PRODUCT MONOGRAPH

[Pr]MITOMYCIN FOR INJECTION

USP

(5 mg and 20 mg per vial)

Antineoplastic

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THERAPEUTIC CLASSIFICATION
Antineoplastic

CAUTION: MITOMYCIN IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS SHOULD BE TAKEN WEEKLY. MITOMYCIN MUST BE DISCONTINUED OR DOSAGE REDUCED UPON EVIDENCE OF ABNORMAL DEPRESSION OF THE BONE MARROW OR THE DEVELOPMENT OF SIGNIFICANT RENAL OR PULMONARY TOXICITY.

ACTION AND CLINICAL PHARMACOLOGY

Mitomycin was first investigated as an antibiotic in Japan. It was then found to be active as an antineoplastic agent. It selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The exact point of mitomycin attachment to DNA remains unknown. There is a correlation between the guanine and cytosine content of DNA and 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 plasma after intravenous administration with a biphasic plasma elimination curve. 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 intravenously, the maximal serum concentrations were 2.4 μg/mL, 1.7 μg/mL and 0.52 μg/mL, respectively.

In general, the smaller the dose, the more rapidly blood levels of mitomycin decreased. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well.

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 doses. In children, excretion of intravenously administered mitomycin is similar.

Mitomycin is not appreciably absorbed from the urinary bladder, following intravesical administration. Serial plasma samples from 55 patients treated with doses of 20 mg to 40 mg of mitomycin by intravesical instillation were assayed. There was no mitomycin detectable (assay limit 10 to 100 ng/mL) in any plasma samples collected during and 30 minutes post-therapy at any dose.

INDICATIONS AND CLINICAL USE

Mitomycin is indicated in the palliative treatment as an adjunct to surgery, radiation or chemotherapy for adenocarcinoma of the stomach and colon.

Mitomycin as a single agent is indicated as topical therapy for superficial (no invasion beyond the lamina propria) transitional cell carcinoma of the urinary bladder. Efficacy has been demonstrated both in patients who have had no prior intravesical chemotherapy and in those who have failed such therapy with Thiotepa or other antineoplastic agents.

CONTRAINDICATIONS

Mitomycin is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

Mitomycin is contraindicated in patients with thrombocytopenia, leukopenia, coagulation disorder, or an increased bleeding tendency due to other causes.

Mitomycin is contraindicated for intravesical administration in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

WARNINGS

It is recommended that mitomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Since facilities for necessary laboratory studies must be available, hospitalization of patients is recommended.

Mitomycin should not be administered to any patient with a white blood cell count below 4000 mm^3 and a platelet count below 150 000 mm^3, or to those with potentially serious infections.

Bone marrow depression, notably thrombocytopenia and leukopenia, is the most severe toxicity (see **ADVERSE REACTIONS**). This may contribute to overwhelming infection in an already compromised, poor risk patient and may result in death.

In the treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit versus the risk of toxicity. Studies have shown that mitomycin is carcinogenic in animals.

Use in Obstetrics
Safe use of mitomycin in pregnant women has not been established. Mitomycin has known teratogenic properties in animals, therefore, the benefits derived from the use of mitomycin in pregnancy must be weighed against the hazards involved.

PRECAUTIONS

Mitomycin should be administered, preferably, to patients who are hospitalized and who can be observed carefully and frequently during and after therapy.

It should be used with extreme caution in patients with significant impairment of renal function.

Since mitomycin has a high incidence of bone marrow depression, particularly thrombocytopenia and leukopenia, the following studies should be obtained frequently during therapy and for at least seven weeks following therapy: platelet count, prothrombin time, bleeding time, white blood count and differential. The persistence of thrombocytopenia below 150 000 mm^3, or a significant prolongation of prothrombin time or bleeding time, or a white blood cell count below 4000 mm^3 is an indication for the termination of therapy.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow depression. A low incidence of septicemic deaths, as a result of leukopenia attributable to the drug, have been reported. 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.

Mitomycin-associated pulmonary toxicity has been reported. Cases have been reported with both single-agent therapy and combination chemotherapy. Dyspnea and nonproductive cough are the usual presenting symptoms. Radiographic evidence of interstitial infiltrates may or may not be present. If other etiologies have been eliminated, a diagnosis of mitomycin-related pulmonary toxicity may be made.

Signs and symptoms of pneumonitis associated with mitomycin may be reversed if appropriate therapy is instituted early and mitomycin is discontinued. Corticosteroids have been reported by several authors to expedite symptomatic relief.

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.

ADVERSE REACTIONS

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Bone Marrow Toxicity

The most serious and most common toxicity of mitomycin is thrombocytopenia and leukopenia which occur anytime within eight weeks after onset of therapy. In a recent study, at a dose of 20 mg/m^2 every six to eight weeks, by itself or in combination with 5-fluorouracil, leukopenia occurred in 74 of 94 patients, with 10 being in the life-threatening category; and thrombocytopenia occurred in 68 of 94 patients, with 18 being in the life-threatening category. In a previous study, at doses of 0.5 mg/kg/day for five days and repeating once monthly, or 0.25 mg/kg every two weeks, leukopenia and/or thrombocytopenia occurred in 605 of 937 patients. The return to normal counts after cessation of therapy was within 10 weeks. 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.

Pulmonary Toxicity
Refer to section on pulmonary toxicity under **PRECAUTIONS**.

Renal Toxicity
A small number of patients demonstrated a significant rise in BUN from a baseline pre-therapy. There appeared to be no correlation between total dose administered or duration of therapy and renal toxicity. Seventy-five percent of the patients with a definite renal toxicity had evidence of metastatic disease. The data, to date, are inconclusive as far as a direct relationship of mitomycin to renal toxicity.

Hemolytic Uremic Syndrome (HUS)
A serious and often fatal syndrome consisting of microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and hypertension has been reported in patients receiving mitomycin. Most of these patients received long-term therapy (6 to 12 months) with mitomycin in combination with fluorouracil and doxorubicin; however, some patients received mitomycin in combination with other drugs or were treated for less than six months.

Acute Side Effects
Fever, hemolytic anemia, anorexia, stomatitis, hypoglycemia, mucositis, and diarrhea have occurred.

Other Undesirable Side Effects
Headache, blurring of vision, confusion, drowsiness, syncope, fatigue, weakness, edema, thrombophlebitis, hematemesis, nausea, vomiting, weight loss, ataxia, and pain. It is difficult to determine whether these side effects are dose-related or due to the primary or metastatic disease process.

Genitourinary Irritation
Genitourinary irritation following intravesical administration indicated dysuria, cystitis, nocturia

and increased frequency of micturition, hematuria, and other symptoms of local irritation. Approximately 25% of the patients treated experienced irritative symptoms, but not all were unequivocally drug-related and may have been symptoms of the disease.

Dermatitis
Dermatitis occurred in approximately 10% of the patients treated. It was commonly manifested as palmar rash with desquamation, generally appearing on the extremities and less often on the trunk, and also as genital rash. Topical steroids have been employed but their therapeutic value has not been determined.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No specific antidote for mitomycin is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

DOSAGE AND ADMINISTRATION

Mitomycin should be given with care to avoid extravasation of the compound into the tissue. If extravasation occurs, cellulitis, ulceration and slough may result.

To reconstitute a vial of mitomycin, add Sterile Water for Injection as listed in the Reconstitution Table below:

Reconstitution Table

Vial Size	Diluent Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Concentration (mg/mL)
5 mg	10	9.5	0.5
20 mg	40	39.0	0.5

Shake well until dissolved. If the product does not dissolve immediately, shake under warm tap

water for approximately two minutes until a solution is obtained.

Intravenous Use
After full hematological recovery from any previous chemotherapy, either of the following Dosage Schedules may be used at 6 to 8 week intervals. Because of cumulative myelosuppression, patients should be re-evaluated after each course of mitomycin and the dose reduced if the patient has experienced any toxicities (see Guide to Dosage Adjustment).

Doses greater than 20 mg/m^2 do not demonstrate increased effectiveness and are more toxic than lower doses.

(1) 20 mg/m^2 intravenously as a single dose via a functioning intravenous catheter.

(2) 2 mg/m^2/day intravenously for 5 days. After a drug free interval of 2 days, 2 mg/m^2/day for 5 days, thus making the total initial dose of 20 mg/m^2 given over 10 days.

Intravesical Use
A dose of 20 to 40 mg intravesically once per week for 8 weeks. Patients are advised to abstain from liquids for 12 hours prior to therapy. The patient is catheterized, the bladder is drained and mitomycin is instilled. The solution should be retained for 2 hours. If desired, the patient may rotate positions every 15 minutes, for maximum area-contact.

The following schedule is suggested as a Guide to Dosage Adjustment:

Guide to Dosage Adjustment

Nadir After Prior Dose		Percentage of Prior Dose to be Given
Leukocytes	**Platelets**	
>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 3000 and platelet count to 75 000.

When mitomycin is used in combination with other myelosuppressive agents, the doses should

be adjusted accordingly. If the disease continues to progress after two courses of mitomycin, the drug should be stopped since chances of response are minimal.

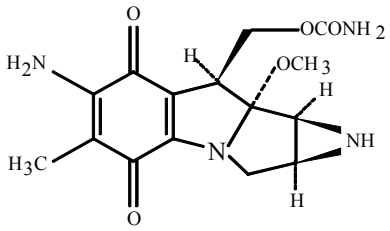
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: mitomycin

Chemical Name: 6-amino-1, 1a, 2, 8, 8a, 8b-hexahydro-8 (hydroxymethyl)-8a-methoxy-5-methylaziridino (2', 3':3, 4) pyrrolo (1, 2-a) indole-4, 7-dione carbamate (ester)

Structural Formula:



Molecular Formula: $C_{15}H_{18}N_4O_5$

Molecular Weight: 334.34

Description: Mitomycin is an antibiotic isolated from the broth of *Streptomyces caespitosus* as deep blue violet crystals. It has a melting point of ≥360°C and is soluble in water and organic solvents. It has a pH of 6.0 - 8.0 in water.

Composition
Each vial contains mitomycin 5 mg and mannitol 10 mg, or mitomycin 20 mg and mannitol 40 mg. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment.

Stability and Storage Recommendations
Store at controlled room temperature (15° - 30°C) protected from light.

Reconstituted Solutions
Solutions for Reconstitution: Sterile Water for Injection

Reconstitution Table

Vial Size	Diluent Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Concentration (mg/mL)
5 mg	10	9.5	0.5
20 mg	40	39.0	0.5

Shake well until dissolved. If the product does not dissolve immediately, shake under warm tap water for approximately two minutes until a solution is obtained.

Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg/mL, mitomycin is stable for 14 days refrigerated or seven days at controlled room temperature (15° - 30°C), protected from light.

Parenteral Products

Reconstituted solutions may be further diluted at controlled room temperature (15° - 30°C) with one of the following diluents to a concentration of 20 to 40 μg/mL:

5% Dextrose Injection
0.9% Sodium Chloride Injection
Sodium Lactate Injection

Reconstituted solutions are stable for 3 hours when further diluted with 5% Dextrose Injection, 12 hours when further diluted with 0.9% Sodium Chloride Injection, and 24 hours when further diluted with Sodium Lactate Injection.

The combination of mitomycin (5 mg to 15 mg) and heparin (1000 units to 10 000 units) in 30 mL of 0.9% Sodium Chloride Injection is stable for 48 hours at room temperature.

The reconstituted and diluted solutions should be inspected for discolouration, haziness, particulate matter and leakage prior to administration. Discard unused portion.

Handling and Disposal

1. Preparation of mitomycin should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel preparing mitomycin should wear PVC gloves, safety glasses, disposal gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with mitomycin should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

Personnel regularly involved in the preparation and handling of mitomycin should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORMS

[Pr] Mitomycin for Injection is supplied as a sterile lyophilized powder with mannitol in single use vials containing 5 mg or 20 mg of mitomycin, packaged individually.

PHARMACOLOGY

Mitomycin disappears rapidly from the plasma and there is no evidence of specific tissue localization.

After intravenous injection in dogs, mitomycin appeared in the urine within 5 to 6 minutes. Eighteen to twenty-nine percent is recovered within one hour. Simultaneous creatinine clearance studies indicate that excretion is primarily by glomerular filtration.

In children given intravenous doses, the urinary recovery was 5 to 20% within one hour and was essentially complete in two hours.

TOXICOLOGY

Acute Toxicity

Species	Route	Number of Successive Daily Doses	LD_{50} (mg/kg/day)
Mice	Intraperitoneal	1	8.5
Mice	Intraperitoneal	5	2.3
Mice	Intravenous	1	7.83
Rats	Intraperitoneal	1	2.5
Rats	Intraperitoneal	5	1.0
Rats	Intravenous	1	3.41
Dogs	Intravenous	1	1.25
Dogs	Intravenous	10	0.125

Repeated Dose Toxicity in Monkeys
No pharmacotoxic signs were observed following intravenous injections of 0.2 or 0.4 mg/kg/day given for 10 consecutive days.

At higher dosage levels (up to 3.2 mg/kg) dose-related pharmacologic signs included moderate to marked anorexia, soft stools, diarrhea, decreased activity, depression, and weight loss. An increase in BUN was noted and on autopsy, damage to renal tubules and the hematopoietic tissue was found.

The toxicity of mitomycin in the four species studied is fairly uniform. Moreover, the constancy of the total dose required to produce lethal effects has been suggested in the toxicity studies. The LD_{50} as a single intravenous dose was about the same as the total dose in a ten-day schedule.

Clinical signs of intoxication in animals were intestinal and hematopoietic disturbances, hyperthermia non-related to agranulocytosis, tissue hemorrhages, and necrotizing nephrosis. Therefore, diarrhea and neutropenia may offer suitable warnings of impending severe intoxication in humans.

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