PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

COSMEGEN 0,5 mg powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml vial contains 500 µg dactinomycin.

Contains mannitol.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Lyophilised powder for solution for injection.

A yellow to orange lyophilized powder in the form of a plug.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Toxic reactions due to COSMEGEN are frequent and may be severe (*see Section 4.8*), thus limiting the dose that may be administered in many cases. However, the severity of toxicity varies markedly and is only partly dependent on the dose administered.

Posology

Intravenous use

The dose of COSMEGEN will vary with the tolerance of the patient, the size and location of the neoplasm, and the concurrent use of other forms of therapy. It may be necessary to reduce the usual dos suggested below when additional chemotherapy or radiation therapy is used concurrently or has been used previously.

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

As there is a greater frequency of toxic effects of COSMEGEN in infants, close monitoring is recommended when COSMEGEN is given to infants.

A wide variety of single agent and combination chemotherapy regimens with COSMEGEN may be used. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of medical practitioners 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.

Nephroblastoma

COSMEGEN 45 micrograms **per kg** intravenously administered in various combinations and schedules with other chemotherapeutic agents.

45 µg/kg (micrograms per kg) correspond to 1 200-1 800 µg/m^2 (micrograms per square meter) or 1,2-1,8 mg/m^2 (milligrams per square meter).

Rhabdomyosarcoma

COSMEGEN 15 micrograms **per kg** intravenously daily for five days administered in various combinations and schedules with other chemotherapeutic agents.

Ewing's Sarcoma

COSMEGEN 1,25 milligrams **per m^2** intravenously administered in various combinations and schedules with other chemotherapeutic agents.

Testicular carcinoma

COSMEGEN 1 000 micrograms **per m^2** intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin.

Gestational trophoblastic neoplasia

COSMEGEN 12 micrograms **per kg** intravenously daily for five days as a single agent.

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

Elderly patients:

The general considerations already outlined also apply to elderly patients. Administration of COSMEGEN to elderly patients may be associated with an increased risk of myelosuppression compared to younger patients.

Regional perfusion in locally recurrent and locoregionally metastatic melanoma

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

For a lower extremity or pelvis - 50 micrograms **per kg** bodyweight.

For an upper extremity - 35 micrograms **per kg** bodyweight.

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

Method of administration

Reconstituted COSMEGEN is for intravenous administration. For instructions on reconstitution of the medicine before administration, *see Section 6.6*.

Although reconstituted COSMEGEN is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion of the solution should be discarded.

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

If COSMEGEN is to be injected directly into the vein without the use of an infusion, the 'two-needle' technique should be used. The calculated dose should be reconstituted and withdrawn from the vial with one sterile needle; direct injection into the vein should then be performed with another sterile needle.

4.3 Contraindications

- Hypersensitivity to dactinomycin or to any of the excipients (see section 6.1).
- Use in patients with varicella or herpes zoster.

  If COSMEGEN is given at or about the time of infection with chickenpox or herpes zoster, a severe generalised disease, which may be fatal can occur.
- Pregnancy

4.4 Special warnings and precautions for use

COSMEGEN should be administered only under the supervision of a medical practitioner who is experienced in the use of a cancer.

COSMEGEN is HIGHLY TOXIC (e.g. corrosive, carcinogenic, mutagenic and teratogenic, etc), therefore, both the powder and solution must be handled and administered with care. Since COSMEGEN is extremely corrosive to soft tissues, it is intended for intravenous administration only. 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 ophthalmic 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 Section 6.6*).

If extravasation occurs during intravenous use, severe damage to soft tissue may occur (*see Section 6.6*).

COSMEGEN, is a toxic medicine, and very careful and frequent observation of the patient for adverse reactions is necessary. These reactions may involve any tissue of the body, most frequently the haematopoietic system resulting in myelosuppression. The possibility of an anaphylactoid reaction should be borne in mind.

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

Veno-occlusive disease

Veno-occlusive disease (primarily hepatic) may result in fatality, particularly in children younger than 48 months (*see Section 4.8*).

COSMEGEN and radiation therapy:

An increased incidence of gastrointestinal toxicity and marrow suppression has been reported with combination therapy incorporating COSMEGEN and radiation.

Moreover, the normal skin, as well as the buccal and pharyngeal mucosa, may show early erythema. A smaller than usual radiation dose administered in combination with COSMEGEN causes erythema and vesiculation, which progress more rapidly through the stages of tanning and desquamation. Healing may occur in four to six weeks. Erythema from previous radiation therapy may be reactivated by COSMEGEN alone, even when radiotherapy was administered many months earlier, and especially when the interval between the two forms of therapy is brief. This potentiation of radiation effect represents a special problem when the radiotherapy involves the mucous membrane. When irradiation is directed toward the nasopharynx, the combination may produce severe oropharyngeal mucositis. Severe reactions may ensue if high doses of both COSMEGEN and radiation therapy are used or if the patient is particularly sensitive to such combined therapy. Particular caution is necessary when administering COSMEGEN within two months of irradiation for the treatment of right-sided nephroblastoma, since hepatomegaly and elevated AST levels have been noted.

In general, COSMEGEN should not be concomitantly administered with radiotherapy in the treatment of nephroblastoma.

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

Laboratory tests

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

Mannitol

COSMEGEN contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Much evidence suggests that COSMEGEN potentiates the effects of X-ray therapy. The converse also appears likely: that COSMEGEN may be more effective when radiation therapy is given concurrently (s*ee Section 4.4*).

COSMEGEN may interfere with bio-assay procedures for the determination of antibacterial medicine levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

COSMEGEN has been shown to be teratogenic in animals and should not be given to pregnant women.

Teratogenicity:

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

Breastfeeding

COSMEGEN should not be administered to mothers who are breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

COSMEGEN may cause fatigue and lethargy which affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. Summary of the safety profile

Toxic effects (except nausea and vomiting) do not usually become apparent until two to four days after a course of therapy is stopped and may not peak until one to two weeks have elapsed. Deaths have been reported. Side effects include the following (frequencies are not known):

b. Tabulated summary of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
Infections and Infestations	Frequency unknown	Sepsis (including neutropenic sepsis) with fatal outcome, infection, pharyngitis
Blood and lymphatic system disorders	Frequency unknown	Anaemia (even to the point of aplastic anaemia), agranulocytosis, disseminated intravascular coagulation (DIC), leukopenia, thrombocytopenia, pancytopenia, reticulocytopenia, neutropenia, febrile neutropenia. Platelet and white blood-cell counts should be performed frequently to detect severe haemopoietic depression. If either count

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
		shows a marked decrease, dactinomycin should be withheld to allow marrow recovery. This often takes up to three weeks.
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Frequency unknown	Anorexia, hypocalcaemia, tumour lysis syndrome.
Nervous system disorders	Frequency unknown	Peripheral neuropathy was commonly observed in patients receiving combination chemotherapy regimens that included dactinomycin. Lethargy.
Eye disorders	Frequency unknown	Optic neuropathy
Vascular disorders	Frequency unknown	Haemorrhage, thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Pneumonitis
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, abdominal pain, diarrhoea, gastro-intestinal ulceration, cheilitis, dysphagia, constipation, esophagitis, proctitis, ulcerative stomatitis,

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
		ascites. Nausea and vomiting, which occur early during the first few hours after administration, may be alleviated by the administration of anti-emetics.
epato-biliary disorders	Frequency unknown	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.
Skin and subcutaneous tissue disorders	Frequency unknown	Alopecia, rash, skin toxicity and dermatitis, erythema multiforme, acne, flare-up of erythema or increased pigmentation of previously irradiated skin. Toxic Epidermal Necrolysis (TEN) and Stevens Johnson

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
		Syndrome (SJS) have been observed from post-marketing experience. 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, connective tissue and bone disorders		Myalgia, growth retardation.
General disorders and administrative site conditions		Epidermolysis, erythema, and oedema, at times severe, have been reported with regional limb perfusion, fatigue, fever, growth retardation, lethargy, malaise. 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.

c. Description of selected adverse reactions

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 haemopoietic depression, increased susceptibility of infection, absorption of toxic products from massive destruction of neoplastic tissue, impaired wound healing and superficial ulceration of the gastric mucosa. Other side effects may include oedema of the extremity involved, damage to the soft tissues of the perfused area, and potentially venous thrombosis.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of overdosage, COSMEGEN therapy should be withdrawn immediately. Limited information is available on overdosage in humans. Manifestations of overdose have included nausea, vomiting, diarrhoea, mucositis including stomatitis, gastro- intestinal ulceration, severe skin disorders including skin exfoliation, exanthema, desquamation and epidermolysis, severe haemopoietic depression, veno-occlusive disease, acute renal failure, sepsis (including neutropenic sepsis) with fatal outcome and death. Treatment should be

symptomatic and supportive. There is no known antidote. It is advisable to check skin and mucous membrane integrity as well as renal, hepatic and bone-marrow functions frequently.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics and related substances: Actinomycines. ATC code: L01DA01

Mechanism of action:

Dactinomycin inhibits the proliferation of cells by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis.

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

5.2 Pharmacokinetic properties

Results of a study in patients with malignant melanoma indicate that dactinomycin (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.

5.3 Preclinical safety data

The international Agency on Research on Cancer has judged that dactinomycin is

a positive carcinogen in animals. Local sarcomas were produced in mice and rats after repeated subcutaneous or intraperitoneal injection. Mesenchymal tumours occurred in male F344 rats given intraperitoneal injections of 50 micrograms per kg, two to five 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 leucocytes, and HELA cells. DNA damage and cytogenetic effects have been demonstrated in the mouse and the rat.

Impairment of fertility

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

Teratogenicity

COSMEGEN has been shown to cause malformations and embryotoxicity in the rat, rabbit and hamster when given in doses of 50-100 micrograms per kg intravenously (three to seven times the maximum recommended human dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

6.2 Incompatibilities

Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute COSMEGEN for injection results in the formation of a precipitate.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light. Although reconstituted COSMEGEN is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion of the solution should be discarded.

6.5 Nature and contents of container

3 ml amber Type I glass vial closed with a dark grey butyl rubber stopper and an aluminium cap with a light blue flip off seal. Pack size: 1 vial in an outer carton.

6.6 Special precautions for disposal and other handling

Reconstitution and administration

Reconstitution:

COSMEGEN is reconstituted by adding 1,1 ml of water for Injections Ph Eur without preservative to the vial.

Only Water for Injections Ph Eur (which does not contain preservatives) should be used. Other injection fluids may cause precipitation. COSMEGEN should be inspected for particulate matter and discoloration, whenever possible. The reconstituted solution is clear and gold- coloured.

Injection:

For injection, 1,0 ml of the reconstituted solution, which will contain 500 micrograms of dactinomycin, is withdrawn into the syringe.

Studies conducted on dactinomycin lyophilized powder for injection demonstrate that drug product diluted at concentrations of 10 µg/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 µg/ml and stored at ambient room temperature showed significantly lower recoveries. Therefore, only product diluted at concentrations greater than 10 µg/ml and stored for not more than 10 hours at ambient room temperature are recommended for administration.

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 drug's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of COSMEGEN for parenteral administration. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes must be avoided. It is recommended that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet. Personnel preparing drugs 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 ophthalmic 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 Section 4.4*).

Care in the administration of COSMEGEN will reduce the chance of perivenous infiltration (*see Section 4.4* and *Section 4.8*). 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 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 drugs 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.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

54/26/0380

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 September 2022.

10 DATE OF REVISION OF THE TEXT

6 September 2022