

## Data Sheet

# COSMEGEN<sup>®</sup>

*Lyophilised Powder for Injection*

*Dactinomycin [Actinomycin D] 0.5 mg per vial*

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### Name of the Medicine

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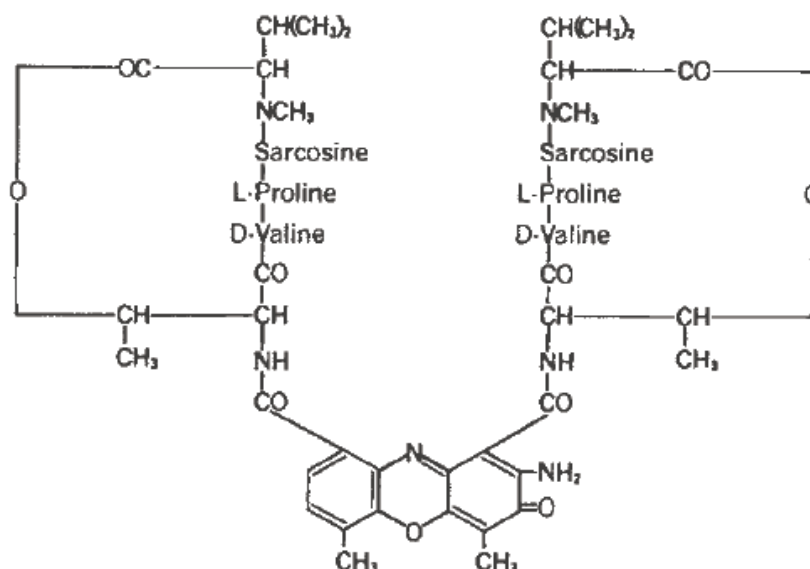
COSMEGEN (dactinomycin) is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Dactinomycin is the principal component of the mixture of actinomycins produced by *Streptomyces parvullus*. The toxic properties of the actinomycins in relation to antibacterial 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 palliative treatment of certain types of cancer.

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### Description

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Dactinomycin is the principal component of the mixture of 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 is  $C_{62}H_{86}N_{12}O_{16}$  and the structural formula is:



Dactinomycin Chemical Abstract Registry (CAS) Number: 50-76-0

COSMEGEN is a sterile, yellow lyophilised powder for injection by the intravenous route or by regional perfusion after reconstitution. Each vial contains 0.5 mg (500 mcg) of dactinomycin and 20.0 mg of mannitol.

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## Clinical Pharmacology

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### **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 disease.

Because the actinomycins are cytotoxic 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 palliative treatment of certain types of cancer.

### **Pharmacokinetics and Metabolism**

Results of a study in patients with malignant melanoma indicate that dactinomycin (<sup>3</sup>H actinomycin D) is minimally metabolised, is concentrated in nucleated cells, and does not penetrate the blood brain barrier. Approximately 30% of the dose was recovered in urine and faeces in one week. The terminal plasma half-life for radioactivity was approximately 36 hours.

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## Indications

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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.

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## Contraindications

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Hypersensitivity to any component of this product.

If dactinomycin is given at or about the time of infection with chicken pox or herpes zoster a severe generalised disease, which may result in death, may occur.

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## Precautions

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### **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. This medicine is extremely corrosive to soft tissue. If extravasation occurs during intravenous use, severe damage to soft tissue will occur (see Special Handling).

As with all antineoplastic agents, dactinomycin 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.

### ***Veno-Occlusive Disease***

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

### ***COSMEGEN and Radiation Therapy***

An increased incidence of gastrointestinal toxicity and marrow suppression has been reported when dactinomycin was given with x-ray therapy. 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 oropharyngealmucositis. *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 dactinomycin in the first two months after 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.

Nausea and vomiting due to dactinomycin make it necessary to give this medicine intermittently. It is extremely important to observe the patient daily for toxic side effects when multiple chemotherapy is employed, since a full course of therapy occasionally is not tolerated. If stomatitis, diarrhoea or severe haemopoietic depression appear during therapy, these medicines should be discontinued until the patient has recovered.

Recent reports indicate an increased incidence of second primary tumours (including leukaemia) following treatment of radiation and antineoplastic agents, such as dactinomycin. 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 dactinomycin. It is advisable to check renal, hepatic and bone marrow function frequently.

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

### **Carcinogenicity/Mutagenicity**

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 and intraperitoneal injection. Mesenchymal tumours occurred in male F344 rats given intraperitoneal injections of 0.05 mg/kg, 2 to 5 times per week for 18 weeks. The first tumour appeared at 23 weeks.

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

### **Impairment of Fertility**

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

### **Use in Pregnancy**

Category D

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.

### **Use in Lactation**

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 reactions in nursing infants from COSMEGEN, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

### **Paediatric Use**

The greater frequency of toxic effects of dactinomycin in infants suggest that this medicine should be given 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 years 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.

### **Effects on Ability to Drive and Operate Machinery**

There are side effects associated with COSMEGEN that may affect some patients' ability to drive or operate machinery (see Adverse Reactions).

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## **Adverse Reactions**

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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 be maximal before 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**

Sepsis (including neutropenic sepsis) with fatal outcome, 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 giving antiemetics.

### **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 Precautions, Veno-Occlusive Disease).

### **Haematological**

Anaemia, even to the point of aplastic anaemia, agranulocytosis, leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, pancytopenia, reticulocytopenia. Platelet and white cell counts should be done *daily* 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, erythema multiforme, flare-up of erythema or increased pigmentation of previously irradiated skin. Toxic Epidermal Necrolysis (TEN) and Stevens Johnson Syndrome (SJS) have been observed from postmarketing experience.

### **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. 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.

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## **Dosage and Administration**

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### **General**

*Not for oral administration.*

Toxic reactions due to COSMEGEN are frequent and may be severe (see Adverse Reactions), 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 15 mcg/kg/day or 400-600 mcg/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.

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 1.25mg/m<sup>2</sup> intravenously administered in various combinations and schedules with other chemotherapeutic agents.

### ***Testicular Carcinoma***

1000 mcg/m<sup>2</sup> 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 1.1 mL 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% or Sodium Chloride Injection either directly or to the tubing of a running intravenous infusion.

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.

Studies conducted on dactinomycin lyophilised powder for injection, demonstrate that drug product diluted at concentrations of 10 mcg/mL or higher in WFI, 0.9% saline and 5% dextrose in glass or PVC infusion containers are stable for up to 10 hours when stored at ambient room temperature. Drug product diluted to concentrations lower than 10 mcg/mL and stored at ambient room temperature showed significantly lower recoveries. Therefore, only drug product diluted at concentrations greater than 10 mcg/mL and stored for not more than 10 hours at ambient room temperature are recommended for administration.

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 and mutagenic 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 Precautions and Dosage and Administration).

### ***Management of Extravasation***

Care in the administration of COSMEGEN will reduce the chance of perivenous infiltration (see Precautions and Adverse Reactions). 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.

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## **Overdosage**

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Manifestations of overdose in patients have included nausea, vomiting, diarrhoea, mucositis including stomatitis, gastrointestinal ulceration, severe skin disorders including skin exfoliation, exanthema, desquamation and epidermolysis, severe haematopoietic depression, veno-occlusive disease, acute renal failure, sepsis (including neutropenic sepsis) with fatal outcome 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.

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## **Presentation and Storage Conditions**

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COSMEGEN injection is a lyophilised powder and is supplied in vials containing 0.5 mg (500 micrograms) of dactinomycin with 20.0 mg of mannitol. In the dry form the compound is an amorphous yellow powder. The solution is clear and gold-coloured.

Store in a dry place below 25°C. Protect from light.

## ***Disposal of Unwanted COSMEGEN***

### **Unwanted Made-Up Solution and Open Empty Vials**

Trisodium phosphate 5% for 30 minutes will destroy COSMEGEN.

### **Unopened Vials**

Incinerate at high temperature (982°C – 1024°C). Allow incinerator to cool. Scrape off the clinkers and re-incinerate them.

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## **Medicine Classification**

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Prescription Medicine

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## **Name and Address**

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Invida Australia Pty Ltd  
C/- Pharmacy Retailing t/a Healthcare Logistics  
58 Richard Pearse Drive  
Airport Oaks  
Mangere  
Auckland

New Zealand

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## **Date of Preparation**

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7 July 2011

Ref: Cosmegen Australian Product Information dated 24 March 2011