Mitomycin (systemic): Drug information

(For additional information see "Mitomycin (systemic): Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Experienced physician:

Mitomycin 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:

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.

Hemolytic uremic syndrome:

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 doses greater than or equal to 60 mg of mitomycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome. The incidence of the syndrome has not been defined.

Brand Names: Canada

Mitomycin For Injection; Mitomycin For Injection USP; Mutamycin

Pharmacologic Category

Antineoplastic Agent, Antibiotic

Dosing: Adult

Gastric cancer: IV: 20 mg/m^2 once every 6 to 8 weeks

Off-label dosing: IV: 7 mg/m^2 (maximum dose: 14 mg) once every 6 weeks for 4 cycles (in combination with cisplatin and fluorouracil) (Ross 2002)

Pancreatic cancer: IV: 20 mg/m^2 once every 6 to 8 weeks

Anal carcinoma (off-label use): IV: 10 mg/m^2 as an IV bolus on days 1 and 29 (maximum: 20 mg/dose)

in combination with fluorouracil and radiation therapy (Ajani 2008; Flam 1996) **or** 10 mg/m^2 on day 1 (maximum dose: 15 mg) in combination with capecitabine and radiation therapy (Meulendijks 2014) **or** 12 mg/m^2 on day 1 (maximum dose: 20 mg) in combination with capecitabine and radiation therapy (Thind 2014)

Bladder cancer (off-label use):

Muscle invasive: IV: 12 mg/m^2 on day 1 (in combination with fluorouracil and radiation) (James 2012)

Nonmuscle invasive (off-label route): Intravesicular instillation:

Low risk of recurrence (uncomplicated): 40 mg as a single dose postoperatively; retain in bladder for 1 to 2 hours (Hall 2007; O'Brien 2013)

Increased risk of recurrence: 20 mg weekly for 6 weeks, followed by 20 mg monthly for 3 years; retain in bladder for 1 to 2 hours (Friedrich 2007) **or** 40 mg weekly for 6 weeks (with urine alkalinization and decreased urine volume to increase drug concentration); retain in bladder for 2 hours (Au 2001)

Cervical cancer, recurrent or metastatic (off-label use): IV: 6 mg/m^2 on day 1 once every 4 weeks (in combination with cisplatin) for a minimum of 2 cycles (preferably 9 cycles) (Wagenaar 2001)

Esophageal cancer, advanced (off-label use): IV: 7 mg/m^2 (maximum dose: 14 mg) once every 6 weeks for 4 cycles (in combination with cisplatin and fluorouracil) (Ross 2002)

Vulvar cancer, advanced (off-label use): IV: 15 mg/m^2 on day 1 every 14 days for 2 cycles (in combination with concomitant radiation and fluorouracil) (Landoni 1996)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

The manufacturer's labeling states to avoid use in patients with serum creatinine >1.7 mg/dL, although no other dosage modifications are provided. The following adjustments have been recommended (Aronoff 2007): Adults:

CrCl <10 mL/minute: Reduce dose to 75% of usual dose.

Continuous ambulatory peritoneal dialysis (CAPD): Reduce dose to 75% of usual dose.

Dosing: Hepatic Impairment

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

Leukocytes 2000 to <3000/mm^3: Hold therapy until leukocyte count ≥4000/mm^3; reduce to 70% of prior

dose in subsequent cycles

Leukocytes <2000/mm^3: Hold therapy until leukocyte count ≥4000/mm^3; reduce to 50% of prior dose in subsequent cycles

Platelets 25,000 to <75,000/mm^3: Hold therapy until platelets ≥100,000/mm^3; reduce to 70% of prior dose in subsequent cycles

Platelets <25,000/mm^3: Hold therapy until platelets ≥100,000 mm^3; reduce to 50% of prior dose in subsequent cycles

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Intravenous:

Generic: 5 mg (1 ea); 20 mg (1 ea); 40 mg (1 ea)

Generic Equivalent Available (US)

Yes

Administration

IV: Administer by slow IV push/bolus via a freely-running saline infusion. Consider using a central venous catheter.

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation.

Extravasation management: If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Initiate dimethyl sulfate (DMSO) antidote. Apply dry cold compress for 20 minutes 4 times/day for 1 to 2 days (Pérez Fidalgo 2012).

DMSO: Apply topically to a region covering twice the affected area every 8 hours for 7 days; begin within 10 minutes of extravasation; do not cover with a dressing (Perez Fidalgo 2012).

Intravesicular (off-label route): Instill into bladder and retain for 1 to 2 hours (Au 2001; Friedrich 2007; Hall 2007; O'Brien 2013); rotate patient every 15 to 30 minutes

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Gastric cancer: Treatment of disseminated adenocarcinoma of the stomach (in combination with other chemotherapy agents) and as palliative treatment when other modalities have failed.

Pancreatic cancer: Treatment of disseminated adenocarcinoma of the pancreas (in combination with other chemotherapy agents) and as palliative treatment when other modalities have failed.

Limitations of use: Not recommended for single-agent primary therapy or to replace appropriate surgery and/or radiotherapy in the treatment of these conditions.

Use: Off-Label

Anal cancer; Bladder cancer; Cervical cancer, recurrent or metastatic; Esophageal cancer, advanced; Vulvar cancer, advanced

Medication Safety Issues

Sound-alike/look-alike issues:

MitoMYcin (Systemic) may be confused with MitoMYcin (Ophthalmic), mitotane, mitoXANTRONE

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Gastrointestinal: Anorexia (14%), nausea (14%), vomiting (14%)

Hematologic & oncologic: Bone marrow depression (64%; onset: 4 weeks; recovery: 8 to 10 weeks), hemolytic-uremic syndrome (HUS; ≤15%), thrombotic thrombocytopenic purpura (TTP; ≤15%)

Miscellaneous: Fever (14%)

1% to 10%:

Dermatologic: Alopecia (4%)

Gastrointestinal: Mucous membrane disease (toxicity: 4%), stomatitis (4%)

Renal: Increased serum creatinine (2%)

<1%, postmarketing, and/or case reports: Adult respiratory distress syndrome (ARDS), bladder spasm (intravesical administration), cardiac failure, dyspnea, extravasation reactions, fibrosis (bladder; intravesical administration), hepatic veno-occlusive disease (SOS), interstitial fibrosis, malaise, nonproductive cough, pulmonary infiltrates, renal failure (irreversible), skin rash, weakness

Contraindications Hypersensitivity to mitomycin or any component of the formulation; thrombocytopenia; coagulation disorders, or other increased bleeding tendency

Warnings/Precautions

Concerns related to adverse effects:

• Bladder fibrosis/contraction: Bladder fibrosis/contraction has been reported with intravesical administration (unlabeled administration route).

• Bone marrow suppression: **[US Boxed Warning]: Bone marrow suppression (thrombocytopenia and leukopenia) is common and may be severe and/or contribute to infections.** WBC and platelet nadir usually occurs at 4 weeks, although may occur at up to 8 weeks; recovery occurs within 10 weeks. Fatalities due to sepsis have been reported; monitor for infections. Myelosuppression is dose-limiting, delayed in onset, and cumulative; therefore, monitor blood counts closely during and for at least 8 weeks following treatment; treatment delay or dosage adjustment may be required for significant thrombocytopenia (platelets <100,000/mm^3) or leukopenia (WBC<4000/mm^3) or a progressive decline in either value.

• Extravasation: Mitomycin is a potent vesicant; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. May cause necrosis and tissue sloughing; delayed erythema and/or ulceration have been reported.

• Heart failure: In a scientific statement from the American Heart Association, mitomycin has been determined to be an agent that may either cause reversible direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: moderate) (AHA [Page 2016]).

• Hemolytic-uremic syndrome: **[US Boxed Warning]: Hemolytic-uremic syndrome (HUS) has been reported (incidence not defined); condition usually involves microangiopathic hemolytic anemia (hematocrit ≤25%), thrombocytopenia (≤100,000/mm^3), and irreversible renal failure (serum creatinine ≥1.6 mg/dL). HUS may occur at any time (either with single agent or combination therapy), is generally associated with single doses ≥60 mg, and HUS symptoms may be exacerbated by blood transfusion.** Other less common effects may include pulmonary edema, neurologic abnormalities, and hypertension. A high mortality from HUS has been reported. HUS may also be associated with doses ≥60 mg.

• Pulmonary toxicity: Cases of acute respiratory distress syndrome (ARDS) have been reported in patients receiving mitomycin in combination with other chemotherapy who were maintained at FIO_2 concentrations >50% perioperatively; use caution to provide only enough oxygen to maintain adequate arterial saturation and avoid overhydration. Pulmonary toxicity has also been reported as dyspnea with nonproductive cough and appearance of pulmonary infiltrates on radiograph; discontinue therapy if pulmonary toxicity occurs and other potential etiologies have been ruled out.

Disease-related concerns:

• Renal impairment: Do not administer if serum creatinine is >1.7 mg/dL; monitor for renal toxicity.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• Vinca alkaloids: Shortness of breath and bronchospasm have been reported in patients receiving vinca alkaloids in combination with mitomycin or who received mitomycin previously; this acute respiratory distress has occurred within minutes to hours following the vinca alkaloid; may be managed with bronchodilators, steroids and/or oxygen.

Other warnings/precautions:

• Experienced physician: **[US Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Metabolism/Transport Effects

Substrate of P-glycoprotein

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Antineoplastic Agents (Vinca Alkaloids): May enhance the adverse/toxic effect of MitoMYcin (Systemic). Specifically, the risk of pulmonary toxicity may be increased. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Pregnancy Implications

Adverse events have been observed in animal reproduction studies.

Breast-Feeding Considerations

It is not known if mitomycin is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Monitoring Parameters

Monitor CBC with differential (repeatedly during therapy and for ≥8 weeks following therapy); serum creatinine; pulmonary function tests; monitor for signs/symptoms of HUS; monitor infusion site.

Mechanism of Action

Mitomycin alkylates DNA to produce DNA cross-linking (primarily with guanine and cytosine pairs) and inhibits DNA and RNA synthesis. Mitomycin is not cell cycle specific but has its maximum effect against cells in late G and early S phases (Perry 2012).

Pharmacodynamics/Kinetics

Metabolism: Primarily hepatic

Half-life elimination: 17 minutes (30 mg dose)

Excretion: Feces (primarily [Perry 2012]); Urine

Pricing: US

Solution (reconstituted) (MitoMYcin Intravenous)

5 mg (1): $272.46

20 mg (1): $707.82

40 mg (1): $1415.64

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Ametycine (FR); Baxmicin (BR); Datisan (AR); Minazol (CO); Mitocin (BD); Mitocyna (PY); Mitomicina (CL); Mitomicina-C (PT); Mitomycin (DE, DK, MY, SE); Mitomycin C (ES,

HK, IL, IN, PL); Mitomycin-C (AT, BG, CH, CN, CY, GR, ID, IT, KR, NL, PH, RU, TH, TR, TW); Mitomycin-C Kyowa (AU, CZ, GB, HU, LU, NZ); Mitomycine (BE); Mitostat (FI); Mitotie (EC, MX); Mixandex (CR, DO, GT, HN, NI, PA, SV); Mutamycin (DK, EE, EG, FI, HR, JO, NO, PT, UY); Mytomycin C (JP); Mytoxid (PH); Riptam (PE); Vesimycin (LK); Vetio (AR)

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