

Name Of Medicine

COSMEGEN[®]

dactinomycin lyophilised powder [actinomycin D]

0.5mg per vial

Presentation

A sterile yellow to orange lyophilised powder for injection by the intravenous route or by regional perfusion after reconstitution. Each vial contains 0.5mg of dactinomycin and 20.0mg of mannitol. The reconstituted solution is clear and gold coloured.

Therapeutic Class

COSMEGEN (dactinomycin, MSD) is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*.

Indications

- COSMEGEN, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of Wilms' tumour, childhood rhabdomyosarcoma, Ewing's sarcoma, and metastatic nonseminomatous testicular cancer.
- COSMEGEN is indicated as a single agent, or as part of a combination chemotherapy regimen, for the treatment of gestational trophoblastic neoplasia.
- COSMEGEN, as a component of regional perfusion in combination with melphalan, is indicated for the treatment of locally recurrent or locoregionally metastatic melanoma.

Dosage and Administration

General

Not for oral administration.

Toxic reactions due to COSMEGEN are frequent and may be severe (see Adverse Effects), thus limiting in many instances the amount that may be administered. However, the severity of toxicity varies markedly and is only partly dependent on the dose employed.

Careful calculation of the dosage should be performed prior to administration of each dose.

Intravenous Use

The dosage of COSMEGEN varies depending on the tolerance of the patient, the size and location of the neoplasm, and the use of other forms of therapy. It may be necessary to decrease the usual dosages suggested below when additional chemotherapy or radiation therapy is used concomitantly or has been used previously.

The dosage of COSMEGEN is calculated in micrograms (mcg). The dose intensity per 2-week cycle for adults or children should not exceed 15mcg/kg/day or 400-600mcg/ square metre of body surface daily intravenously for five days. Calculation of the dosage for obese or oedematous patients should be on the basis of surface area in an effort to relate dosage to lean body mass.

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A wide variety of single agent and combination chemotherapy regimens with COSMEGEN may be employed. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of physicians familiar with current oncologic practices and new advances in therapy. The following suggested regimens are based upon a review of current literature concerning therapy with COSMEGEN and are on a per-cycle basis.

Wilms' Tumour

Regimens of 45 mcg/kg intravenously administered in various combinations and schedules with other chemotherapeutic agents.

Rhabdomyosarcoma

Regimens of 15 mcg/kg intravenously daily for five days administered in various combinations and schedules with other chemotherapeutic agents.

Ewing's Sarcoma

Regimens of 1.25 mg/m² intravenously administered in various combinations and schedules with other chemotherapeutic agents.

Testicular Carcinoma

1000 mcg/m² intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin.

Gestational Trophoblastic Neoplasia

12 mcg/kg intravenously daily for five days as a single agent.

500 mcg intravenously on Days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and cisplatin.

Regional Perfusion in Locally Recurrent and Locoregionally Metastatic Melanoma

The dosage schedules and the technique itself vary from one investigator to another; the published literature, therefore, should be consulted for details. In general, the following doses are suggested:

50 mcg (0.05 mg) per kilogram of body weight for lower extremity or pelvis.

35 mcg (0.035 mg) per kilogram of body weight for upper extremity.

It may be advisable to use lower doses in obese patients, or when previous chemotherapy or radiation therapy has been employed.

Administration

COSMEGEN may be reconstituted by adding 1.1ml of Sterile Water for Injection (without preservative) using aseptic precautions. The resulting solution of dactinomycin will contain approximately 500 mcg or 0.5 mg per ml.

Parenteral agent products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstituted, COSMEGEN is a clear, gold-coloured solution.

Once reconstituted, the solution of COSMEGEN can be added to infusion solutions of Dextrose Injection 5 percent or Sodium Chloride Injection either directly or to the tubing of a running intravenous infusion.

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Although reconstituted COSMEGEN is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute COSMEGEN for injection, results in the formation of a precipitate.

Partial removal of dactinomycin from intravenous solutions by cellulose ester membrane filters used in some intravenous in-line filters has been reported.

Since COSMEGEN is extremely corrosive to soft tissue, precautions for materials of this nature should be observed.

COSMEGEN is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. Since COSMEGEN is extremely corrosive to soft tissue, it is intended for intravenous use. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes must be avoided. Appropriate protective equipment should be worn when handling COSMEGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. (See Dosage and Administration, *Special Handling*).

If the medicine is given directly into the vein without the use of an infusion, the "two-needle technique" should be used. Reconstitute and withdraw the calculated dose from the vial with one sterile needle. Use another sterile needle for direct injection into the vein.

Special Handling

Animal studies have shown dactinomycin to be corrosive to skin, irritating to the eyes and mucous membranes of the respiratory tract and highly toxic by the oral route. It has also been shown to be carcinogenic, mutagenic, embryotoxic and teratogenic. Due to the medicine's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of COSMEGEN for parenteral administration. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. It is recommended that the preparation of injectable antineoplastic medicines should be performed in a Class II laminar flow biological safety cabinet. Personnel preparing medicines of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments, and shoe covers. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapours and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several guidelines for proper handling and disposal of antineoplastic medicines have been published and should be considered.

Accidental Contact Measures

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and

shoes cleaned thoroughly before reuse. (See Warnings and Precautions and Dosage and Administration).

Management of Extravasation

Care in the administration of COSMEGEN will reduce the chance of perivenous infiltration. (See Warnings and Precautions and Adverse Effects). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of COSMEGEN, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes 4 times daily for 3 days may be useful. The benefit of local administration of medicines has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

Contraindications

Hypersensitivity to any component of this product.

COSMEGEN should not be given at or about the time of infection with chicken pox or herpes zoster because of the risk of severe generalised disease, which may result in death.

Warnings and Precautions

General

COSMEGEN should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. **Due to the toxic properties of dactinomycin (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently.**

COSMEGEN is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. Since COSMEGEN is extremely corrosive to soft tissues, it is intended for intravenous use. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling COSMEGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. (See Dosage and Administration, *Special Handling*).

If extravasation occurs during intravenous use, severe damage to soft tissues may occur (see Dosage and Administration, *Special Handling*).

As with all antineoplastic agents, COSMEGEN is a toxic medicine and very careful and frequent observation of the patient for adverse reactions is necessary. These reactions

may involve any tissue of the body most commonly the haematopoietic system resulting in myelosuppression. As such live virus vaccines should not be administered during therapy with COSMEGEN. The possibility of an anaphylactoid reaction should be borne in mind.

It is extremely important to observe the patient daily for toxic adverse effects when combination chemotherapy is employed, since a full course of therapy occasionally is not tolerated. If stomatitis, diarrhoea, or severe haematopoietic depression appear during therapy, these medicines should be discontinued until the patient has recovered.

VENO-OCCLUSIVE DISEASE

Veno-occlusive disease (primarily hepatic) may result in fatality, particularly in children younger than 48 months. (See Adverse Effects, *Hepatic*).

COSMEGEN and Radiation Therapy

An increased incidence of gastrointestinal toxicity and marrow suppression has been reported with combined therapy incorporating COSMEGEN and radiation. Moreover, the normal skin, as well as the buccal and pharyngeal mucosa, may show early erythema. A smaller than usual radiation dose administered in combination with COSMEGEN causes erythema and vesiculation, which progress more rapidly through the stages of tanning and desquamation. Healing may occur in four to six weeks rather than two to three months. Erythema from previous radiation therapy may be reactivated by COSMEGEN alone, even when radiotherapy was administered many months earlier, and especially when the interval between the two forms of therapy is brief. This potentiation of radiation effect represents a special problem when the radiotherapy involves the mucous membrane. When irradiation is directed toward the nasopharynx, the combination may produce severe oropharyngeal mucositis. Severe reactions may ensue if high doses of both COSMEGEN and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.

Particular caution is necessary when administering COSMEGEN within two months of irradiation for the treatment of right-sided Wilms' tumour, since hepatomegaly and elevated AST levels have been noted. In general, COSMEGEN should not be concomitantly administered with radiotherapy in the treatment of Wilms' tumour unless the benefit outweighs the risk.

Reports indicate an increased incidence of second primary tumours (including leukaemia) following treatment with radiation and antineoplastic agents, such as COSMEGEN. Multi-modal therapy creates the need for careful, long-term observation of cancer survivors.

COSMEGEN and Regional Perfusion Therapy

Complications of the perfusion technique are related mainly to the amount of medicine that escapes into the systemic circulation and may consist of haematopoietic depression, absorption of toxic products from massive destruction of neoplastic tissue, increased susceptibility to infection, impaired wound healing, and superficial ulceration of the gastric mucosa. Other side effects may include oedema of the extremity involved, damage to soft tissues of the perfused area, and (potentially) venous thrombosis.

Laboratory Tests

Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic disease and receiving COSMEGEN. Renal, hepatic, and bone marrow functions should be assessed frequently.

COSMEGEN may interfere with bioassay procedures for the determination of antibacterial medicine levels.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. COSMEGEN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse effects in nursing infants from COSMEGEN, a decision should be made as to discontinue nursing and/or the medicine, taking into account the importance of the medicine to the mother.

Paediatric Use

The greater frequency of toxic effects of COSMEGEN in infants suggest that this medicine should be administered to infants only over the age of 6 to 12 months.

Use in the Elderly

Clinical studies of COSMEGEN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, a published meta-analysis of all studies performed by the Eastern Cooperative Oncology Group (ECOG) over a 13 year period suggests that administration of COSMEGEN to elderly patients may be associated with an increased risk of myelosuppression compared to younger patients.

Animal Toxicology

The intravenous LD₅₀ of dactinomycin in the rat is 460 mcg/kg. The oral LD₅₀ of dactinomycin is 7.8 mg/kg and 7.2 mg/kg in the mouse and rat, respectively.

Carcinogenesis.

The International Agency on Research on Cancer has judged that dactinomycin is a positive carcinogen in animals. Local sarcomas were produced in mice and rats after repeated subcutaneous or intraperitoneal injection. Mesenchymal tumours occurred in male F344 rats given intraperitoneal injections of 50mcg/kg, 2 to 5 times per week for 18 weeks. The first tumour appeared at 23 weeks.

Mutagenesis

Dactinomycin has been shown to be mutagenic in a number of test systems in vitro and in vivo including human fibroblasts and leucocytes, and HELA cells. DNA damage and cytogenetic effects have been demonstrated in the mouse and the rat.

Impairment of Fertility

Adequate fertility studies have not been reported, although, reports suggest an increased incidence of infertility following treatment with other antineoplastic agents.

Teratogenic Effects

Dactinomycin has been shown to cause malformations and embryotoxicity in the rat, rabbit and hamster when given in doses of 50-100mcg/kg intravenously (3-7 times the maximum recommended human dose).

Adverse Effects

Toxic effects (excepting nausea and vomiting) usually do not become apparent until two to four days after a course of therapy is stopped, and may not peak until one to two weeks have elapsed. Deaths have been reported. However, adverse reactions are usually

reversible on discontinuance of therapy.

They include the following:

Miscellaneous: Malaise, fatigue, lethargy, fever, myalgia, proctitis, hypocalcaemia, growth retardation, infection

Lung: Pneumonitis

Oral: cheilitis, dysphagia, oesophagitis, ulcerative stomatitis, pharyngitis,

Gastrointestinal: anorexia, nausea, vomiting, abdominal pain, diarrhoea, gastrointestinal ulceration. Nausea and vomiting, which may occur early during the first few hours after administration, may be alleviated by the administration of anti-emetics.

Hepatic: Liver toxicity including liver function test abnormalities, ascites, hepatomegaly, hepatitis, and hepatic failure with reports of death. Hepatic veno-occlusive disease, which may be associated with intravascular clotting disorder and multi-organ failure, has been reported in patients receiving COSMEGEN as part of a multi-medicine chemotherapy regimen (see Warnings and Precautions, *Veno-Occlusive Disease*).

Haematologic: anaemia, even to the point of aplastic anaemia, agranulocytosis, leukopaenia, thrombocytopaenia, pancytopaenia, reticulocytopenia. Platelet and white cell counts should be performed frequently to detect severe haematopoietic depression. If either count markedly decreases, the medicine should be withheld to allow marrow recovery. This often takes up to three weeks.

Dermatologic: alopecia, skin eruptions, acne, flare-up of erythema or increased pigmentation of previously irradiated skin.

Soft Tissue: dactinomycin is extremely corrosive. If extravasation occurs during intravenous use, severe damage to soft tissues will occur. In at least one instance, this has led to contracture of the arms (see Dosage and Administration, *Management of Extravasation*). Epidermolysis, erythema, and oedema, at times severe, have been reported with regional limb perfusion.

Laboratory Tests

Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic disease and receiving COSMEGEN. Renal, hepatic, and bone marrow functions should be assessed frequently.

Interactions

It has been reported that dactinomycin may interfere with bioassay procedures for the determination of antibacterial medicine levels.

Overdosage

Manifestations of overdosage in patients have included nausea, vomiting, diarrhoea, mucositis including stomatitis, gastrointestinal ulceration, skin disorders including exanthema, desquamation and epidermolysis, severe haematopoietic depression, veno-occlusive disease, acute renal failure and death. No specific information is available on the treatment of overdosage with COSMEGEN. Treatment is symptomatic and supportive. It is advisable to check skin and mucous membrane integrity as well as renal, hepatic, and

bone marrow functions frequently.

Actions

Generally, the actinomycins exert an inhibitory effect on gram-positive and gram-negative bacteria and on some fungi. However, the toxic properties of the actinomycins (including dactinomycin) in relation to antibacterial activity are such as to preclude their use as antibiotics in the treatment of infectious diseases.

Because the actinomycins are cytotoxic, they have an antineoplastic effect which has been demonstrated in experimental animals with various types of tumour implants. This cytotoxic action is the basis for their use in the treatment of certain types of cancer.

Experimental evidence indicates that dactinomycin acts by forming complexes with deoxyribonucleic acid (DNA) and selectively inhibiting the DNA-directed synthesis of ribonucleic acid (RNA). Dactinomycin is thought to inhibit protein synthesis by inhibiting the synthesis of messenger RNA. Dactinomycin inhibits DNA synthesis but at much higher concentrations than are required to inhibit RNA synthesis.

Pharmacokinetics

After single or multiple IV doses, dactinomycin is rapidly distributed into and extensively bound to body tissues. Results of a study with ³H-actinomycin D in patients with malignant melanoma indicate that dactinomycin is minimally metabolised, is concentrated in nucleated cells, and does not appreciably penetrate the blood brain barrier (< 10%). Approximately 30% of the dose is recovered in urine and faeces in one week. The terminal plasma half-life for radioactivity was approximately 36 hours.

Pharmaceutical Precautions

Store in a dry place at 25°C (77°F).
Protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

COSMEGEN is available in single vials each containing 0.5mg of dactinomycin.

Further Information

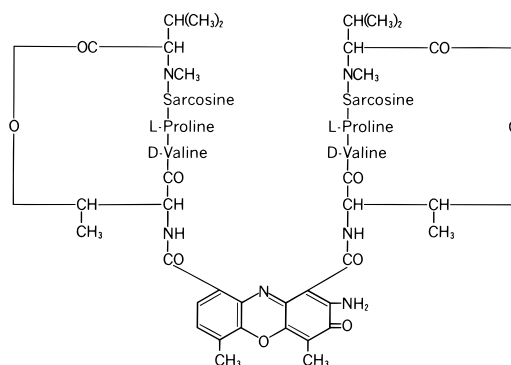
Dactinomycin is the principle component of the mixture of actinomycins produced by *Streptomyces parvullus*. The toxic properties of the actinomycins in relation to antibacterial activity preclude their use as antibiotics in the treatment of infectious diseases, however, they have an antineoplastic effect which has been demonstrated in experimental animals with various types of tumour implant. This cytotoxic action is the basis for their use in the treatment of certain types of cancer.

Description

Dactinomycin is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Dactinomycin is the principal component of the mixture of

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actinomycins produced by *Streptomyces parvullus*. Unlike other species of *Streptomyces*, this organism yields an essentially pure substance that contains only traces of similar compounds differing in the amino acid content of the peptide side chains. The molecular formula $C_{62}H_{86}N_{12}O_{16}$ and the structural formula is:



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