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. 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

COSMEGEN is a cytotoxic, antineoplastic antibiotic with immunosuppressant properties.

COSMEGEN, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of Wilms' tumor, 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.

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 discolouration 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 the active substance or any of the excipients listed in Section 6.1.

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.

Contraception in males and females

Advise females of reproductive potential to use effective contraception during treatment with COSMEGEN and for at least 7 months after the final dose.

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraceptionn during treatment with COSMEGEN and for at least 4 months after the final dose.

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 to:
https://pophealth.my.site.com/carmreportnz/s/

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.

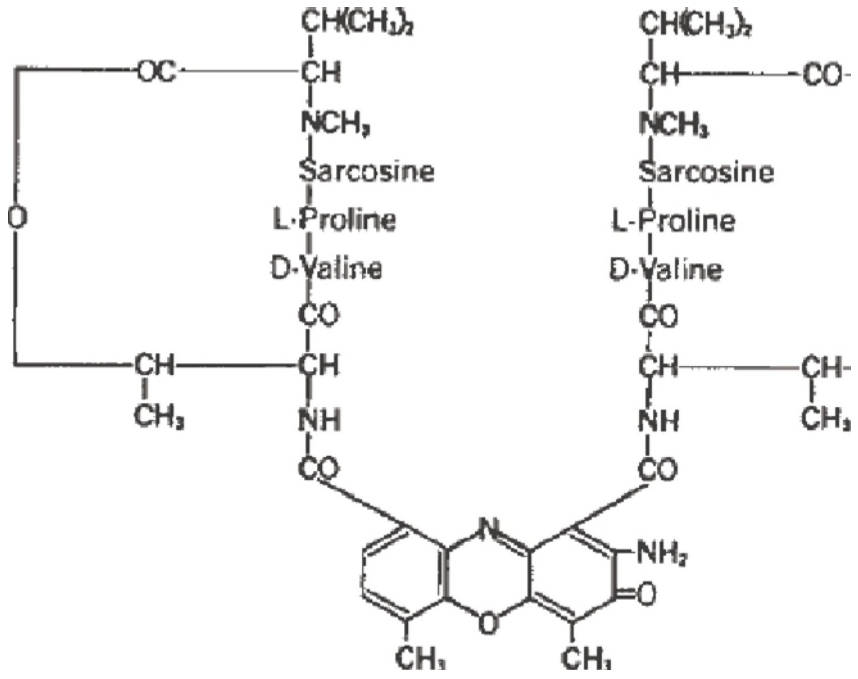
For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

The structural formula is:



CAS Number

50-76-0

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.

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Castlereagh Street,

Sydney, NSW, 2000

Australia

Phone: +61 (0)408 061 403

rrdaustraliainfo@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

30 July 2025

Summary table of changes

Section changed	Summary of new information
4.1	Update of section 4.1 to align with UK SmPC
4.3	Editorial update to warning regarding hypersensitivity
4.8	Addition of warning regarding use of contraception during treatment with COSMEGEN.
2, 5.1	Editorial update to move chemical structure to Section 5.1
4.8, 4.9	Editorial update to AE and overdose reporting information