SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COSMEGEN® LYOVAC* 500 micrograms powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

'Cosmegen' Lyovac is supplied as a yellow-orange, lyophilised powder, in a vial containing 500 micrograms dactinomycin with 20 mg mannitol E421.

3. PHARMACEUTICAL FORM

Lyophilised powder for solution for injection.

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 Posology and method of administration

Toxic reactions due to 'Cosmegen' are frequent and may be severe (see 4.8 'Undesirable effects'), thus limiting the amount that may be administered in many cases. However, the severity of toxicity varies markedly and is only partly dependent on the dosage used.

Posology

Intravenous use
The dosage of 'Cosmegen' will vary with 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 reduce the usual dosage suggested below when additional chemotherapy or radiation therapy is used concurrently or has been employed previously.

The dosage 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 dosage 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, 'Cosmegen' should only be given to infants under the age of 12 months, when the benefit outweighs the risk.

A wide variety of single agent and combination chemotherapy regimens with 'Cosmegen' may be employed. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of physicians familiar with current oncologic practices and new advances in therapy. The following suggested regimens are based upon a review of current literature concerning therapy with 'Cosmegen' and are on a per-cycle basis.

Wilms's Tumor
Regimens of 45 micrograms per kg intravenously administered in various combinations and schedules with other chemotherapeutic agents.

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

Ewing's Sarcoma
Regimens of 1.25 milligrams per m^2 intravenously administered in various combinations and schedules with other chemotherapeutic agents.

Testicular carcinoma
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
12 micrograms per kg intravenously daily for five days as a single agent.

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 dosage 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 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

When reconstituted, the solution of dactinomycin can be added to an infusion solution of 5% dextrose injection or sodium chloride injection, either directly or into the tubing of a running intravenous infusion.

Although reconstituted 'Cosmegen' is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion 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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contra-indications

Hypersensitivity to any component of this product.

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.

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 a cancer chemotherapeutic agent. Due to the toxic properties of dactinomycin (e.g. corrosivity, carcinogenicity, mutagenicity, teratogenicity). Special handling procedures should be reviewed prior to handling and followed diligently.

'Cosmegen' is HIGHLY TOXIC and both powder and solution must be handled and administered with care. Since 'Cosmegen' is extremely corrosive to soft tissues, it is intended for intravenous use. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling 'Cosmegen'. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt 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 6.6 'Instructions for use/handling').

If extravasation occurs during intravenous use, severe damage to soft tissue may occur (see 6.6 'Instructions for use/handling').

'Cosmegen', like all antineoplastic agents, is a toxic drug, and very careful and frequent observation of the patient for adverse reactions is necessary. These reactions may involve any tissue of the body, most commonly the haematopoietic system resulting in myelosuppression. 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 employed, since a full course of therapy is occasionally not tolerated. If stomatitis, diarrhoea or severe haematopoietic depression appear during therapy, these drugs 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 4.8 'Undesirable effects: *Gastro-intestinal*').

'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 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 'Cosmegen' within two months of irradiation for the treatment of right-sided Wilm's tumor, since hepatomegaly and elevated AST levels have been noted.

In general, 'Cosmegen' should not be concomitantly administered with radiotherapy in the treatment of Wilm's tumor unless the benefit outweighs the risk.

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.

4.5 Interaction with other medicinal products 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. See 4.4 ''Cosmegen and radiation therapy'

'Cosmegen' may interfere with bio-assay procedures for the determination of antibacterial drug levels.

4.6 Fertility, pregnancy and lactation

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

'Cosmegen', dactinomycin should not be administered to mothers who are breast-feeding.

4.7 Effects on ability to drive and use machines

There are no data available. The potential side effects, fatigue and lethargy, should be taken into account (see 4.8 'Undesirable effects').

4.8 Undesirable effects

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. However, side effects are usually reversible on discontinuing therapy, they include the following:

Infections and infestations:
Sepsis (including neutropenic sepsis) with fatal outcome, infection, pharyngitis

Metabolism and nutrition disorders:
Anorexia, hypocalcemia, tumour lysis syndrome.

Respiratory, thoracic and mediastinal disorders:
Pneumonitis, pneumothorax (observed as a result of antitumor effect of chemotherapy including dactinomycin).

Gastrointestinal disorders:
Nausea, vomiting, abdominal pain, diarrhoea, gastro-intestinal ulceration, cheilitis, dysphagia, constipation, esophagitis, proctitis, ulcerative stomatitis, ascites. Nausea and vomiting, which occur early during the first few hours after administration, may be alleviated by the administration of anti-emetics.

Hepatobiliary disorders:

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.

Blood and lymphatic system disorders:
Anaemia (even to the point of aplastic anaemia), agranulocytosis, disseminated intravascular coagulation (DIC), leucopenia, thrombocytopenia, pancytopenia, reticulocytopenia, neutropenia, febrile neutropenia. Platelet and white blood-cell counts should be performed frequently to detect severe haemopoietic depression. If either count shows a marked decrease, dactinomycin should be withheld to allow marrow recovery. This often takes up to three weeks.

Skin and subcutaneous tissue disorders:
Alopecia, rash, skin toxicity and dermatitiss, erythema multiforme, acne, 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.
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 disorders:
Myalgia, growth retardation.

General disorders and administrative site conditions:
Fatigue, pyrexia, malaise.

Immune system disorders:
Hypersensitivity

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

Eye disorders:
Optic neuropathy

Vascular disorders:
Haemorrhage, thrombophlebitis

'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 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.

4.9 Overdose

In the event of overdosage, dactinomycin 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

Mode of action: 'Cosmegen' 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.

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.

5.2 Pharmacokinetic properties

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

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

The shelf-life is 36 months.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Glass vials containing 500 micrograms dactinomycin with 20 mg mannitol.

6.6 Special precautions for disposal and other handling

Reconstitution and administration
'Cosmegen is reconstituted by adding 1.1 ml of water for Injections Ph Eur without preservative to the vial. For injection, 1.0 ml of the reconstituted solution, which will contain 500 micrograms of dactinomycin, is withdrawn into the syringe. 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.

Studies conducted on dactinomycin lyophilized powder for injection demonstrate that drug product diluted at concentrations of 10 mcg/mL or higher in WFI, 0.9% saline and 5% dextrose in glass or PVC infusion containers are stable for up to 10 hours when stored at ambient room temperature. Drug product diluted to concentrations lower than 10 mcg/mL and stored at ambient room temperature showed significantly lower recoveries. Therefore, only drug product diluted at concentrations greater than 10 mcg/mL and stored

for not more than 10 hours at ambient room temperature are recommended for administration.

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 drugs 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 4.4 'Special warnings and precautions for use').

Care in the administration of 'Cosmegen' will reduce the chance of perivenous infiltration (See 4.4 'Special warnings and precautions for use' and 4.8 'Undesirable effects'). 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. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

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LEGAL CATEGORY

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