DRUG NAME: Mitomycin

SYNONYM(S): mitomycin C,[1] MMC[2]

COMMON TRADE NAME(S): MUTAMYCIN®

CLASSIFICATION: antitumour antibiotic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Mitomycin is derived from *Streptomyces caespitosus*[3] and has antineoplastic activity similar to that of the alkylating agents.[1] Mitomycin selectively inhibits the synthesis of DNA by causing cross-linking,[1,3] degrades preformed DNA, and causes nuclear lysis and formation of giant cells.[4] At high concentrations, cellular RNA and protein synthesis may also be suppressed.[1,3] Mitomycin is cell cycle phase-nonspecific, although it has its maximum effect in late G- and early S-phases.[4]

PHARMACOKINETICS:

Oral Absorption	no information found	
Distribution	rapidly cleared from plasma[1,3]	
	cross blood brain barrier?[4]	unlikely
	volume of distribution[4]	22 L/m^2
	plasma protein binding	no information found
Metabolism	rapidly inactivated in the liver, kidneys, spleen, brain, heart, and plasma[1]; metabolic pathways saturated at relatively low doses	
	active metabolite(s)	no information found
	inactive metabolite(s)[1]	yes
Excretion	primarily hepatic[3,4]; occurs in other tissues	
	urine[1,3]	≤10% unchanged; dose related
	feces[1]	minimal
	terminal half life[4]	50 min
	clearance	no information found
Children	excretion in children is similar to adults	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
Anal cancer[5]
*Bladder cancer (intravesical)
*Colon cancer
*Gastric cancer
Liver cancer[5]
Pseudomyxoma peritonei[7]

Other uses:
Cervical cancer[5]
Ocular cancer (topical)[6]
Pancreatic cancer[5]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Carcinogenicity: Carcinogenic in mice and rats when administered in doses approximating usual therapeutic amounts.[1,3]

Mutagenicity: No information found.

Fertility: Effect on fertility is not known.[1]

Pregnancy: FDA Pregnancy Category D.[4] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[8,9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia (19-24%)[4]; hemolytic anemia
	leukopenia (50-79%, severe 11%); within 8 weeks; cumulative
	thrombocytopenia (40-72%, severe 19%); within 8 weeks; apparent recovery may occur, followed by further depression[1]
cardiovascular (general)	CHF (3-15%)[4]; with doses >30 mg/m^2
constitutional symptoms	fever[1,3] (14%)[4]
	malaise (≤10%)[1,4]; prolonged
dermatology/skin	*extravasation hazard:* vesicant[10]
	alopecia (1-10%)
	cellulitis at the injection site; occasionally severe
	dermatitis (10%); commonly palmar rash with desquamation, typically on the extremities, less often on the trunk and genitals
	induration[1]
	mucocutaneous toxicity (4%)[1,3]; including mouth ulcers, desquamation, and pruritus[1]
	nail banding/discolouration (>10%)[4]
	rash (≤10%)[3,4]
gastrointestinal	*emetogenic potential:* low[11]
	anorexia[1,3] (14%)[4]
	diarrhea
	mucositis

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nausea (14%)[4]; typically within 1-2 hours and may continue for 2-3 days[1]
	stomatitis (1-10%)[3,4]
	vomiting (14%)[4]; typically within 1-2 hours and subsides rapidly[1]
infection	septicemia
metabolic/laboratory	elevated BUN and/or Cr (2%);[1] may be related to cumulative dose; risk increases substantially[1] at doses ≥50 mg/m^2
	hypoglycemia
neurology	paresthesia[1] (1-10%)[4]
pain	injection site pain[1]
pulmonary; refer to paragraph following **Side Effects** table	adult respiratory distress syndrome
	bronchospasm
	cough (≤7%)[1,4]
	dyspnea (≤10%)[1,4]
	infiltrates (1-10%)[4]
	pneumonitis (1-10%)[4]
renal/genitourinary	***local irritation*** (25%); includes cystitis, dysuria, hematuria, increased frequency of micturition, nocturia; dose related;[1] with intravesical
	renal failure (1%)[4]
	ulcer at the site of tumour resection, asymptomatic; with intravesical[1]
syndromes	hemolytic uremic syndrome (HUS)(<1%);[4] see paragraph following the **Side Effects** table

Adapted from standard reference[3] unless specified otherwise.

Pulmonary toxicity typically presents as dyspnea and nonproductive cough.[3] Interstitial infiltrates may or may not be present on X-ray.[3] Pneumonitis may be reversed if mitomycin is discontinued and treatment is instituted early.[3] Corticosteroids have been reported to help with symptoms but their therapeutic value has not been determined.[1,3] Administration of vinca alkaloids to patients who have previously or simultaneously received mitomycin may cause severe or life-threatening dyspnea and bronchospasm within minutes to hours.[1,3] Bronchodilators, steroids, and/or oxygen have produced symptomatic relief.[3] In the perioperative setting use only enough oxygen to provide adequate arterial saturation.[3] Cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at fraction of inspired oxygen (FiO_2) concentrations >50%.[3]

Hemolytic Uremic Syndrome consisting of microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and hypertension has been reported.[1] Pulmonary edema, if present, appears to be a particularly grave prognostic factor.[1] HUS is correlated with total dose (single doses ≥60 mg or cumulative dose ≥50 mg/m^2) and total duration of therapy (>5-11 months).[4] These patients typically received long-term (6-12 months) therapy in combination with fluorouracil and doxorubicin; however, some patients received other combinations or were treated for less than six months.[1] HUS can vary from a chronic course with mild anemia and slowly progressive renal impairment, to a fulminant course with severe anemia, rapid deterioration of renal function, and death.[1] Optimum management has not been established but early treatment with corticosteroids, plasma exchange, plasmapheresis, and/or IV vincristine have been beneficial in some patients.[1]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
vinca alkaloids[4]	shortness of breath and bronchospasm have been reported in patients receiving vinca alkaloids in combination with or after mitomycin	unknown	may be managed with bronchodilators, steroids and/or oxygen

SUPPLY AND STORAGE:

***Injection*:**

Accord Healthcare Inc. supplies mitomycin as a lyophilized powder in 20 mg single-use vials. Store at room temperature. Protect from light.[12]

Teva supplies mitomycin as a lyophilized powder in 20 mg single-use vials. Store at room temperature. Protect from light.[13]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- if the product does not dissolve immediately, allow the vial to stand at room temperature until complete dissolution occurs[1]
- ***for intravesical use***:
  - mitomycin has been added to lidocaine gel immediately prior to intravesical administration[14]
  - a concentrated solution (2mg/mL) of mitomycin has been used for intravesical administration[9,15-17]; to prevent precipitation, solution should be freshly prepared and not refrigerated[18]
  - normal saline has been used as the diluent for reconstitution (in place of SWI) in combination with a warm water bath and incubator to improve the solubility of concentrated mitomycin solutions for intravesical use[19]

Mitomycin Eye Drops:
- mitomycin eye drops 0.2-0.4 mg/mL (0.02-0.04%) can be prepared with sterile water for injection (SWI)[20-23]
- final product is stable for 2 days at room temperature, 14 days refrigerated[24,25]; some data suggest that lowering of the pH below 7 may result in shorter stability[24]

To achieve a 0.2 mg/mL (**0.02%**) eye drop solution:
- reconstitute 20 mg vial of mitomycin with 40 mL SWI to give a concentration of 0.5 mg/mL
- transfer 6 mL (3 mg) to a sterile 15 mL eye dropper bottle
- add 9 mL SWI to the eye dropper bottle to give a concentration of 0.2 mg/mL (0.02%)

To achieve a 0.4 mg/mL (**0.04%**) eye drop solution:
- reconstitute 20 mg vial of mitomycin with 40 mL SWI to give a concentration of 0.5 mg/mL
- transfer 12 mL (6 mg) to a sterile 15 mL eye dropper bottle
- add 3 mL of SWI to the eye dropper bottle to give a concentration of 0.4 mg/mL (0.04%)

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Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous[4]	***slow IV push***, into tubing of running IV; see ***Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion[4]	over 15-30 min
Continuous infusion	no information found
Intraperitoneal	***run into abdominal cavity as rapidly as possible;*** dwell for 23 hours with abdominal drains clamped, then drain[26]
	hyperthermic intraperitoneal chemotherapy (HIPEC): pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[27-31]
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical[15-17,32-34]	***instill and retain for 1-2 h***
Ocular (topical)[6]	has been used

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	4-8 weeks[4,26,35-37]:	***10-15 mg/m^2 IV for one dose on day 1 or 3***
	6-8 weeks[1,3,4,37,38]:	10-20 mg/m^2 IV for one dose on day 1
	6-8 weeks[3]:	2 mg/m^2 IV once daily for 5 consecutive days on days 1-5 and on days 8-12 (total dose per cycle 20 mg/m^2)
Ocular (topical):	n/a[6]:	0.02-0.04% drops qid for 7-28 days
Intravesical:	weekly[9,15,16,32-34,39,40]:	induction: 20-60 mg ***instilled intravesically once weekly for 6-8 weeks*** (total dose per cycle 120-480 mg)

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BC Cancer usual dose noted in ***bold, italics***

monthly[16,34,39,41,42]: maintenance: 20-60 mg ***instilled intravesically once monthly**** for ***1***-3 ***years, starting after induction***

*(a maintenance schedule of every 3 months has also been used)[41]

once[42,43]: 40 mg instilled intravesically postoperatively for one dose on day 1

Concurrent radiation: use caution in patients who have received radiation therapy; reduce dose in patients who are receiving radiation therapy simultaneously[4]

Dosage in myelosuppression: modify according to protocol by which patient is being treated or refer to guidelines below:
no repeat dosage should be given until WBC has returned to 3 x 10^9/L and platelet count to 75 x 10^9/L[1,3]

The following guideline has been suggested[3]:

Nadir After Prior Dose (x 10^9/L)		% of Prior Dose to be Given
WBC	platelets	
≥3	≥75	100
2 – 2.9	25 – 74.9	70
<2	<25	50

Dosage in renal failure: The manufacturer and others recommend to not administer if serum creatinine is >150 µmol/L[1,3,4]
The following guideline has also been recommended[4,44]:

Creatinine clearance (mL/min)	**Dose**
≥10	100%
<10	75%

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in µmol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: no information found

Dosage in dialysis[44]: peritoneal dialysis: dose as for CrCl <10mL/min
intermittent hemodialysis, continuous renal replacement therapy: no information found

Children: safety and efficacy have not been established[1]; has been used[4]

Intravenous:
Cycle Length:
6-8 weeks[4]: 10-20 mg/m^2 IV for one dose on day 1

4-6 weeks[4]: 3 mg/m^2 IV once daily for 5 consecutive days starting on day 1

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