DACTINomycin (dak ti noe MYE sin)

**Related Information**
- Management of Chemotherapy-Induced Nausea and Vomiting in Adults on page 2455
- Management of Drug Extravasations on page 2467
- Prevention of Chemotherapy-Induced Nausea and Vomiting in Children on page 2488
- Safe Handling of Hazardous Drugs on page 2497

**Pharmacologic Category** Antineoplastic Agent, Antibiotic

**Use**
- **Ewing sarcoma:** Treatment of Ewing sarcoma (as part of a multi-phase, combination chemotherapy regimen)
- **Gestational trophoblastic neoplasia:** Treatment of gestational trophoblastic neoplasia in post-menarchal patients (as a single agent or as part of a combination chemotherapy regimen)
- **Rhabdomyosarcoma:** Treatment of rhabdomyosarcoma (as part of a multi-phase, combination chemotherapy regimen)
- **Solid tumors:** Palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies (as a component of regional perfusion) in adult patients
- **Wilms tumor:** Treatment of Wilms tumor (as part of a multi-phase, combination chemotherapy regimen)

**Labeled Contraindications** There are no contraindications listed in the manufacturer's labeling.

**Pregnancy Considerations** Based on data from animal reproduction studies and its mechanism of action, dactinomycin may cause fetal harm if administered to a pregnant female. Verify pregnancy status of females of reproductive potential prior to initiating dactinomycin therapy; effective contraception should be used during therapy and for at least 6 months after the last dactinomycin dose. When used for gestational trophoblastic neoplasm, unfavorable outcomes have been reported when subsequent pregnancies occur within 6 months of treatment. It is recommended to use effective contraception for 6 months to 1 year after therapy (Matsui 2004; Seckl 2013). Males with female partners of reproductive potential should use effective contraception during therapy and for 3 months after the last dactinomycin dose.

**Breastfeeding Considerations** It is not known if dactinomycin is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and (based on limited data) for 14 days after the last dactinomycin dose.

**Warnings/Precautions** Dactinomycin is a vesicant (Pérez Fidalgo 2012); ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. Severe local tissue damage (blistering, ulcerations, and persistent pain) requiring wide excision surgery followed by split-thickness skin grafting may occur. Immediately interrupt the infusion if signs/symptoms of extravasation occur. Apply dry, cold compresses to the site of extravasation for 20 minutes, 4 times per day for 1 to 2 days (Pérez Fidalgo 2012). Monitor closely; plastic surgery consultation may be necessary if extravasation occurs. Severe and fatal myelosuppression (neutropenia, thrombocytopenia, and anemia) may occur. The neutrophil nadir typically occurs 14 to 21 days after administration. Obtain complete blood counts prior to each cycle; delay the next dactinomycin dose if severe myelosuppression has not improved. Based on the severity of myelosuppression and disease state being treated, consider
dose reduction in patients with prolonged myelosuppression. Severe mucocutaneous toxicity, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, may occur. Permanently discontinue dactinomycin if a severe mucocutaneous reaction occurs. Dactinomycin may cause hepatotoxicity; monitor AST, ALT, alkaline phosphatase, and bilirubin prior to and during dactinomycin therapy. May also cause severe and fatal hepatic sinusoidal obstruction syndrome (SOS; formerly called veno-occlusive liver disease); risk factors include age <4 years or concomitant radiotherapy. Use with caution in hepatobiliary dysfunction. Monitor for signs or symptoms of hepatic SOS, including bilirubin >1.4 mg/dL, unexplained weight gain, ascites, hepatomegaly, or unexplained right upper quadrant pain (Arndt 2004). If SOS develops, consider delaying the next dactinomycin dose. May require therapy interruption, dose reduction, or permanent discontinuation (based on the severity of the reaction and disease being treated).

Dactinomycin potentiates the effects of radiation therapy; use with caution in patients who have received radiation therapy. Reduce the dactinomycin dose by 50% in patients who are receiving dactinomycin and concomitant radiation therapy. Combination with radiation therapy may result in increased toxicity (eg, GI toxicity, myelosuppression, or erythema and vesiculation of the skin or buccal and pharyngeal mucosa). Radiation recall risk appears to be highest when administered within 2 months of prior radiation, although the risk can still occur with distant radiation exposure.

Dactinomycin is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011). Renal function abnormalities may occur with dactinomycin; monitor creatinine and electrolytes frequently during treatment. The risk of secondary malignancies (including leukemia) is increased with dactinomycin use. Dosage is usually expressed in MICROgrams. Calculate the dose for obese or edematous patients based on ideal body weight. Avoid administration of live vaccines prior to and during dactinomycin treatment. Potentially significant drug-drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

**Adverse Reactions**

Frequency not defined:
- Cardiovascular: Thrombophlebitis
- Central nervous system: Fatigue, malaise, peripheral neuropathy
- Dermatologic: Acne vulgaris, alopecia, chelitis, dermatitis, erythema multiforme, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Endocrine & metabolic: Growth suppression, hypocalcemia
- Gastrointestinal: Abdominal pain, anorexia, aphthous stomatitis, constipation, diarrhea, dysphagia, esophagitis, gastrointestinal ulcer, mucositis, nausea, proctitis, vomiting
- Hematologic & oncologic: Anemia, bone marrow depression, disseminated intravascular coagulation, febrile neutropenia, hemorrhage, leukopenia, neutropenia ( nadir: 14 to 21 days), pancytopenia, reticulocytopenia, second primary malignant neoplasm (including leukemia), thrombocytopenia, tumor lysis syndrome
- Hepatic: Abnormal hepatic function tests, ascites, hepatic failure, hepatic sinusoidal obstruction syndrome, hepatitis, hepatomegaly, hepatotoxicity, severe hepatic disease (hepatoopathy-thrombocytopenia syndrome, Farrugia 2011)
- Hypersensitivity: Hypersensitivity reaction
Infection: Infection, sepsis  
Neuromuscular & skeletal: Myalgia  
Ophthalmic: Optic neuropathy  
Renal: Renal function abnormality, renal failure syndrome, renal insufficiency  
Respiratory: Pneumonitis, pneumothorax  
Miscellaneous: Fever, radiation recall phenomenon

Drug Interactions

**Metabolism/Transport Effects Substrate** of OATP1B1/1B3 (SLCO1B1/1B3), P-glycoprotein/ABCB1

Avoid Concomitant Use

Avoid concomitant use of DACTINomycin with any of the following: BCG (Intravesical); Cladribine; Deferiprone; Dipyrone; Natalizumab; Pimecrolimus; Tacrolimus (Topical); Vaccines (Live)

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

**Storage/Stability** Store intact vials at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from light and humidity. According to the manufacturer's labeling, recommended final concentrations (>10 mcg/mL) in D5W or NS should be stored for no more than 4 hours from reconstitution to completion of infusion (due to the lack of preservative).

**Preparation for Administration: Adult** Reconstitute initially with 1.1 mL of preservative-free SWFI to yield a concentration of 500 mcg/mL. Further dilute in D5W or NS to a recommended concentration of >10 mcg/mL. Cellulose ester membrane filters should not be used during preparation or administration.

**Mechanism of Action** Dactinomycin binds to the guanine portion of DNA intercalating between guanine and cytosine base pairs inhibiting DNA and RNA synthesis and protein synthesis

**Pharmacodynamics/Kinetics**

Distribution: Children: Extensive extravascular distribution (59 to 714 L) (Veal 2005); does not penetrate blood-brain barrier  
Metabolism: Minimally hepatic (Perry 2012)  
Half-life elimination: 30 to 40 hours (Perry 2012); Children: Range: 14 to 43 hours (Veal 2005)  
Excretion: ~30% in urine and feces within 1 week

**Dosing**

**Adult & Geriatric Note:** Dactinomycin may be prescribed in MICRO-grams (eg, 150 mcg), although many regimens list the dose in MILLI-grams (eg, mg/kg or mg/m²). Reduce the dactinomycin dose by 50% during concomitant radiation. Dactinomycin is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011). Calculate the dose for obese or edematous patients based on ideal body weight (manufacturer's labeling).
Ewing sarcoma: IV:

**VAIA regimen:** Adults ≤35 years: 500 mcg/m²/dose for 3 days (dactinomycin alternates with doxorubicin) every 3 weeks for 14 cycles (in combination with vincristine, ifosfamide, and mesna) (Paulussen 2008)

**VAC/IE regimen:** Adults ≤30 years: 1,250 mcg/m² on day 1 of each odd-numbered 21-day cycle (dactinomycin is substituted for doxorubicin after a maximum doxorubicin dose is reached; in combination with vincristine, cyclophosphamide, and mesna; alternating with IE [ifosfamide, mesna, and etoposide] on even-numbered cycles); continue through cycle 17 (Grier 2003)

**Manufacturer’s labeling:** 1,250 mcg/m² once every 3 weeks for 51 weeks (as part of a combination chemotherapy regimen)

Gestational trophoblastic neoplasm: IV:

**Nonmetastatic or metastatic low-risk disease:** 1.25 mg/m² every 2 weeks as a single agent; continue until human chorionic gonadotropin (hCG) level normalizes (Osborne 2011) or (manufacturer’s labeling) 12 mcg/kg/day for 5 days (as a single agent)

**Metastatic high-risk disease (off-label dosing):**

**EMA-CO regimen:** 500 mcg/dose on days 1 and 2 every 2 weeks (in combination with etoposide, methotrexate, leucovorin, cyclophosphamide, and vincristine); continue for at least 2 treatment cycles after a normal hCG level (Escobar 2003; Lurain 2006)

**EMA-EP regimen:** 500 mcg/dose on days 1 and 2 every 2 weeks (in combination with etoposide, methotrexate, leucovorin, and cisplatin); continue for 2 to 4 treatment cycles after a normal hCG level (Ghaemmaghami 2004)

**EP-EMA regimen:** EMA: 500 mcg/dose on day 1 every 2 weeks (in combination with etoposide, methotrexate, leucovorin, and cisplatin); alternating weekly with EP (etoposide and cisplatin) (Newlands 2000)

**Manufacturer’s labeling:** 500 mcg/dose on days 1 and 2 every 2 weeks for up to 8 weeks

Ovarian germ cell tumors, malignant (off-label use): IV: VAC regimen: 500 mcg daily for 5 days every 4 weeks (in combination with vincristine and cyclophosphamide) for ~1 year (Gershenson 1985) or 300 mcg/m²/day for 5 days every 4 weeks (in combination with vincristine and cyclophosphamide) for at least 10 cycles (Slayton 1985)

Regional perfusion in solid tumors (dosages and techniques may vary by institution; in combination with melphalan): Manufacturer’s labeling: Lower extremity or pelvis: 50 mcg/kg once; upper extremity: 35 mcg/kg once

Regional limb perfusion: Soft tissue sarcoma (locally advanced/unresectable): Isolated limb infusion protocol: 50 to 100 mcg/L of tissue in 400 mL warmed, heparinized NS (in combination with melphalan) over 20 to 30 minutes (Moncrieff 2008).

Rhabdomyosarcoma: IV:

**VAC regimen:** Patients <50 years: 45 mcg/kg (maximum dose: 2,500 mcg) every 3 weeks; duration of therapy depends on risk status (in combination with vincristine and cyclophosphamide, and mesna); dose omission required following radiation therapy (Raney 2011)

**VA regimen:** Patients <50 years: 45 mcg/kg (maximum dose: 2,500 mcg) every 3 weeks for ~1 year (in combination with vincristine); dose omission required following radiation therapy (Raney 2011)
Manufacturer's labeling: Dosing in the prescribing information may not reflect current clinical practice; 15 mcg/kg/day for 5 days every 3 to 9 weeks for up to 112 weeks (as part of a combination chemotherapy regimen).

Wilms tumor: IV:
VAD regimen (preoperative induction): Patients <30 years: IV: 45 mcg/kg/dose (maximum: 2,300 mcg/dose) on day 1 of weeks 1, 4, 7, and 10 (in combination with vincristine and doxorubicin) (Ehrlich 2017).

DD-4A regimen (postoperative): Patients <30 years: 45 mcg/kg/dose (maximum dose: 2,300 mcg/dose) on day 1 of weeks 1, 7, 13, 19, and 25 (in combination with vincristine, doxorubicin, and radiation). Note: The first dose of dactinomycin administered following whole lung or whole abdomen irradiation should be decreased by 50% (Ehrlich 2017).

EE-4A regimen (pre- or postoperative): Patients <30 years: 45 mcg/kg/dose (maximum dose: 2,300 mcg/dose) on day 1 of weeks 1, 4, 7, 10, 13, 16, and 19 (in combination with vincristine) (Ehrlich 2017).

Manufacturer's labeling: 45 mcg/kg once every 3 to 6 weeks for up to 26 weeks (as part of a combination chemotherapy regimen)

Renal Impairment: Adult There are no dosage adjustments provided in the manufacturer's labeling; however, based on the amount of urinary excretion, dosage adjustments may not be necessary (Kintzel 1995).

Hepatic Impairment: Adult
There are no dosage adjustments provided in manufacturer's labeling. The following adjustments have also been recommended: Any transaminase increase: Reduce dose by 50%; may increase by monitoring toxicities (Floyd 2006).

Obesity: Adult
Calculate the dose for obese or edematous patients based on ideal body weight (manufacturer's labeling).

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

Adjustment for Toxicity: Adult
Muco-cutaneous reaction, severe: Permanently discontinue dactinomycin.
Myelosuppression, severe: Consider treatment delay or dose reduction in patients with prolonged myelosuppression based on the reaction severity and the disease being treated.
Sinusoidal obstruction syndrome (SOS, also known as veno-occlusive disease): If SOS develops, consider delaying the next dactinomycin dose. Resume, reduce dose, or permanently discontinue dactinomycin based on the reaction severity and the disease being treated.
Concurrent radiation therapy: May require dactinomycin dose reduction (50%) or dose omission; refer to specific protocol.

Pediatric Note: Medication orders for dactinomycin are commonly written in MICROgrams (eg, mcg/kg, mcg/m²) although many regimens list the dose in MILLIgrams (eg, mg/kg or mg/m²); use extra precaution. The dose intensity per 2-week cycle for adults and children should not exceed 15 mcg/kg/day for 5 days or 400 to 600 mcg/m²/day for 5 days.
The manufacturer recommends calculation of the dosage for obese or edematous adult patients on the basis of body surface area in an effort to relate dosage to lean body mass.

**Ewing sarcoma:** Children and Adolescents: VAIA regimen: Limited data available: IV: 500 mcg/m²/dose for 3 days (dactinomycin alternating with doxorubicin) every 3 weeks for 14 cycles (in combination with vincristine, ifosfamide, and mesna) (Paulussen 2008)

**Kaposi sarcoma:** Limited data available: Children and Adolescents: IV: 420 mcg/m²/day for 5 days every 4 weeks (in various combination regimens) (Olweny 1974)

**Rhabdomyosarcoma:** VAC regimen: Limited data available:
- Infants: IV: 25 mcg/kg every 3 weeks, weeks 0 to 45 (in combination with vincristine and cyclophosphamide, and mesna); dose omission required following radiation therapy (Raney 2011)
- Children and Adolescents: IV: 45 mcg/kg (maximum dose: 2,500 mcg/dose) every 3 weeks, weeks 0 to 45 (in combination with vincristine and cyclophosphamide, and mesna); dose omission required following radiation therapy (Raney 2011)

**Wilms tumor:** Note: Regimen selection based on multiple factors including the extent of disease at diagnosis, response to induction chemotherapy, and extent of surgical resection.

**EE-4A regimen:** Note: If the radiation field includes the whole lung or whole abdomen, reduce dose 50% during irradiation therapy
- Infants: IV: 23 mcg/kg/dose (maximum dose: 2,300 mcg/dose) over 1 to 5 minutes on day 1 of weeks 1, 4, 7, 10, 13, 16, and 19 (in combination with vincristine) (Ehrlich 2017)
- Children and Adolescents: IV: 45 mcg/kg/dose (maximum dose: 2,300 mcg/dose) over 1 to 5 minutes on day 1 of weeks 1, 4, 7, 10, 13, 16, and 19 (in combination with vincristine) (Ehrlich 2017)

**VAD regimen:** Limited data available:
- Infants: IV: 23 mcg/kg/dose (maximum dose: 2,300 mcg/dose) over 1 to 5 minutes on day 1 of weeks 1, 4, 7, and 10 (in combination with vincristine and doxorubicin) (Ehrlich 2017)
- Children and Adolescents: IV: 45 mcg/kg/dose (maximum dose: 2,300 mcg/dose) over 1 to 5 minutes on day 1 of weeks 1, 4, 7, and 10 (in combination with vincristine and doxorubicin) (Ehrlich 2017)

**Chemotherapy Regimens**

**Bone sarcoma (Ewing sarcoma):** VAC Alternating With IE (Ewing Sarcoma) on page 2426

**Gestational trophoblastic tumor:**
- EMA/CO (Gestational Trophoblastic Tumor) on page 2312
- EMA-EP (Gestational Trophoblastic Tumor) on page 2313
- EP-EMA (Gestational Trophoblastic Tumor) on page 2314

**Ovarian cancer:** VAC (Ovarian) on page 2427

**Soft tissue sarcoma (rhabdomyosarcoma):**
- VAC (Rhabdomyosarcoma) on page 2427
- VA (Rhabdomyosarcoma) on page 2429

**Administration:** Adult Dactinomycin is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011).

IV: Infuse over 10 to 15 minutes; may also be administered as a slow IV push (off-label rate) in some protocols. Do not filter with cellulose ester membrane filters.
Regional perfusion: Technique may vary by institution; consult protocol for details. Local reactions including epidermolysis, erythema, and edema have been reported (may be severe).

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation.

**Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry cold compresses for 20 minutes 4 times a day for 1 to 2 days (Pérez Fidalgo 2012).

**Administration: Pediatric**

Parenteral: May administer undiluted into the side-port of a free flowing IV infusion by slow IVP over a few minutes; or may further dilute and administer as IV infusion over 10 to 15 minutes; consider a D5W or NS flush before and after a dactinomycin dose to ensure venous patency. Cellulose ester membrane filters may partially remove dactinomycin from solution and should not be used during administration. Avoid extravasation; do not give IM or SubQ.

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry cold compresses for 20 minutes 4 times a day for 1 to 2 days (Pérez Fidalgo 2012).

**Vesicant/Extravasation Risk** Vesicant

**Emetic Potential** Children and Adults: High (>90%)

**Monitoring Parameters** CBC prior to each treatment cycle, liver function tests (eg, AST, ALT, total bilirubin, alkaline phosphatase), renal function tests, and electrolytes; verify pregnancy status in females of reproductive potential prior to therapy initiation. Monitor for signs/symptoms of hepatic sinusoidal obstruction syndrome, including unexplained weight gain, ascites, hepatomegaly, or unexplained right upper quadrant pain (Arndt 2004). Monitor for signs/symptoms of secondary malignancy, extravasation, mucocutaneous reactions, and radiation recall.

**Dosage Forms: US**

**Solution Reconstituted, Intravenous:**
- Cosmegen: 0.5 mg (1 ea)
- Generic: 0.5 mg (1 ea)

**Solution Reconstituted, Intravenous [preservative free]:**
- Generic: 0.5 mg (1 ea)

**Dalteparin** (dal TE pa rin)

**Pharmacologic Category** Anticoagulant; Anticoagulant, Low Molecular Weight Heparin

**Use**

Anticoagulant for hemodialysis and hemofiltration (Fragmin [Canadian product only]): Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency

Non-ST elevation acute coronary syndromes: Prevention of ischemic complications in patients with unstable angina or non-Q-wave myocardial infarction on concurrent aspirin therapy.