



## PHARMACOLOGY

### 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 actinomycin D) 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 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 actinomycin D (3H-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.

## INDICATIONS

### Wilms' Tumour

The neoplasm responding most frequently to COSMEGEN is Wilms' tumour. With low doses of both actinomycin D and radiotherapy, temporary objective improvement may be as good as and may last longer than with higher doses of each given alone. In the National Wilms' Tumour study, combination therapy with actinomycin D and vincristine together with surgery and radiotherapy, was shown to have significantly improved the prognosis of patients in groups II and III. Actinomycin D and vincristine were given for a total of seven cycles, so that maintenance therapy continued for approximately 15 months.

Postoperative radiotherapy in group I patients and optimal combination chemotherapy for those in group IV are unsettled issues. About 70 percent of lung metastases have disappeared with an appropriate combination of radiation, actinomycin D and vincristine.

### Rhabdomyosarcoma

Temporary regression of the tumour and beneficial subjective results have occurred with actinomycin D in rhabdomyosarcoma which, like most soft tissue sarcomas, is comparatively radio-resistant.

Several groups have reported successful use of cyclophosphamide, vincristine, actinomycin D and doxorubicin hydrochloride in various combinations. Effective combinations have included vincristine and actinomycin D; vincristine, actinomycin D and cyclophosphamide (VAC therapy) and all four drugs in sequence. At present, the most effective treatment for children with inoperable or metastatic rhabdomyosarcoma has been VAC chemotherapy. Two thirds of these children were doing well without evidence of disease at a median time of three years after diagnosis.

### Carcinoma of Testis and Uterus

The sequential use of actinomycin D and methotrexate, along with meticulous monitoring of human chorionic gonadotrophin levels until normal, has resulted in survival in the majority of women with metastatic choriocarcinoma. Sequential therapy is used if there is:

1. Stability in gonadotrophin titres following two successive courses of an agent.
2. Rising gonadotrophin titres during treatment.
3. Severe toxicity preventing adequate therapy.

In patients with non-metastatic choriocarcinoma, actinomycin D or methotrexate or both, have been used successfully, with or without surgery.

Actinomycin D has been beneficial as a single agent in the treatment of metastatic nonseminomatous testicular carcinoma when used in cycles of 500 mcg/day for five consecutive days, every 6-8 weeks for periods of four months or longer.

#### Other Neoplasms

Actinomycin D has been given intravenously or by regional perfusion, either alone or with other antineoplastic compounds or x-ray therapy, in the palliative treatment of Ewing's sarcoma and sarcoma botryoides. For non-metastatic Ewing's sarcoma, promising results were obtained when actinomycin D (45 mcg/m<sup>2</sup>) and cyclophosphamide (1200 mg/m<sup>2</sup>) were given sequentially and with radiotherapy, over an 18 month period. Those with metastatic disease remain the subject of continued investigation with a more aggressive chemotherapeutic regimen employed initially.

Temporary objective improvement and relief of pain and discomfort have followed the use of actinomycin D usually in conjunction with radiotherapy for sarcoma botryoides. This palliative effect ranges from transitory inhibition of tumour growth to a considerable but temporary regression in tumour size.

#### COSMEGEN and Radiation Therapy

Much evidence suggests that actinomycin D potentiates the effects of x-ray therapy. The converse also appears likely; i.e. actinomycin D may be more effective when radiation therapy is also given.

With combined actinomycin D - radiation therapy, the normal skin, as well as the buccal and pharyngeal mucosa, showed early erythema. A smaller than usual x-ray dose when given with actinomycin D 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 x-ray therapy may be reactivated by actinomycin D alone, even when irradiation occurred 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 irradiation treatment area includes 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 actinomycin D and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.

Because of this potentiating effect, actinomycin D may be tried in radio-sensitive tumours not responding to doses of x-ray therapy that can be tolerated. Objective improvement in tumour size and activity may be observed when lower, better tolerated doses of both types of therapy are employed.

#### COSMEGEN and Perfusion Technique

Actinomycin D alone or with other antineoplastic agents has also been given by the isolation-perfusion technique, either as palliative treatment or as an adjunct to resection of a tumour. Some tumours considered resistant to chemotherapy and radiation therapy may respond when the drug is given by the perfusion technique. Neoplasms in which actinomycin D has been tried by this technique include various types of sarcoma, carcinoma, and adenocarcinoma.

In some instances tumours regressed, pain was relieved for variable periods, and surgery made possible. On other occasions, however, the outcome has been less favourable. Nevertheless, in selected cases, the drug by perfusion may provide more effective palliation than when given systemically.

Actinomycin D by the isolation-perfusion technique offers certain advantages, provided leakage of the drug through the general circulation into other areas of the body is minimal. By this technique the drug is in continuous contact with the tumour for the duration of treatment.

The dose may be increased well over that used by the systemic route, usually without adding to the danger of toxic effects. If the agent is confined to an isolated part, it should not interfere with the patient's defence mechanism. Systemic absorption of toxic products from neoplastic tissue can be minimised by removing the perfusate when the procedure is finished.

## **CONTRAINDICATIONS**

Hypersensitivity to any component of this product.

If actinomycin D 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.

## **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 actinomycin D (eg 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 drug 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, actinomycin D is a toxic drug and very careful and frequent observations 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 actinomycin D 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 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 actinomycin D 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 actinomycin D make it necessary to give this drug 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 haematopoietic depression appear during therapy, these drugs 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 actinomycin D. 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 drug 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 actinomycin D. It is advisable to check renal, hepatic, and bone marrow function frequently.

It has been reported that actinomycin D may interfere with bioassay procedures for the determination of antibacterial drug levels.

### CARCINOGENICITY/MUTAGENICITY

The International Agency on Research on Cancer has judged that actinomycin D 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.

Actinomycin D 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 drug is excreted in human milk. Because many drugs 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 drug, taking into account the importance of the drug to the mother.

### PAEDIATRIC USE

The greater frequency of toxic effects of actinomycin D in infants suggests that this drug 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.

### **ADVERSE REACTIONS**

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 discontinuation 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 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 multidrug 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 drug should be withheld to allow marrow recovery. This often takes up to three weeks.

Dermatological. 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 Tissues. Actinomycin D 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

## DOSAGE AND ADMINISTRATION

### General

#### Not for oral administration

Toxic reactions due to actinomycin D are frequent and may be severe (see ADVERSE REACTIONS), thus limiting in many instances the amount that may be given. However, the severity of toxicity varies markedly and is only partly dependent on the dose employed. The drug must be given in short courses.

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

### Intravenous Use

The dosage of actinomycin D 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 other chemotherapy or x-ray therapy is used concomitantly or has been used previously.

The dosage of COSMEGEN is calculated in micrograms (mcg). The dosage for adults or children should not exceed 15 mcg/kg or 400-600 mcg/square metre of body surface daily intravenously for five days. The usual adult dosage is 500 micrograms (0.5 mg) daily intravenously for a maximum of 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.

Adults: The usual adult dosage is 500 mcg (0.5 mg) daily intravenously for a maximum of five days.

Children: In children 15 mcg (0.015 mg) per kilogram of body weight is given intravenously daily for five days. An alternative schedule is a total dosage of 2500 mcg (2.5 mg) per square metre of body surface given intravenously over a one week period.

In both adults and children, a second course may be given after at least three weeks have elapsed, provided all signs of toxicity have disappeared.

### Administration

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

Parenteral drug 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 actinomycin D can be further diluted with infusion solutions such as 5% glucose or 0.9% sodium chloride, either directly or added to the tubing of a running intravenous infusion. However, only solutions diluted to concentrations of 10µg/mL or higher should be used for administration. This is because diluted solutions below 10µg/mL suffer a loss in potency.

Although reconstituted and further diluted solutions of Cosmegen are physically and chemically stable for up to 10 hours at ambient room temperature, the product does not contain any anti-microbial preservative. Consequently, to reduce microbiological hazard, any reconstituted and/or further diluted solution should be used as soon as practicable. If storage is necessary, hold at 2-8°C (Refrigerate. Do not freeze) for not more than 24 hours. Any unused portion must be discarded.

Do not use Water for Injections containing a preservative (benzyl alcohol or parabens) to reconstitute Cosmegen powder for injection because this will result in the formation of a precipitate.

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

Since actinomycin D 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. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Should accidental eye contact occur, copious irrigation with water 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 (see SPECIAL HANDLING.)

If the drug 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.

#### Isolation-Perfusion Technique

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.

Complications of the perfusion technique are related mainly to the amount of drug that escapes into the systemic circulation and may consist of haemopoietic 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.

### **SPECIAL HANDLING**

Due to the drug's toxic and mutagenic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of COSMEGEN for parenteral administration. The United States National Institute of Health presently recommends that the preparation of injectable antineoplastic drugs would be performed in a Class II laminar flow biological safety cabinet and that personnel preparing drugs of this class should wear surgical gloves and a closed front surgical-type gown with knit cuffs.

### **MANAGEMENT OF EXTRAVASATION**

Stop the infusion and disconnect the IV administration set, but leave the cannula or needle in situ. Attempt to aspirate the extravasated drug via the cannula or needle. Elevate the limb and apply a cold compress for 45 minutes.

There is no generally-accepted antidote for local use, but the following have been used with some success:

Sodium thiosulphate 25% (1.6 mL + 3 mL of water for Injection)

Sodium thiosulphate 10% (4 mL + 6 mL of Water for Injection)

Ascorbic acid injection (50 mg/mL) (1 mL)



In severe cases, debridement may become necessary

### **DISPOSAL OF UNWANTED COSMEGEN**

(a) Unwanted made-up solution and open empty vials:

Trisodium phosphate 5% for 30 minutes will destroy COSMEGEN.

(b) Unopened vials:

Incinerate at high temperature (982°C - 1204°C). Allow incinerator to cool. Scrape off the clinkers and re-incinerate them.

### **OVERDOSAGE**

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.

### **PRESENTATION**

Injection COSMEGEN is a lyophilised powder and is supplied as follows: vials containing 0.5 mg (500 micrograms) of actinomycin D with 20.0 mg of mannitol. In the dry form the compound is an amorphous yellow powder. The solution is clear and gold-coloured.

### **STORAGE**

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

### **NAME AND ADDRESS OF THE SPONSOR**

#### Australia

A.Menarini Australia Pty Ltd  
Level 8, 67 Albert Ave,  
Chatswood NSW 2067

#### New Zealand

A.Menarini New Zealand Pty Ltd  
4 Whetu Place,  
Rosedale, 0632  
Auckland

### **NEW ZEALAND POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC  
GOODS (THE ARTG)**

22/07/1991

**DATE OF MOST RECENT AMENDMENT**

29<sup>th</sup> April 2016