MITOMYCIN (Systemic)

Introduction

Revised: 9/29/97

VA CLASSIFICATION (Primary/Secondary)¾AN200/DE600
Commonly used brand name(s):Mutamycin.
Another commonly used name is mitomycin-C .

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antineoplastic.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Carcinoma, gastric (treatment)

[Carcinoma, esophageal (treatment)] *

Carcinoma, pancreatic (treatment)

[Carcinoma, anal (treatment)] *

[Carcinoma, colorectal (treatment)]

[Carcinoma, breast (treatment)] *

[Carcinoma, head and neck (treatment)] *

[Carcinoma, biliary (treatment)] *

[Carcinoma, lung, non-small cell (treatment)] *

[Carcinoma, cervical (treatment)] *¾Mitomycin is indicated, in combination with other agents, for palliative treatment of adenocarcinoma of the stomach or pancreas unresponsive to surgery and/or radiotherapy 1.

Mitomycin is also used for treatment of anal 5 or esophageal 4 carcinomas, adenocarcinoma of the colon or breast 7 ; some head and neck tumors 7 ; and advanced biliary 8 , non-small-cell lung 7 , and cervical 6 squamous cell carcinomas 3.

[Carcinoma, bladder (treatment)]¾Mitomycin is used for topical treatment of superficial transitional cell carcinoma of the urinary bladder 2.

[Leukemia, chronic myelocytic (treatment)] *¾Mitomycin is used for treatment of chronic myelocytic leukemia 3.

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾334.34 2

Mechanism of action/Effect:

Mitomycin is classified as an antibiotic but is not useful as an antimicrobial agent because of its toxicity. Mitomycin is cell cycle-phase nonspecific, although it is most active in the G and S phases of cell division. After enzyme activation in the tissues, it functions as a bifunctional or trifunctional alkylating agent. Mitomycin causes cross-linking of DNA and inhibits DNA synthesis and, to a lesser extent, also inhibits RNA and protein synthesis.

Distribution:

Does not cross the blood-brain barrier.

Biotransformation:

Hepatic (primarily); some in other tissues 1.

Half-life:

Initial, following 30-mg bolus injection¾17 minutes 1.

Elimination:

Renal (10% unchanged); the percentage of a dose excreted in urine increases with increasing doses due to saturation of metabolic pathways at relatively low doses 1.

Precautions to Consider

Carcinogenicity/Mutagenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use. Although information is limited, available data seem to indicate that the carcinogenic risk is greatest with the alkylating agents.
Mitomycin is carcinogenic in rats and mice 1.

Pregnancy/Reproduction

Fertility¾Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking antineoplastic therapy, especially with the alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents. The effects of mitomycin on fertility are not known 1.

Pregnancy¾First trimester: It is usually recommended that use of antineoplastics, especially combination chemotherapy, be avoided whenever possible, especially during the first trimester. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the mutagenic, teratogenic, and carcinogenic potential of these medications must be considered.
Other hazards to the fetus include adverse reactions seen in adults.
In general, use of a contraceptive is recommended during cytotoxic drug therapy.
Mitomycin is reported to cause teratogenicity in animals 1.

Breast-feeding

Although very little information is available regarding distribution of antineoplastic agents into breast milk, breast-feeding is not recommended while mitomycin is being administered because of the risks to the infant (adverse effects, mutagenicity, carcinogenicity).

Pediatrics

Appropriate studies on the relationship of age to the effects of mitomycin have not been performed in the pediatric population. However, pediatrics-specific problems that would limit the usefulness of this medication in children are not expected.

Geriatrics

No information is available on the relationship of age to the effects of mitomycin in geriatric patients. However, elderly patients are more likely to have age-related renal function impairment, which may require caution in patients receiving mitomycin.

Dental

The bone marrow depressant effects of mitomycin may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. Dental work, whenever possible, should be completed prior to initiation of therapy or deferred until blood counts have returned to normal.

Patients should be instructed in proper oral hygiene during treatment, including caution in use of regular toothbrushes, dental floss, and toothpicks.
Mitomycin may also cause stomatitis 1 associated with considerable discomfort.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Blood dyscrasia-causing medications (see Appendix II)

(leukopenic and/or thrombocytopenic effects of mitomycin may be increased with concurrent or recent therapy if these medications cause the same effects; dosage adjustment of mitomycin, if necessary, should be based on blood counts)

>> Bone marrow depressants, other (see Appendix II) or

Radiation therapy

(additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively)

Doxorubicin

(concurrent use may result in increased cardiotoxicity; it is recommended that the total dose of doxorubicin not exceed 450 mg per square meter of body surface)

Vaccines, killed virus

(because normal defense mechanisms may be suppressed by mitomycin therapy, the patient's antibody response to the vaccine may be decreased. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year)

>> Vaccines, live virus

(because normal defense mechanisms may be suppressed by mitomycin therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side/adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunization of these patients should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician managing the mitomycin therapy. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying

disease, and other factors; estimates vary from 3 months to 1 year. Patients with leukemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. Immunization with oral poliovirus vaccine should also be postponed in persons in close contact with the patient, especially family members)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Blood urea nitrogen (BUN) and

Creatinine, serum

(concentrations may be increased, indicating renal toxicity)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Bone marrow depression

>> Chickenpox, existing or recent (including recent exposure) or

>> Herpes zoster

(risk of severe generalized disease)

>> Coagulation disorders

>> Infection

>> Renal function impairment

(use is not recommended in patients with a serum creatinine greater than 1.7 mg per 100 mL 1)

Sensitivity to mitomycin 1

>> Caution should be used also in patients who have received previous cytotoxic drug therapy or radiation therapy.

Patient monitoring

>> Blood urea nitrogen (BUN) concentrations and

>> Creatinine concentrations, serum

(recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

>> Hematocrit or hemoglobin and

>> Leukocyte count, total and, if appropriate, differential and

>> Observation for fragmented red blood cells on peripheral blood smears and 1

>> Platelet count

(determinations recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

Note: It is recommended that renal and hematologic function be followed during and for at least 8 weeks after mitomycin therapy, especially in patients receiving doses of 60 mg or more, to detect possible hemolytic-uremic syndrome or bone marrow depression. 1

Side/Adverse Effects

Note: Many "side effects" of antineoplastic therapy are unavoidable and represent the medication's pharmacologic action. Some of these (for example, leukopenia and thrombocytopenia) are actually used as parameters to aid in individual dosage titration.
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Leukopenia (fever or chills; cough or hoarseness; lower back or side pain; painful or difficult urination)¾usually asymptomatic; thrombocytopenia (unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin)¾usually asymptomatic

Note: Leukopenia and thrombocytopenia occur up to 8 weeks after initiation of therapy (average, 4 weeks), and counts return to normal within 10 weeks after therapy is stopped, although in about 25% of episodes counts do not recover. Severity of bone marrow depression varies and determines subsequent dosage of mitomycin. 1

Incidence less frequent

Pneumopathy (cough; shortness of breath); renal toxicity (blood in urine; decreased urination; shortness of breath; swelling of feet or lower legs); stomatitis (sores in mouth and on lips)

Note: Pneumopathy usually occurs after several doses; it can be severe and may be life-threatening 1.

Renal toxicity has included a hemolytic-uremic syndrome (consisting of microangiopathic hemolytic anemia [hematocrit 25% or less], irreversible renal failure, thrombocytopenia [platelet count less than 100,000], and less frequently, pulmonary hypertension, neurologic abnormalities, and hypertension), which is fatal in greater than 50% of cases. Renal failure without hemolysis has also been reported. The syndrome may occur at any time during therapy with mitomycin, alone or in combination with other chemotherapy. Use of blood product transfusions may exacerbate the symptoms in some patients. Incidence appears to be greatest in patients receiving doses of mitomycin of 60 mg or greater. 1

Incidence rare

Bloody vomit; thrombophlebitis or cellulitis (redness or pain, especially at site of injection)¾caused by extravasation

Note: Extravasation may also occur without accompanying burning or stinging. Delayed erythema and ulceration have occurred weeks to months after mitomycin administration, at or distant from the injection site. 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Loss of appetite; nausea and vomiting

Note: Nausea and vomiting usually occur within 1 to 2 hours; vomiting usually stops in 3 to 4 hours, while nausea may persist for 2 or 3 days.

Incidence less frequent

Numbness or tingling in fingers and toes; purple-colored bands on nails¾occur with repeated doses; skin rash; unusual tiredness or weakness¾may last several days to 3 weeks
Those not indicating need for medical attention

Incidence less frequent

Loss of hair
Those indicating the need for medical attention if they occur after medication is discontinued

Bone marrow depression (black, tarry stools; blood in urine or stools; cough or hoarseness; fever or chills; lower back or side pain; painful or difficult urination; pinpoint red spots on skin; unusual bleeding or bruising); possible hemolytic-uremic syndrome (blood in urine, decreased urination, shortness of breath, swelling of feet or lower legs); delayed skin reaction (red or painful skin)

Note: Cumulative myelosuppression may occur with repeated doses 1.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Mitomycin (Systemic).
As an aid to patient consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

Conditions affecting use, especially:

Sensitivity to mitomycin
Pregnancy¾Use not recommended because of mutagenic, teratogenic, and carcinogenic potential; advisability of using contraception; telling physician immediately if pregnancy is suspected
Breast-feeding¾Not recommended because of risk of serious side effects
Other medications, especially other bone marrow depressants or previous cytotoxic drug or radiation therapy
Other medical problems, especially chickenpox, coagulation disorders, herpes zoster, other infections, or renal function impairment
Proper use of this medication

Caution in taking combination therapy; taking each medication at the right time

Frequency of nausea and vomiting; importance of continuing medication despite stomach upset

>> Proper dosing
Precautions while using this medication

>> Importance of close monitoring by physician

>> Avoiding immunizations unless approved by physician; other persons in patient's household should avoid immunizations with oral poliovirus vaccine; avoiding persons who have taken oral poliovirus vaccine or wearing a protective mask that covers nose and mouth

Caution if bone marrow depression occurs

>> Avoiding exposure to persons with infections, especially during periods of low blood counts; checking with physician immediately if fever or chills, cough or hoarseness, lower back or side pain, or painful or difficult urination occurs

>> Checking with physician immediately if unusual bleeding or bruising; black, tarry stools; blood in urine or stools; or pinpoint red spots on skin occur

Caution in use of regular toothbrush, dental floss, or toothpick; physician, dentist, or nurse may suggest alternatives; checking with physician before having dental work done

Not touching eyes or inside of nose unless hands washed immediately before

Using caution to avoid accidental cuts with use of sharp objects such as safety razor or fingernail or toenail cutters

Avoiding contact sports or other situations where bruising or injury could occur

>> Possibility of local tissue injury and scarring if infiltration of intravenous solution occurs or as delayed reaction; telling doctor or nurse right away about redness, pain, or swelling at injection or any other site

Side/adverse effects

Importance of discussing possible effects, including cancer, with physician

Signs of potential side effects, especially leukopenia, thrombocytopenia, pneumopathy, renal toxicity, stomatitis, bloody vomit, thrombophlebitis, or cellulitis caused by extravasation

Physician or nurse can help in dealing with side effects

Possibility of hair loss; should return after treatment has ended

General Dosing Information

Patients receiving mitomycin should be under supervision of a physician experienced in cancer chemotherapy.
A variety of dosage schedules and regimens of mitomycin in combination with other antitumor agents are used. The prescriber may consult the medical literature as well as the manufacturer's literature in choosing a specific dosage.
Mitomycin is usually administered intravenously via a functioning intravenous catheter.
Care must be taken to avoid extravasation during intravenous administration because of the risk of severe ulceration and necrosis. 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. Delayed erythema and ulceration occurring either at or distant from the injection site have been reported weeks to months following mitomycin administration, even when no evidence of extravasation was observed during administration. Skin grafting has been required in some of the cases. 1

Mitomycin must not be administered intramuscularly or subcutaneously because it will cause local tissue necrosis.
Mitomycin has also been administered intra-arterially (for example, into hepatic artery) for treatment of some tumors.
Dosage of mitomycin subsequent to the initial course should be adjusted to meet the individual requirements of each patient, on the basis of hematological response of the patient to the previous dose. An additional course of mitomycin should be given only after circulating blood elements have returned to acceptable levels (leukocytes above 3000 per cubic millimeter and platelets above 75,000 per cubic millimeter). 1

Patients who have not responded after two courses of mitomycin are unlikely to show a response 1.

Special precautions are recommended in patients who develop thrombocytopenia as a result of administration of mitomycin. These may include extreme care in performing invasive procedures; regular inspection of intravenous sites, skin (including perirectal area), and mucous membrane surfaces for signs of bleeding or bruising; limiting frequency of venipuncture and avoiding intramuscular injections; testing urine, emesis, stool, and secretions for occult blood; care in use of regular toothbrushes, dental floss, toothpicks, safety razors, and fingernail and toenail cutters; avoiding constipation; and using caution to prevent falls and other injuries. Such patients should avoid alcohol and any aspirin intake because of the risk of gastrointestinal bleeding. Platelet transfusions may be required.
Patients who develop leukopenia should be observed carefully for signs of infection. Antibiotic support may be required. In neutropenic patients who develop fever, broad-spectrum antibiotic coverage should be initiated empirically, pending bacterial cultures and appropriate diagnostic tests.
Topical bladder instillations with 20 to 40 mg of mitomycin in a strength of 1 mg per mL in distilled water, which is retained for as long as possible (usually 2 to 3 hours), are used once weekly for 8 procedures per course in the treatment of small bladder papillomas.

Safety considerations for handling this medication

There is limited but increasing evidence and concern that personnel involved in preparation and administration of parenteral antineoplastics may be at some risk because of the potential mutagenicity, teratogenicity, and/or carcinogenicity of these agents, although the actual risk is unknown. USP advisory panels recommend cautious handling both in preparation and disposal of antineoplastic agents. Precautions that have been suggested include:
· Use of a biological containment cabinet during reconstitution and dilution of parenteral medications and wearing of disposable surgical gloves and masks.
· Use of proper technique to prevent contamination of the medication, work area, and operator during transfer between containers (including proper training of personnel in this technique).
· Cautious and proper disposal of needles, syringes, vials, ampuls, and unused medication.A number of medical centers have developed detailed guidelines for handling of antineoplastic agents.

Combination chemotherapy

Mitomycin may be used in combination with other agents in various regimens. As a result, incidence and/or severity of side effects may be altered and different dosages (usually reduced) may be used.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

MITOMYCIN FOR INJECTION USP

Usual adult and adolescent dose

Carcinoma, gastric or
Carcinoma, pancreatic or
[Carcinoma, colorectal]¾

Intravenous, 20 mg per square meter of body surface area as a single dose repeated every six to eight weeks [1], [2].

A suggested dosage adjustment schedule for subsequent doses is:

Nadir after Prior Dose (cells per cubic millimeter)		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

Usual adult prescribing limits

Doses greater than 20 mg per square meter of body surface area appear to be no more effective than lower doses and increase the risk of toxicity [1].

Usual pediatric dose

See Usual adult and adolescent dose.

Size(s) usually available:

U.S.¾5 mg (Rx)[Mutamycin (mannitol 10 mg)]

20 mg (Rx)[Mutamycin (mannitol 20 mg)]

40 mg (Rx)[Mutamycin (mannitol 80 mg)]

Canada¾5 mg (Rx)[Mutamycin (mannitol 10 mg)]

20 mg (Rx)[Mutamycin (mannitol 20 mg)]

40 mg (Rx)[Mutamycin (mannitol 80 mg)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

Preparation of dosage form:

Mitomycin for Injection USP is reconstituted for intravenous use by adding 10 mL (5-mg vial), 40 mL (10-mg vial), or 80 mL (40-mg vial) of sterile water for injection to the vial and shaking to dissolve, allowing to stand at room temperature if necessary until solution occurs [1] ; a blue-gray solution is produced.
Reconstituted solutions may be further diluted with 5% dextrose injection, 0.9% sodium chloride injection, or sodium lactate injection for administration by intravenous infusion [1].

Stability:

Reconstituted solutions of mitomycin are stable for 14 days refrigerated or 7 days at room temperature, when protected from light. When further diluted for administration by intravenous infusion, reconstituted solutions are stable for 3 hours in 5% dextrose injection, 12 hours in 0.9% sodium chloride injection, or 24 hours in sodium lactate injection at room temperature