

# NEW ZEALAND DATA SHEET

## 1. COSMEGEN 500mg powder for injection

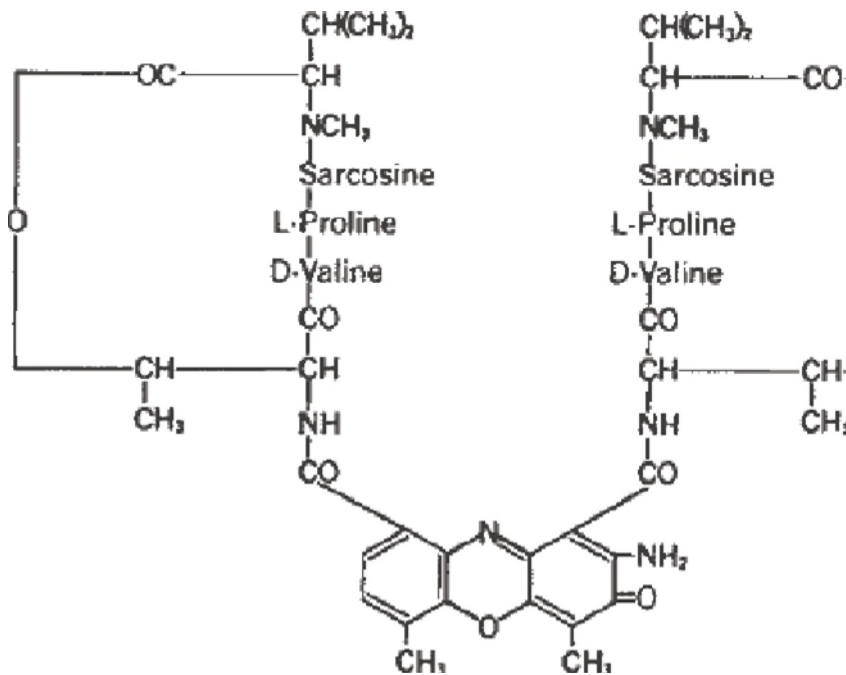
COSMEGEN 500mg powder for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COSMEGEN contains 500 micrograms (0.5 milligrams) of dactinomycin and 20.0 milligrams of mannitol.

The molecular formula of dactinomycin is  $C_{62}H_{86}N_{12}O_{16}$ .

The structural formula is:



## CAS Number

50-76-0

For the full list of excipients, see Section 6.1 List of excipients.

## 3. PHARMACEUTICAL FORM

COSMEGEN is a sterile, yellow lyophilised powder for injection by the intravenous route or by regional perfusion after reconstitution.

## **4. CLINICAL PARTICULARS**

### **4.1 THERAPEUTIC INDICATIONS**

#### **Wilms' Tumour**

The neoplasm responding most frequently to COSMEGEN is Wilms' tumour. With low doses of both dactinomycin 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 dactinomycin and vincristine together with surgery and radiotherapy, was shown to have significantly improved the prognosis of patients in groups II and III. Dactinomycin 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, dactinomycin and vincristine.

#### **Rhabdomyosarcoma**

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

Several groups have reported successful use of cyclophosphamide, vincristine, dactinomycin and doxorubicin hydrochloride in various combinations. Effective combinations have included vincristine and dactinomycin; vincristine, dactinomycin 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.

The sequential use of dactinomycin 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:

- Stability in gonadotrophin titres following two successive courses of an agent.
- Rising gonadotrophin titres during treatment.

#### **Severe toxicity preventing adequate therapy**

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

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

## **Other Neoplasms**

Dactinomycin 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 dactinomycin (45 microgram/m<sup>2</sup>) and cyclophosphamide (1200 milligram/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 dactinomycin 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 dactinomycin potentiates the effects of x-ray therapy. The converse also appears likely; i.e. dactinomycin may be more effective when radiation therapy is also given.

With combined dactinomycin - 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 dactinomycin 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 dactinomycin 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 dactinomycin and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.

Because of this potentiating effect, dactinomycin 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**

Dactinomycin 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 dactinomycin 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.

Dactinomycin 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.

## **4.2 DOSE AND METHOD OF ADMINISTRATION**

### **Dosage**

Not for oral administration

Toxic reactions due to dactinomycin are frequent and may be severe (see 4.8 UNDESIRABLE EFFECTS), 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 dactinomycin 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 micrograms/kg or 400-600 micrograms/square metre of body surface daily intravenously for five days. The usual adult dosage is 500 micrograms (0.5 milligrams) 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 micrograms (0.5 milligrams) daily intravenously for a maximum of five days.

*Children:* In children 15 micrograms (0.015 milligrams) per kilogram of body weight is given intravenously daily for five days. An alternative schedule is a total dosage of 2500 micrograms (2.5 milligrams) 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.

### **Method of administration**

COSMEGEN may be reconstituted by adding 1.1 millilitres (mL) of Sterile Water for Injection (without Preservative) using aseptic precautions. The resulting solution of dactinomycin will contain approximately 500 microgram or 0.5 milligrams 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 dactinomycin 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 10 micrograms/mL or higher should be used for administration. This is because diluted solutions below 10 micrograms/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 dactinomycin from intravenous solutions by cellulose ester membrane filters used in some intravenous in-line filters has been reported.

Since dactinomycin 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 below.)

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 micrograms (0.05 milligrams) per kilogram of body weight for lower extremity or pelvis. 35 micrograms (0.035 milligrams) 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 milligrams/mL) (1 mL)

In severe cases, debridement may become necessary.

## **4.3 CONTRAINDICATIONS**

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.

## **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 (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 under 4.2 DOSE AND METHOD OF ADMINISTRATION).

As with all antineoplastic agents, dactinomycin 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 4.8 UNDESIRABLE EFFECTS, 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 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 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 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 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 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.

### **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.

### **Paediatric use**

The greater frequency of toxic effects of dactinomycin in infants suggests that this drug should be given to infants only over the age of 6 to 12 months.

### **Effects on 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 drug levels.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

None known.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on 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.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 UNDESIRABLE 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 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, pyrexia, proctitis, hypocalcaemia, infection.

Lung. Pneumonitis, pneumothorax (observed as a result of antitumor effect of chemotherapy including dactinomycin).

Oral. Cheilitis, dysphagia, oesophagitis, ulcerative stomatitis, pharyngitis.

Gastrointestinal. Anorexia, nausea, vomiting, abdominal pain, diarrhoea, tumour lysis syndrome, constipation, gastrointestinal ulceration, ascites. 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, 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Veno-occlusive disease). Hepatic encephalopathy, pleural effusion as a complication of various hepatic disorders.

Haematological. Anaemia, even to the point of aplastic anaemia, agranulocytosis, disseminated intravascular coagulation (DIC), 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, rash, skin toxicity and dermatitis, 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. 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.

Musculoskeletal and connective tissue. Myalgia, growth retardation.

Immune system. Hypersensitivity

Nervous System. Peripheral neuropathy was commonly observed in patients receiving combination chemotherapy regimens that included dactinomycin, Lethargy

Eye. Optic neuropathy

Vascular. Haemorrhage, thrombophlebitis

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.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 OVERDOSE**

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or National Poisons Centre on 0800 POISON (0800 764766) in New Zealand.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

COSMEGEN (dactinomycin) is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Dactinomycin is the principle component of the mixture of actinomycins produced by *Streptomyces parvullus*. Generally, the actinomycins exert an

inhibitory effect on gram-positive and gram-negative bacteria and on some fungi. 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.

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.

### **Clinical Trials**

In the National Wilms' Tumour study, combination therapy with dactinomycin and vincristine together with surgery and radiotherapy, was shown to have significantly improved the prognosis of patients in groups II and III. Dactinomycin and vincristine were given for a total of seven cycles, so that maintenance therapy continued for approximately 15 months.

### **5.2 PHARMACOKINETIC PROPERTIES**

Results of a study in patients with malignant melanoma indicate that dactinomycin (3H-dactinomycin) 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.

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

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.

#### **Carcinogenicity**

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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Each vial contains 500 micrograms (0.5 milligrams) of dactinomycin and 20.0 milligrams of mannitol.

## **6.2 INCOMPATIBILITIES**

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.

## **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

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

## **6.5 NATURE AND CONTENTS OF CONTAINER**

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

COSMEGEN is supplied in packs of 1 vial.

## **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

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 - 1204°C). Allow incinerator to cool. Scrape off the clinkers and re-incinerate them.

## **7. MEDICINE SCHEDULE**

Prescription Medicine

## **8. SPONSOR**

### **Sponsor in Australia**

Recordati Rare Diseases Australia, Pty Ltd.

Suite 1802, Level 18, 233

Castlereagh Street,

Sydney, NSW, 2000

Australia

Phone: +61 (0)408 061 403

rrdaustrialainfo@recordati.com

### **Sponsor in New Zealand**

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

58 Richard Pearse Drive  
 Airport Oaks, Mangere  
 Mt. Wellington,  
 New Zealand  
 Phone: (09) 918 5100

**9. DATE OF FIRST APPROVAL**

31/12/1969

**10. DATE OF REVISION OF THE TEXT**

May 2023

**Summary table of changes**

Section changed	Summary of new information
Section 4.8	<p><b>ADVERSE EFFECTS (UNDESIRABLE EFFECTS)</b></p> <ul style="list-style-type: none"> <li>○ <b>Addition</b> of undesirable effects: tumour lysis syndrome, pneumothorax (observed as a result of antitumor effect of chemotherapy including dactinomycin), constipation, Hepatic encephalopathy, pleural effusion as a complication of various hepatic disorders, Disseminated Intravascular coagulation, rash, Hypersensitivity, Peripheral neuropathy was commonly observed in patients receiving combination chemotherapy regimens that included dactinomycin, Optic neuropathy, Haemorrhage, thrombophlebitis</li> <li>○ <b>Move</b> of “ascites” to a different SOC; move of “myalgia and growth retardation” to a different SOC</li> <li>○ <b>Replacement</b> of “skin eruptions” with “rash, skin toxicity and dermatitis”; replacement of “fever” with “pyrexia”</li> </ul>
8	Sponsor’s details have been updated