Preparation of Solution for Intravenous Administration

Dactinomycin is *highly toxic* and thus both powder and/or solution must be handled and administered with care. Dactinomycin for Injection is extremely corrosive to soft tissues and hence intended for intravenous use. Inhalation of dust or vapors and contact with skin or mucous membranes especially those of the eyes must be avoided. Appropriate protective equipment should be worn when handling Dactinomycin for Injection. 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 ophthalmologic 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.

TINOWEL™ should be reconstituted by adding 1.1 ml of Sterile Water for Injection (without preservative) using aseptic precautions and the resulting solution of TINOWEL™ will contain approximately 500 mcg (0.5 mg) per ml. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstituted, Dactinomycin for Injection is a clear, gold colored solution. Once reconstituted, the solution of TINOWEL™ may be infused with solutions of 5 % Dextrose Injection or Sodium Chloride Injection either directly or to the tubing of a running intravenous infusion. Although reconstituted TINOWEL™ is chemically stable, the product does not contain a preservative and accidental microbial contamination might result, thus any unused portion should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute TINOWEL™ will result in precipitation.

TINOWEL™ may be partially removed from intravenous solutions by the use of cellulose ester membrane filters used in some intravenous in-lines. The "two-needle technique" should be employed if the drug is given directly into the vein without the use of an infusion by reconstitute and withdrawing the calculated dose from the vial with one sterile needle and using another sterile needle for direct injection into the vein. Any unused portion of the TINOWEL™ solution should be discarded.

Management of Extravasation

Care taken in the administration of TINOWEL™ will reduce the chance of perivenous infiltration and may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of Dactinomycin for Injection 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 occur the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes q.i.d. for 3 days may be useful. 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.

STORAGE

Store at a temperature not exceeding 25 °C (77 °F); excursions are permitted to 15-30 °C (59-86 °F). Protect unopened vials from light and humidity. Any unused portion of the Dactinomycin for Injection solution should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute Dactinomycin for Injection will result in precipitation.

PRESENTATION

TINOWEL™ is a lyophilized powder. In the dry form the compound is an amorphous yellow to orange powder. The reconstituted solution is clear, gold colored and essentially free from visible particles.

TINOWEL™ is supplied in 3 ml amber colored glass vials containing 0.5 mg (500 micrograms) of Dactinomycin USP and 20 mg of Mannitol IP.

HANDLING AND DISPOSAL

Animal studies report that dactinomycin to be corrosive to skin, irritating to the eyes and mucous membranes of the respiratory tract and highly toxic by the oral route. Dactinomycin 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 Dactinomycin for injection for parenteral administration. Inhalation of dust or vapors and contact with skin or mucous membranes especially those of the eyes, must be avoided. Care must be taken to avoid exposure during pregnancy. It is recommended that the preparation of dactinomycin be performed in a Class II laminar flow biological safety cabinet. All personnel preparing such antineoplastic drugs should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments may be used based upon the task being performed (e.g., sleeve-lets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing. Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
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Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700DTL

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Dactinomycin for Injection USP

TINOWEL™

Lyophilized

FOR I.V INFUSION ONLY

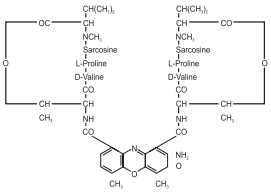
Rx only

WARNING

TINOWEL™ should be administered only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Dactinomycin for Injection is ***Highly Toxic*****;** thus both powder and solution must be handled and administered with care. Due to the toxic properties (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently. Inhalation of dust or vapors and contact with skin or mucous membranes especially the eyes must be avoided, dactinomycin is extremely corrosive to soft tissues. Exposure to dactinomycin during pregnancy must be avoided. Extravasation during intravenous use may result in severe damage to soft tissues.

DESCRIPTION

Dactinomycin is a member of the actinomycins, a group of polypeptide antibiotics produced by various species *and usually isolated from the soil bacteria of the genus Streptomyces*. Dactinomycin is the principal component of the mixture of actinomycins produced by *Streptomyces Parvullus which u*nlike other species of *Streptomyces* yields an essentially pure substance that contains only traces of similar compounds differing in the amino acid content of the peptide side chains. Dactinomycin appears as red shiny crystals and is soluble in dichloromethane and methanol. The melting point of dactinomycin is 245-255 °C. Dactinomycin should be protected from light. The empirical formula is $C_{62}H_{86}N_{12}O_{16}$ and the structural formula is:



TINOWEL™ is a sterile, yellow to orange lyophilized powder for injection meant to be administered intravenously or by regional perfusion after reconstitution.

COMPOSITION

TINOWEL™ is available as a 0.5 mg dose presented in 3 ml amber glass vials (sterile freeze dried powder for reconstitution).

Each sterile lyophilized vial contains:

Dactinomycin USP	0.5 mg
Mannitol IP	20 mg

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

Generally actinomycins exert an inhibitory effect on gram-positive, 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 tumor implants. This cytotoxic action is the basis for their use in the treatment of certain types of cancer. Dactinomycin is believed to produce its cytotoxic effects by binding DNA and inhibiting RNA synthesis.

PHARMACOKINETICS & PHARMACODYNAMICS

Studies in patients with malignant melanoma indicate that dactinomycin (3H actinomycin D) is poorly absorbed from the gastrointestinal tract but rapidly distributes into nucleated cells (bone marrow, tumour cells > plasma). Dactinomycin also crosses across the placenta but is not highly protein bound and is minimally metabolized. Clearance from blood is approximately 85 % in 2 minutes while 50-90 % may be excreted in bile within 24 hours. As much as 15-30 % of the dose may be recovered unchanged from feces, over one week. 12-20 % excretion from urine in 24 hours and 15 % in one week has also been seen. The terminal plasma half life is approximately 36 hours and may be prolonged with hepatic dysfunction.

INDICATION(S)

TINOWEL™ as part of a combination chemotherapy and/or multimodality treatment regimen is indicated for the treatment of Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, nonseminomatous testicular cancer.

Dactinomycin for Injection is indicated as a single agent or as part of a combination chemotherapy regimen for the treatment of gestational trophoblastic neoplasia. TINOWEL™ as a component of regional perfusion is indicated for the palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies.

Other uses of TINOWEL™ include treatment for Germ cell tumors, Kaposi's sarcoma, Melanoma and Osteogenic sarcoma.

CONTRA INDICATION(S)

TINOWEL™ should not be given at or about the time of infection with chickenpox or herpes zoster because of the risk of severe generalized disease which may result in death. Hypersensitivity to any component of Dactinomycin for Injection is contraindicated.

WARNING(S)

Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents such as Dactinomycin for Injection. Multi-modal therapy needs careful, long term observation of cancer survivors/patients.

Pregnancy Category D

Dactinomycin for Injection may cause fetal harm when administered to a pregnant woman. Dactinomycin for Injection has been shown to cause malformations and embryotoxicity in rat, rabbit and hamster when given in doses of 50-100 mcg/kg (approximately 0.5-2 times the maximum recommended daily human dose on a body surface area basis). If Dactinomycin for Injection is used during pregnancy or if the patient becomes pregnant while receiving Dactinomycin for Injection, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential must be warned to avoid becoming pregnant when on treatment with Dactinomycin for Injection.

PRECAUTION(S)

General

Dactinomycin for Injection is *Highly Toxic* and thus both powder and solution must be handled and administered with care. Since Dactinomycin for Injection is extremely corrosive to soft tissues, it is intended for intravenous use. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes must be avoided. Appropriate protective equipment should be worn when handling Dactinomycin for Injection. 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 ophthalmologic consultation. Should accidental skin contact occur, the affected part must be thoroughly irrigated immediately with copious amounts of water and all contaminated clothing/footware be removed. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. As with all antineoplastic agents Dactinomycin for Injection is a toxic drug, thus it is very essential to carefully and frequent observe the patient for adverse reactions. Adverse reactions may involve any tissue of the body but most commonly the hematopoietic system resulting in myelosuppression. As such, live virus vaccines should not be administered during therapy with Dactinomycin for Injection. 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 combination chemotherapy is employed since a full course of therapy may occasionally not be tolerated. If stomatitis, diarrhea or severe hematopoietic 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 when on treatment with Dactinomycin for Injection.

Dactinomycin for Injection and Radiation Therapy

Increased incidence of gastrointestinal toxicity and marrow suppression has been reported with combined therapy incorporating Dactinomycin for Injection and radiation. The normal skin as well as the buccal and pharyngeal mucosa may show early erythema. A smaller than usual dose of radiation when administered in combination with Dactinomycin for Injection may cause erythema and vesiculation, which may 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 Dactinomycin for Injection alone; even when radiotherapy may have been 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 Dactinomycin for Injection and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.

Particular caution is necessary when administering Dactinomycin for Injection within two months of irradiation for the treatment of right sided Wilms' tumor since hepatomegaly, elevation in elevated AST (SGOT), bilirubin levels and ascites have been reported. In general Dactinomycin for Injection should not be concomitantly administered with radiotherapy in the treatment of Wilms' tumor unless the benefit of such a treatment outweighs the risk.

Dactinomycin for Injection and Regional Perfusion Therapy

Complications of perfusion technique are related mainly to the amount of drug that escapes into the systemic circulation and may consist of hematopoietic 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 edema of the extremity involved, damage to soft tissues of the perfused area and (potentially) venous thrombosis.

Laboratory Tests

Many abnormalities of renal, hepatic and bone marrow function have been reported in patients with neoplastic diseases receiving Dactinomycin for Injection. Renal, hepatic, and bone marrow functions should be assessed frequently. Dactinomycin may interfere with bioassay procedures for the determination of antibacterial drug levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents such as Dactinomycin for Injection. Multi-modal therapy needs careful, long term observation of cancer survivors/patients.

Dactinomycin has been reported by The International Agency on Research on Cancer as a positive carcinogen in animals. Local sarcomas have been reported, produced in mice and rats after repeated subcutaneous or intraperitoneal injection. Mesenchymal tumors occurred in male F344 rats given intraperitoneal injections (50 mcg/kg) at a frequency of 2 to 5 times per week for 18 weeks; the intial tumor was reported to appear at 23 weeks.

Dactinomycin has been shown to be mutagenic in a number of test systems *in vitro* and *in vivo* including human fibroblasts, leukocytes and HeLa cells. DNA damage and cytogenetic effects have been demonstrated in mouse and rat. However adequate fertility studies have not been reported although reports suggest an increased incidence of infertility following treatment with other antineoplastic agents.

Pregnancy

Pregnancy Category D

Nursing Mothers

It is not known whether Dactinomycin is excreted in human milk however because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Dactinomycin for Injection a decision should be made by the treating physician and the patient as to discontinuation of nursing and/or drug, taking into account the importance of the drug to the mother.

Pediatric Use

The greater frequency of toxic effects of Dactinomycin for Injection in infants, suggest

Pregnancy

Pregnancy Category D

Nursing Mothers

It is not known whether Dactinomycin is excreted in human milk however because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Dactinomycin for Injection a decision should be made by the treating

physician and the patient as to discontinuation of nursing and/or drug, taking into account the importance of the drug to the mother.

Pediatric Use

The greater frequency of toxic effects of Dactinomycin for Injection in infants, suggest that Dactinomycin for Injection should be administered to infants only over the age of 6 to 12 months.

Geriatric Use

Clinical studies of Dactinomycin for Injection report the insufficient inclusion of subjects aged 65 and over to determine whether they respond differently from younger subjects, thus clinical experience has not identified differences in responses between the elderly and younger patients. However a published metaanalysis of all studies performed by the Eastern Cooperative Oncology Group (ECOG) over a 13 year period suggests that the administration of Dactinomycin for Injection to elderly patients may be associated with an increased risk of myelosuppression compared to younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

ADVERSE REACTION(S)

Toxic effects (excepting nausea and vomiting) usually do not become apparent until two to four days after the course of therapy is stopped and may not peak until one to two weeks have elapsed. Deaths have also been reported. However adverse reactions are usually reversible on discontinuance of therapy; these include:

Miscellaneous: malaise, fatigue, lethargy, fever, myalgia, proctitis, hypocalcemia, growth retardation and infection.

Oral: cheilitis, dysphagia, esophagitis, ulcerative stomatitis and pharyngitis.

Lung: pneumonitis.

Gastrointestinal: anorexia, nausea, vomiting, abdominal pain, diarrhea and gastrointestinal ulceration. Nausea and vomiting which occur early during the first few hours after administration may be alleviated by the administration of anti-emetics.

Hepatic: liver toxicity including liver function test abnormalities, ascites, hepatomegaly, hepatitis, hepatic failure with reports of death, hepatic veno-occlusive disease which may be associated with intravascular clotting disorder and multi-organ failure.

Hematologic: anemia, even to the point of aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, pancytopenia, reticulocytopenia, neutropenia, febrile neutropenia. Platelet and white cell counts should be performed *frequently* to detect severe hematopoietic depression. If either count markedly decreases the drug should be withheld to allow marrow recovery which may often take up to three weeks.

Dermatologic: alopecia, skin eruptions, acne, flare-up of erythema or increased pigmentation of previously irradiated skin.

Soft tissues: Dactinomycin is extremely corrosive. If extravasation occurs during intravenous use, severe damage to soft tissues will occur; reports suggest that at least one instance has led to contracture of the arms. Epidermolysis, erythema and edema at times severe have been reported with regional limb perfusion.

Abnormalities in laboratory tests: Many abnormalities of renal, hepatic and bone marrow function have been reported in patients with neoplastic diseases receiving Dactinomycin for Injection hence these functions should be monitored and assessed frequently.

OVERDOSAGE(S)

Reports suggest that Dactinomycin is lethal to mice and rats at intravenous doses of 700 and 500 mcg/kg, respectively (approximately 3.8 and 5.4 times the maximum recommended daily human dose on a body surface area basis, respectively). The oral LD_{50} of dactinomycin is 7.8 mg/kg and 7.2 mg/kg in mouse and rat, respectively. Manifestations of overdose in patients include nausea, vomiting, diarrhea, mucositis including stomatitis, gastrointestinal ulceration, skin disorders including exanthema, desquamation, epidermolysis, severe hematopoietic depression, veno-occlusive disease, acute renal failure and death. No specific information is available on the treatment of overdosage with Dactinomycin for Injection. Treatment is often symptomatic and supportive hence it is advisable to check skin and mucous membrane integrity as well as renal, hepatic and bone marrow functions frequently.

DOSAGE & ADMINISTRATION

Not for oral administration

Toxic reactions due to TINOWEL™ are frequent and may be severe, thus limiting in many instances the amount that may be administered. However the severity of toxicity varies markedly and is only partly dependent on the dose employed. Careful calculation of the dosage should be performed prior to administration of each dose.

Intravenous Use

The dosage of TINOWEL™ 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 additional chemotherapy or radiation therapy is used concomitantly or has been used previously.

The dosage for TINOWEL™ is calculated in micrograms (mcg). The dose intensity per 2 week cycle for adults or children should not exceed 15 mcg/kg/day or 400-600 mcg/m^2/day intravenously for five days. Calculation of the dosage for obese or edematous patients should be performed on the basis of surface area in an effort to more closely relate dosage to lean body mass. A wide variety of single agent and combination chemotherapy regimens with TINOWEL™ 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 Dactinomycin for Injection and are on a per cycle basis.

Wilms' Tumor, Childhood Rhabdomyosarcoma and Ewing's Sarcoma

An i.v daily dose of 15 mcg/kg for five days administered in various combinations and schedules with other chemotherapeutic agents is the usual regimen utilized in the treatment of Wilms' tumor, rhabdomyosarcoma and Ewing's sarcoma.

Metastatic Nonseminomatous Testicular Cancer

The usual regimen includes an i.v dose of 1000 mcg/m^2 on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine and cisplatin.

Gestational Trophoblastic Neoplasia

The treatment dose for Gestational trophoblastic neoplasia is usually 12 mcg/kg i.v daily for five days as a single agent or 500 mcg i.v on days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and cisplatin.

Regional Perfusion in Locally Recurrent and Locoregional Solid Malignancies

The dosage schedules and the technique itself may vary from one investigator to another; hence the published literature should be consulted for details. Usually the following doses are suggested:

50 mcg (0.05 mg) per kilogram of body weight for lower extremity or pelvis.

35 mcg (0.035 mg) per kilogram of body weight for upper extremity.

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