Drug Monograph

A - Drug Name

DACTINomycin

SYNONYM(S): actinomycin D

COMMON TRADE NAME(S): Cosmegen®

back to top

B - Mechanism of Action and Pharmacokinetics

Dactinomycin is a derivative of Streptomyces parvulus. At low concentrations, dactinomycin inhibits DNA-primed RNA synthesis by intercalating with guanine residues of DNA. At higher concentrations, it also inhibits DNA synthesis. Interstrand and DNA-protein cross-links may also occur. Dactinomycin is considered to be cell cycle phase-nonspecific. It appears to be a radiosensitizer.

Absorption	Oral: Poorly absorbed from gastrointestinal tract	
Distribution	Rapid entry into nucleated cells (bone marrow, tumour cells > plasma), crosses placenta.	
	Cross blood brain barrier?	no
	Volume of distribution	no information found
	PPB	Not highly protein bound
Metabolism	Minimally metabolized	
	Active metabolites	no

	Inactive metabolites	yes
Elimination	85% cleared from blood in 2 minutes	
	Feces	50-90% excreted in bile within 24h; 15% of dose recovered in feces in 1 week
	Urine	12-20% in 24 h; 15% of dose recovered unchanged in 1 week
	Half-life	36 hours; prolonged with hepatic dysfunction

back to top

C - Indications and Status

Health Canada Approvals:

As part of a combination chemotherapy in:

- Rhabdomyosarcoma
- Wilms' tumour
- Ewing's sarcoma

As single agent, or part of a combination chemotherapy in:

- Gestational trophoblastic neoplasia

back to top

D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Flushing (face, torso)	I
Dermatological	Alopecia (rare, mild-moderate)	E

	Radiation recall reaction	I
	Rash	I E
	Skin hyperpigmentation (in previous irradiated areas)	D
Gastrointestinal	Abdominal pain	I
	Anorexia	I
	Diarrhea (30%)	E
	Mucositis (30%) (may be severe)	E
	Nausea, vomiting	I
General	Fatigue	I E
	Fever, chills	I
Hematological	Disseminated intravascular coagulation (rare)	E
	Myelosuppression ± infection, bleeding (may be severe)	E
Hepatobiliary	↑ LFTs (may be severe)	E
	Veno-occlusive disease (rare)	E
Hypersensitivity	Drug reaction	I
Injection site	Injection site reaction (pain)	I
Metabolic / Endocrine	↓ Ca (rare)	I
Musculoskeletal	Myalgia	E
Neoplastic	Secondary malignancy (rare)	L
Ophthalmic	Optic nerve disorder rare	E
Respiratory	Pneumonitis (rare)	E D

* "*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)

Dactinomycin is extremely corrosive. The **tissue necrosis** that occurs with **extravasation** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected.

Dactinomycin has the potential to enhance radiation injury to tissues; it may increase gastrointestinal toxicity or marrow suppression when given with radiation. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of dactinomycin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Hepatotoxicity has occurred in children with Wilms' tumour, especially if they have received right-sided abdominal irradiation. This may manifest as increased AST (SGOT) and bilirubin levels, ascites and liver enlargement. In some cases, thrombocytopenia may accompany hepatotoxicity. Factors associated with severe hepatotoxicity include concurrent administration of other hepatotoxic agents, especially halogenated anesthetics, using single-dose dactinomycin as opposed to a 5 day regimen, doses of dactinomycin ≥60 mcg/kg and radiation.

There is an increased incidence of secondary malignancies and leukemias.

back to top

E - Dosing

Refer to protocol by which patient is being treated. Dosage may be reduced and/or delayed in patients with bone marrow depression due to previous or concomitant cytotoxic/radiation therapy.

Dosage should be based on BSA in obese or edematous patients to relate dosage to lean body mass.

Adults:

Numerous dosing schedules and regimens exist depending on disease, response and concomitant therapy. See individual regimen for dosing details.

Dosing information from some regimens described in literature:

- 0.045 mg/kg IV x on day 1; q3 weeks (max 2.5mg used in some protocols) in various schedules and combinations with other chemotherapy agents
- 0.012-0.015 mg/kg IV (max 0.5mg used in some protocols) x 5 days in various schedules, as single agent or in combination with other chemotherapy agents
- 1.25 mg/m^2 in various schedules and combinations with other chemotherapy agents
- 0.5 mg on days 1 and 2 (part of EMA-CO regimen)

Dosage with Toxicity:

Hold treatment if stomatitis, diarrhea or severe myelosuppression occurs.

Dosage in myelosuppression:

- Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-hematologic Toxicities".

Dosage with Hepatic Impairment:

Adjustment required in moderate to severe hepatic impairment; no specific recommendations found. May consider dose reduction by 33-50% in hyperbilirubinemia.

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

Increased risk of myelosuppression in the elderly as compared to younger patients. Consider starting at the low end of the dosing range.

Children:

Refer to protocol being used. Should be given to infants only over the age of 6 to 12 months because of toxic effects of dactinomycin.

Intravenous: q 3-4 w: 0.015mg/kg/day for 5 days

back to top

F - Administration Guidelines

- Slow push through sidearm of free flowing IV (5% Dextrose or Normal Saline).
- May be mixed in a minibag (Normal Saline or D5W; concentration must be at least 0.01 mg/mL); Infuse over 10-15 minutes.
- Do not use cellulose ester membrane filters, since these may filter out dactinomycin.
- Reconstitute dactinomycin by adding 1.1 mL of sterile water for injection (without preservative) using aseptic precautions. Precipitation occurs if sterile water containing preservatives is used.
- Dactinomycin is extremely corrosive to soft tissue, irritating to the eyes and mucous membranes; precautions for materials of this nature should be observed.
- Protect from light.

back to top

G - Special Precautions

Contraindications:

Dactinomycin is **contraindicated** in patients who are hypersensitive to the drug or to any ingredients in the formulation, or those infected with chickenpox or herpes zoster as generalized infection may occur. Avoid the use of live vaccines.

Other Drug Properties:

- Known radiosensitizer: Yes
  Dactinomycin should be used with caution in patients who have had or who are having pelvic or abdominal radiation, as the risks of hepatic and marrow toxicities are increased. Dactinomycin should not be administered concurrently with radiotherapy in Wilms' tumour unless benefit outweighs the risk.
- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Teratogenicity: Yes
  Dactinomycin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Breastfeeding: Contraindicated
  Breastfeeding is not recommended due to the potential secretion into breast milk.
- Fertility effects: Unknown

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
radiation	↑ toxicity	radiosensitizer	Caution
Halogenated inhalation anesthetics (e.g., enflurane, halothane)	↑ hepatotoxicity	Additive	Caution

back to top

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
Renal function tests	Baseline and periodic
Liver function tests	Baseline and periodic
CBC	Baseline and regular
Clinical assessment of GI, pneumonitis, skin, hepatic and local toxicity	At each visit

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

back to top

K - References

Arndt C, Hawkins D, Anderson JR, et al. Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. J Clin Oncol 2004;22:1894-901.

Cancer Drug Manual: Dactinomycin. British Columbia Cancer Agency (BCCA), October 1, 2009.

Clinical Practice Guidelines: Gestational Trophoblastic Disease. Society of Obstetricians and

Gynecologists of Canada, 2002.

Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001; 19: 3091-102.

Crist W, Gehan EA, Ragab AH, et al. The third intergroup rhabdomyosarcoma study. J Clin Oncol 1995;13:610-30.

Dactinomycin: AHFS Drug Information. American Society of Health-Systems Pharmacists, 2009.

Escobar PF, Lurain JR, Singh DK, et al. Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. Gynecologic Oncology 2003;91:552–7.

Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 1998;16:237-245.

Green DM, Norkool P, Breslow NE, et al. Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the National Wilms' Tumor Study. JCO 1990:8(9);1525-30.

Green DM, Finklestein JZ, Norkool P, et al. Severe hepatic toxicity after treatment with single-dose dactinomycin and vincristine. A report of the National Wilms' Tumor Study. Cancer 1988;62(2):270-3.

Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol 2004;22(14):2873-6.

Osathanondh R, Goldstein DP, Pastorfide GB, et al. Actinomycin D as the primary agent for gestational trophoblastic disease. Cancer 1975;36(3):863-6.

Pappo AS, Lyden E, Breitfeld P, et al. Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol 2007;25(4):362-9.

Product Monograph: Cosmegen® (Dactinomycin). Lundbeck Inc., November 7, 2011.

June 2019 Updated emetic risk category

back to top

L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top