Mitozytrex™
(mitomycin for injection)

WARNINGS

Mitozytrex should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of mitomycin (see **"WARNINGS"** and **"ADVERSE REACTIONS"** sections).

Hemolytic Uremic Syndrome (HUS), a serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure has been reported in patients receiving systemic mitomycin. The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs, however, most cases occur at cumulative doses ≥ 60 mg of mitomycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome.

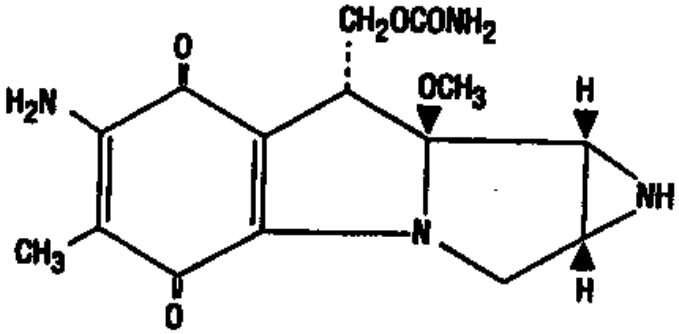
The incidence of the syndrome has not been defined.

DESCRIPTION

Mitozytrex is a sterile dry mixture of Mitomycin, USP and hydroxypropyl â cyclodextrin (HPβCD) (glucopyranose polymers used as solubilizing agent), which when reconstituted with Sterile Water for Injection provides a solution for intravenous administration. **Mitozytrex** is supplied in vials containing 5 mg of mitomycin. Each 5 mg vial of **Mitozytrex** contains mitomycin 5 mg and HPβCD 2 g.

Mitozytrex contains mitomycin, an antibiotic isolated from the broth of *Streptomyces caespitosus* which has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

Mitomycin is a blue-violet crystalline powder with the molecular formula of $C_{15}H_{18}N_4O_5$ and a molecular weight of 334.33. Its chemical name is 7-amino-9α-methoxymitosane and it has the following structural formula:



CLINICAL PHARMACOLOGY

Mitomycin selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

In humans, mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. After injection of 30 mg, 20 mg, or 10 mg I.V., the maximal serum concentrations were 2.4 μg/mL, 1.7 μg/mL, and 0.52 μg/mL, respectively. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradation pathways.

Approximately 10% of a dose of mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose. In children, excretion of intravenously administered mitomycin is similar. Approximately 80-90% of HPβCD, the solubilizing agent in **Mitozytrex**, is eliminated through the kidneys, and greater than 93% is excreted unchanged in the urine within 12 hours after dosing.

Mitozytrex was found bioequivalent to mitomycin in an open-label randomized cross-over study in cancer patients who received single doses (15 mg/m^2 by a 30-minute infusion) of each formulation. In another open-label study, sequential cycles of **Mitozytrex** showed similar pharmacokinetics to mitomycin when administered every 6 weeks (15 mg/m^2 by a 30-minute infusion). The maximal serum concentration of mitomycin ranged from 0.38 to 1.89 µg/mL after a 30-minute infusion of 15 mg/m^2 **Mitozytrex**. The disposition of mitomycin is biphasic with a mean terminal half life of 46 minutes.

Special populations: ***Renal Insufficiency*** **–** In a study where a single intravenous dose of 200 mg of HPβCD was given to subjects with severe renal impairment (creatinine clearance $\leq$ 19 mL/min), clearance of HPβCD was reduced six-fold compared to subjects with normal renal function. Mitomycin is associated with renal toxicity. **Mitozytrex** should not be used in patients with serum creatinine greater than 1.7 mg percent.

INDICATIONS AND USAGE

Mitozytrex is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. **Mitozytrex** is not recommended to replace appropriate surgery and/or radiotherapy.

CONTRAINDICATIONS

Mitozytrex is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to mitomycin or **Mitozytrex** in the past.

Mitozytrex is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

WARNINGS

Patients being treated with mitomycin must be observed carefully and frequently during and after therapy.

Bone Marrow Suppression

The use of mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least eight weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm^3 or a WBC

below 4,000/mm^3 or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Hemolytic Uremic Syndrome. (See **Black Box WARNINGS** and **ADVERSE REACTIONS** sections).

Renal Toxicity

Patients receiving mitomycin should be observed for evidence of renal toxicity. Mitomycin should not be given to patients with a serum creatinine greater than 1.7 mg percent. (See **CLINICAL PHARMACOLOGY: Special populations and PRECAUTIONS** for information on the HPβCD excipient of **Mitozytrex.**)

Bladder Toxicity

Bladder fibrosis/contraction has been reported with intravesical administration of mitomycin (not an approved route of administration), which in rare cases has required cystectomy. The safety of intravesical administration of **Mitozytrex** and its HPβCD excipient has not been studied. Evidence of bladder toxicities have been observed following parenteral administration of the HP βCD excipient of **Mitozytrex** as single and repeat doses equal to or greater than 0.15g/m^2 and 0.5g/m^2 in rodents and dogs, respectively (about 1/60^{th} and 1/20^{th} the amount of HPβCD administered per recommended human intravenous dose of **Mitozytrex** on a mg/m^2 basis). Findings included edema, inflammation, cellular inclusions and bladder stones associated with metaplasia; findings persisted at least 3 months following dosing.

Carcinogenicity

Mitozytrex contains the excipient HPβCD, which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unclear. (See **PRECAUTIONS**)

Pregnancy

Mitozytrex can cause fetal harm when administered to a pregnant woman. If **Mitozytrex** is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Studies in both mice and rats at mitomycin doses equal to or greater than 0.5 mg/kg/day (about $1/10^{th}$ and $1/5^{th}$, respectively, of the recommended human dose on a mg/m^2 basis), administered intraperitoneally during the period of organogenesis showed a significant decrease in number of live fetuses; mitomycin was lethal to dams at 2 mg/kg/day (about 4/10's the recommended human dose on a mg/m^2 basis) in mice. Evidence of fetotoxicity, including delayed fetal development (e.g., depressed fetal body weights, incomplete ossification), fetal external anomalies (e.g., exencephaly, club foot, cleft palate, maldirection of digits, kinked tail), and neonatal anomalies (hydronephrosis, retarded development of reproductive organs) was observed in mice and rats administered doses equal to or greater than 0.05 mg/kg/day (about $1/100^{th}$ and $1/50^{th}$, respectively, of the recommended human dose on a mg/m^2 basis). In a separate study, mitomycin was administered to pregnant female mice; offspring exhibited significantly retarded reproductive tract development.

In two separate studies, HPβCD, the excipient for **Mitozytrex**, was fetotoxic (decreased number of live fetuses, depressed fetal body weight, incomplete ossification) in rats dosed by gavage and intravenously at doses equal to or greater than 50 and 250mg/kg/day, respectively (about $1/30^{th}$ and $1/6^{th}$ the amount of HPβCD administered per recommended human dose of **Mitozytrex** on a mg/m^2 basis).

PRECAUTIONS

Pulmonary

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received mitomycin. The onset of this acute respiratory distress occurred within minutes to hours after the vinca alkaloid injection. The total number of doses for each drug has varied considerably. Bronchodilators, steroids and/or oxygen have produced symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and overhydration should be avoided.

Renal Toxicity (See **WARNINGS** section).

Patients receiving **Mitozytrex** should be observed for evidence of renal toxicity. **Mitozytrex** should not be given to patients with a serum creatinine greater than 1.7 mg percent. (See **CLINICAL PHARMACOLOGY: Special populations**)

Nephrotoxicity, including irreversible renal necrosis, was observed in rodents and non-rodents following parenteral administration of HPβCD, the excipient contained in **Mitozytrex**. This nephrotoxicity appeared to be the result of the accumulation and recrystallization of HPβCD in the proximal tubules of the kidney.

As severe renal impairment prolongs the elimination rate of HPβCD, **Mitozytrex** should not be used in patients with severe renal dysfunction (creatinine clearance < 30mL/min). (See **CLINICAL PHARMACOLOGY: Special populations**).

Bladder Toxicity

Bladder fibrosis/contraction has been reported with intravesical administration of mitomycin (not an approved route of administration), which in rare cases has required cystectomy. The safety of intravesical administration of **Mitozytrex** and its HP βCD excipient has not been studied. (See **WARNINGS**).

Carcinogenesis

Mitomycin is carcinogenic in mice and rats. Three different strains of mice administered intraperitoneal mitomycin at 0.2ug/mouse (about 1.6 times the recommended human dose on a mg/m^2 basis) twice weekly for 35 doses exhibited increases in undifferentiated sarcomas by study week 40. Likewise, subcutaneous administration of mitomycin produced undifferentiated sarcomas in two of four mouse strains tested. Following bladder installation in rats, mitomycin produced bladder papillomas and dysplasia.

HPβCD is carcinogenic in rats. A conventional carcinogenesis study at doses of 500 to 5000mg/kg/day HPβCD (about 1/3rd to 3 times the amount of HPβCD per recommended human dose of **Mitozytrex** on a mg/m^2 basis) administered in the feed for 25 months revealed a significant increase in the incidence of hyperplasia and adenoma and adenocarcinoma of the exocrine pancreas. Similar findings were not observed in the untreated control group and are not reported in historical controls. Development of these tumors may theoretically be related to a

mitogenic action of cholecystokinin. A significant trend was also observed in adenocarcinoma of the large intestine and mammary gland of rats of this same study administered 5000mg/kg/day HP βCD (about 3 times the amount of HPβCD per recommended human dose of **Mitozytrex** on a mg/m^2 basis). These findings were not observed in mice administered the same doses of HPβCD for 22-23 months. The clinical relevance of these findings is unclear.

Mutagenesis

Mitomycin is a known mutagen and clastogen. Mitomycin has been shown to be positive in the Ames bacterial mutation assay, chromosomal aberrations assays in mice, Chinese hamsters and human lymphocytes, unscheduled DNA synthesis assay in human lymphocytes, micronucleus test in mice and human lymphocytes and somatic mutation and recombination assays in *Drosophila melanogaster.*

Impairment of Fertility

Intraperitoneal administration of mitomycin to male mice in a single dose of 5mg/kg (about equal to the recommended human dose on a mg/m^2 basis) or 1mg/kg (about 1/5th the recommended human dose on a mg/m^2 basis) for 5 days significantly decreased sperm production, sperm count and sperm motility and resulted in reduced pregnancy rates and an increased frequency of malformations. Doses of 2 and 4mg/kg/day administered intravenously to female mice (about 2/5ths and 4/5ths the recommended human dose on a mg/m^2 basis) inhibited fertilization and implantation.

Pregnancy

Pregnancy Category D (See **WARNINGS)**

Nursing Mothers

It is not known if mitomycin 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 **Mitozytrex**, it is recommended that nursing be discontinued when receiving **Mitozytrex** therapy. (See **WARNINGS** and **PRECAUTIONS**).

Pediatric Use - Safety and effectiveness in pediatric patients have not been established.

Geriatric Use - Clinical studies of **Mitozytrex** did not include sufficient numbers of subjects aged 65 and over to determine whether they tolerate the drug differently than younger subjects. In general, elderly patients should be treated with caution due to the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety of **Mitozytrex** at a dose of 15 mg/m^2 by 30-minute infusion was evaluated in a single-arm study of 116 adult cancer patients. One to four doses were administered at 6-week intervals. The toxicity profile of **Mitozytrex** was similar to that reported for mitomycin.

The following adverse reactions were observed in early studies of mitomycin:

Bone Marrow Toxicity—This was the most common and most serious toxicity, occurring in 605 of 937 patients (64.4%) treated with mitomycin. Thrombocytopenia and/or leukopenia may occur anytime within 8 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenic or thrombocytopenic episodes did not recover. Mitomycin produces cumulative myelosuppression.

Integument and Mucous Membrane Toxicity—This has occurred in approximately 4% of patients treated with mitomycin. Cellulitis at the injection site has been reported and is occasionally severe. Stomatitis and alopecia also occur frequently. Rashes are rarely reported. The most important dermatological problem with this drug, however, is the necrosis and consequent sloughing of tissue which results if the drug is extravasated during injection. Extravasation may occur with or without an accompanying stinging or burning sensation and even if there is adequate blood return when the injection needle is aspirated. There have been reports of delayed erythema and/or ulceration occurring either at or distant from the injection site, weeks to months after mitomycin, even when no obvious evidence of extravasation was observed during administration. Skin grafting has been required in some of the cases.

Renal Toxicity—2% of 1,281 patients treated with mitomycin demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between total dose administered or duration of therapy and the degree of renal impairment.

Pulmonary Toxicity—This has occurred infrequently but can be severe and may be life threatening. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin-induced

pulmonary toxicity. If other etiologies are eliminated, mitomycin therapy should be discontinued. Steroids have been employed as treatment of this toxicity, but the therapeutic value has not been determined. A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively.

Hemolytic Uremic Syndrome (HUS)—This serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia (hematocrit ≤ 25%), thrombocytopenia (≤100,000/mm^3), and irreversible renal failure (serum creatinine ≥ 1.6 mg/dL) has been reported in patients receiving systemic mitomycin. Microangiopathic hemolysis with fragmented red blood cells on peripheral blood smears has occurred in 98% of patients with the syndrome. Other less frequent complications of the syndrome may include pulmonary edema (65%), neurologic abnormalities (16%), and hypertension. Exacerbation of the symptoms associated with HUS has been reported in some patients receiving blood product transfusions. A high mortality rate (52%) has been associated with this syndrome.

The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs. Less frequently, HUS has also been reported in patients receiving combinations of cytotoxic drugs not including mitomycin. Of 83 patients studied, 72 developed the syndrome at total doses exceeding 60 mg of mitomycin. Consequently, patients receiving ≥ 60 mg of mitomycin should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombocytopenia and decreased renal function.

The incidence of the syndrome has not been defined.

Therapy for the syndrome is investigational.

Cardiac Toxicity—Congestive heart failure, often treated effectively with diuretics and cardiac glycosides, has rarely been reported. Almost all patients who experienced this side effect had received prior doxorubicin therapy.

Acute Side Effects Due to Mitomycin were fever, anorexia, nausea, and vomiting. They occurred in about 14% of 1,281 patients.

Other—Headache, blurring of vision, confusion, drowsiness, syncope, fatigue, edema, thrombophlebitis, hematemesis, diarrhea, and pain. These did not appear to be dose related and were not unequivocally drug related. They may have been due to the primary or metastatic disease processes. Malaise and asthenia have been reported as part of postmarketing surveillance. Bladder fibrosis/contraction has been reported with intravesical administration (not an approved route of administration. The safety of intravesical administration of

Mitozytrex and its HPβCD excipient has not been studied. (See **WARNINGS** and **PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION

Mitozytrex should be given intravenously only, using care to avoid extravasation of the compound. If extravasation occurs, cellulitis, ulceration and slough may result.

Each vial contains mitomycin 5 mg and HP βCD 2 g. To administer, add 8.5 mL of Sterile Water for Injection. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

Repeat doses of **Mitozytrex** have only been evaluated at a dose of 15mg/m^2. After full hematological recovery (see guide to dosage adjustment) from any previous chemotherapy, the following dosage schedule may be used at 6 to 8 week intervals:

> 15 mg/m^2 intravenously as a single dose via a functioning intravenous catheter

Because of cumulative myelosuppression, patients should be fully reevaluated after each course of **Mitozytrex**, and the dose reduced if the patient experiences significant toxicity.

The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		
Leukocytes/mm^3	Platelets/mm^3	Percentage of Prior Dose to be Given
>4000	>100,000	100%
3000-3999	75,000-99,999	100%
2000-2999	25,000-74,999	70%
<2000	<25,000	50%

No repeat dosage should be given until leukocyte count has returned to 4000/mm^3 and platelet count to 100,000/mm^3.

When **Mitozytrex** is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues to progress after two courses of **Mitozytrex**, the drug should be stopped since chances of response are minimal.

Stability:

1. **Mitozytrex** stored at controlled room temperature 15°-30° C (59°-86°F) and protected from light is stable for the lot life indicated on the package.

2. **Reconstituted** with Sterile Water for Injection to a concentration of 0.5 mg per mL, the reconstituted **Mitozytrex** solution should be used within 24 hours.

3. **Diluted** in various IV fluids at room temperature, to a concentration of 40 micrograms per mL:

IV Fluid	Stability
5% Dextrose Injection	no more than 4 hours
0.9% Sodium Chloride Injection	no more than 48 hours
Sodium Lactate Injection	no more than 24 hours

4. The combination of **Mitozytrex** (5 mg to 15 mg) and heparin (1,000 units to 10,000 units) in 30 mL of 0.9% Sodium Chloride Injection is stable for 72 hours at room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Mitozytrex (mitomycin for injection)

NDC 62701-030-01 – 5 mg mitomycin in an amber vial, individually packaged in single cartons.

Storage: Store dry powder at controlled room temperature 15 to 30 C (59 to 86 F), protected from light. Once reconstituted, protect the reconstituted solution from light.

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC: Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institutes of Health; 1992. US Dept of Health and Human Services, Public Health Service Publication NIH 92-2621.

3. AMA Council on Scientific Affairs. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985;253:1590-1591.

4. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

5. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents*. Med J Australia.* 1983;1:426-428.

6. Jones RB, Frank R, Mass T. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-*A Cancer J for Clin*. 1983;33:258-263.

7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.

8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines)*. Am J Health-Syst Pharm.* 1996;53-1669-1685.

Manufactured for **SuperGen, Inc.**
Dublin, CA 94568

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GO-P-05

NDC 62701-030-01

Mitozytrex™

(mitomycin for injection, USP)

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5 mg

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Rx only

WARNING: Must be administered IV to avoid tissue damage.

SuperGen

This vial contains Mitomycin, USP 5 mg and hydroxypropyl β cyclodextrin 2 g. Add 8.5 mL Sterile Water for Injection, USP. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained. Each mL of reconstituted solution will contain 0.5 mg mitomycin and have a pH between 5.5 and 8.5.

USUAL DOSAGE: See package insert for full prescribing information.

Storage: Store at Controlled Room Temperature 15° to 30°C (59° to 86°F), protected from light. Protect reconstituted solution from light.

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NDC 62701-030-01

Mitozytrex™
(mitomycin for injection, USP)
5 mg

SuperGen®

NDC 62701-030-01

Mitozytrex™
(mitomycin for injection, USP)
5 mg

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Mitozytrex™
(mitomycin for injection, USP)
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