare Diseases Canada Inc. supplies dactinomycin as 0.5 mg (500 mcg) vials of lyophilized powder. Store at room temperature. Protect from light.[9]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:
- avoid use of sterile water containing preservatives (benzyl alcohol or parabens) for reconstitution as precipitate will result[2]
- compatible with D5W and saline solutions[2]
- avoid the use of in-line cellulose ester membrane filters for administration as partial removal of dactinomycin has been reported[2,3]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous[3]	not used due to corrosive nature
Intramuscular[3]	not used due to corrosive nature
***Direct intravenous*[12,13,15]**	***into tubing of running IV***; see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion[4-6]	infuse over 10-15 minutes
Continuous infusion[16]	has been used
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found
Regional isolation perfusion therapy[3,4]	has been used

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.

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***Adults*:**

For each two week course of therapy, maximum dose should not exceed 0.015 mg/kg or 0.4-0.6 mg/m^2 IV once daily for 5 consecutive days.[9]

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

	Cycle length:	
Intravenous:	***3-6 weeks***[9,17-21]:	***0.04 mg/kg*** (range 0.04-0.045 mg/kg) ***IV for one dose on day 1*** (total dose per cycle 0.04 mg/kg [range 0.04-0.045 mg/kg])
	2 weeks[9,22-24]:	***0.5 mg IV once daily for 2 consecutive days starting on day 1*** (total dose per cycle 1.0 mg)
	2 weeks[25,26]:	***0.6 mg/m^2 IV once daily for 2 consecutive days starting on day 1*** (total dose per cycle 1.2 mg/m^2)
	2 weeks[25,27,28]:	***1.25 mg/m^2 IV for one dose on day 1*** (total dose per cycle 1.25 mg/m^2)
	3 weeks[9,24,29]:	1.25 mg/m^2 IV for one dose on day 1 (total dose per cycle 1.25 mg/m^2)
	2 weeks[9,22,24,27]:	0.012 mg/kg IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 0.06 mg/kg)
	3-9 weeks[24,29]:	0.015 mg/kg IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 0.075 mg/kg)
	n/a[24]:	0.035-0.050 mg/kg IV for one dose

Concurrent radiation: reported to cause increased sensitivity to radiation therapy; reduce dose in patients who are receiving concurrent radiation therapy[2,3]

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: no adjustment required[2]

Dosage in hepatic failure: consider dose reduction in moderate to severe hepatic failure; may reduce dose by 30-50% for hyperbilirubinemia[2]

Dosage in dialysis: no information found

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Children:

For each two week course of therapy, maximum dose should not exceed 0.015 mg/kg or 0.4-0.6 mg/m^2 IV once daily for 5 consecutive days.[9]

	Cycle Length:	
Intravenous:	3-6 weeks[9,19-21,30,31]:	0.045 mg/kg IV for one dose on day 1 (total dose per cycle 0.045 mg/kg)
	3-6 weeks[31,32]:	0.05 mg/kg IV for one dose on day 1 (total dose per cycle 0.05 mg/kg)
	3-6 weeks[21,24,30,31]:	0.023-0.025 mg/kg IV for one dose on day 1 (total dose per cycle 0.023-0.025 mg/kg])
	3-9 weeks[9,24,33]:	0.015 mg/kg IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 0.075 mg/kg)
	3 weeks[9,24,29]:	1.25 mg/m^2 IV for one dose on day 1 (total dose per cycle 1.25 mg/m^2)
	6 weeks[30]:	1.35 mg/m^2 IV for one dose on day 1 (total dose per cycle 1.35 mg/m^2)
	4 weeks[24]:	0.42 mg/m^2 IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 2.1 mg/m^2)
	3 weeks[24]:	0.5 mg/m^2 IV once daily for 3 consecutive days starting on day 1 (total dose per cycle 1.5 mg/m^2)

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