PRESCRIBING INFORMATION

[Pr]MITOMYCIN FOR INJECTION USP

5 mg/vial
20 mg/vial

Powder for Solution

Antineoplastic

Pfizer Canada Inc.
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
August 28, 2018

Submission Control No.: 218896

PRESCRIBING INFORMATION

[Pr]MITOMYCIN FOR INJECTION USP

5 mg/vial
20 mg/vial

Powder for Solution
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

Mitomycin was investigated at first 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) secondary to alkylation. The molecular site of DNA binding has been identified as the guanine-N^2 link in the minor groove of B-DNA. At high concentrations of the drug, cellular RNA and protein syntheses 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 IV, the maximal serum concentrations were 2.4 mcg/mL, 1.7 mcg/mL and 0.52 mcg/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 20-40 mg of Mitomycin by intravesical instillation were assayed. There was no Mitomycin detectable (assay limit 10-100 ng/mL) in any plasma samples collected during and 30 minutes post-therapy at any dose.

INDICATIONS AND CLINICAL USES

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 4,000 mm^3 and a platelet count below 150,000 mm^3 or to those with potentially serious infections.

Bone manow depression, notably thrombocytopenia and leukopenia, is the most severe toxicity (see **ADVERSE REACTIONS).** This may contribute to overwhelming infection in already compromised, poor risk patients 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 Pregnancy:

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 WBC below 4,000 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 %.

Mitomycin-associated pulmonary toxicity has been reported. Cases have been reported with both single-agent therapy and combination chemotherapy. Dyspnea and non-productive cough are the usual presenting symptoms. Radiographic evidence of interstitial infiltrates mayor 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. The use of Mitomycin should be 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 or 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 $Fi0_2$, concentrations greater than 50% preoperatively. 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

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 Mucus 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 in **PRECAUTIONS**.

Renal Toxicity:

A small number of patients demonstrated a significant rise in BUN from a base-line 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: have been headache, blurring of vision, confusion, drowsiness, syncope, fatigue, weakness, edema, thrombophlebitis, hematemesis, nausea, vomiting, weight loss, ataxia and pain. These do not appear to be dose-related and it was difficult to determine whether these were dose-related or due to the primary or metastatic disease process.

Genito-urinary 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: 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

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.

RECONSTITUTION

To reconstitute a vial of 5 mg or 20 mg of Mitomycin for Injection USP, add 10 mL or 40 mL of Sterile Water for Injection, respectively, to obtain an approximate concentration of 0.5 mg/mL.

Intravenous Use:

After full hematological recovery from any previous chemotherapy, either of the following Dosage Schedules may be used at 6 to 8 weeks 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:

20 - 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, bladder drained and Mitomycin 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:

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.

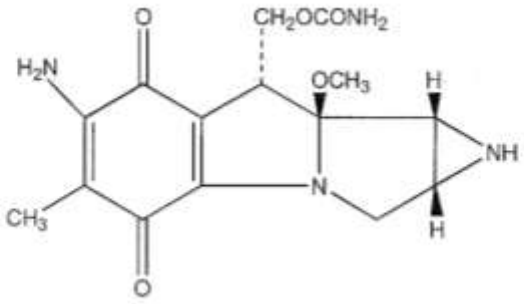
PHARMACEUTICAL INFORMATION

CHEMISTRY - DRUG SUBSTANCE

Proper Name: Mitomycin

Chemical Name: 6-amino-l, lα, 2,8, 8α, 8β-hexahydro-8-(hydroxymethyl)-8α-methoxy-5-methylazirino (2',3' :3,4)pyrrolo(1,2-α) 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 5 mg vial contains Mitomycin for Injection USP (5 mg/vial) and Mannitol, USP (10 mg/vial) as sterile lyophilized powder.

Each 20 mg vial contains Mitomycin for Injection USP (20 mg/vial) and Mannitol, USP (40 mg/vial) as sterile lyophilized powder.

RECONSTITUTION

Solutions for Reconstitntion: Sterile Water for Injection

To reconstitute a vial of 5 mg or 20 mg of Mitomycin for Injection USP, add 10 mL or 40 mL of Sterile Water for Injection, respectively, to obtain an approximate concentration of 0.5 mg/mL.

STABILITY AND STORAGE RECOMMENDATIONS

1. Mitomycin vials should be stored between 15 - 25°C and protected from light.

2. Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg/mL, Mitomycin for Injection USP is stable for 72 hour refrigerated (2 - 8°C), or 24 hours at controlled room temperature (15 - 25°C). Protect from light.

3. Diluted in varions IV fluids at controlled room temperatme (15 - 25°C), to a concentration of 20 to 40 micrograms per mL:

IV Fluid	Stability
0.9 % Sodium Chloride Injection	11 hours
Sodium Lactate Injection	24 hours

4. 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 24 hours at controlled room temperature (15 - 25°C).

WARNING

The reconstituted and diluted solutions should be inspected visually for discoloration, haziness, precipitation, 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, disposable 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 if sealed. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

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

AVAILABILITY OF DOSAGE FORMS

Mitomycin for Injection USP is available as a single use vial as a sterile lyophilized powder in vials containing either 5 mg of mitomycin and 10 mg of mannitol or 20 mg of mitomycin and 40 mg of mannitol. Contains no preservatives.

Last revised: August 28, 2018

Pfizer Canada Inc.
Kirkland, Québec
H9J 2M5