

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Mitomycin, Powder for Injection, 5 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Mitomycin 5 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection. Blue-violet cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mitomycin for Injection is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitomycin is not recommended to replace appropriate surgery and/or radiotherapy.

4.2 Dose and method of administration

Dose:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Mitomycin should be given intravenously only, using care to avoid extravasation of the compound. If extravasation occurs, cellulitis, ulceration, and slough may result.

Each vial contains either mitomycin 5 mg and mannitol 10 mg. To administer, add Sterile Water for Injection, 10 mL. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

After full haematological recovery (see guide to dosage adjustment) from any previous chemotherapy, the following dosage schedule may be used at 6 to 8 week intervals:

20 mg/m² intravenously as a single dose via a functioning intravenous catheter.

Because of cumulative myelosuppression, patients should be fully reevaluated after each course of mitomycin, and the dose reduced if the patient has experienced any toxicities. Doses greater than 20 mg/m² have not been shown to be more effective, and are more toxic than lower doses.

The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		
Leukocytes/mm ³	Platelets/mm ³	Percentage of Prior Dose to be Given
> 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 4000/mm³ and a platelet count to 100,000/mm³.

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.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Patients being treated with mitomycin must be observed carefully and frequently during and after therapy.

The use of mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least eight weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm³ or a WBC below 4,000/mm³ or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicæmia as a result of leukopaemia due to the drug.

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.

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 FIO₂ 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.

Bladder fibrosis/contraction has been reported with intravesical administration (not an approved route of administration), which in rare cases has required cystectomy.

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

Elderly

Insufficient data from clinical studies of mitomycin are available for patients 65 years of age and older to determine whether they respond differently than younger patients. Postmarketing surveillance suggests that elderly patients may be more susceptible than younger patients to injection site reactions (see section 4.8 Undesirable effects: Integument and Mucous Membrane Toxicity) and hypersensitivity reactions. In general, caution should be exercised when prescribing to elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.5 Interaction with other medicines and other forms of interaction

Myelotoxic interactions with other bone marrow-toxic treatment modalities (especially other cytotoxic medicinal products, radiation) are possible.

Combination with vinca alkaloids or bleomycin may reinforce pulmonary toxicity.

An increased risk of haemolytic-uremic syndrome has been reported in patients receiving a concomitant administration of mitomycin and fluorouracil or tamoxifen.

In animal experiments, pyridoxine hydrochloride (vitamin B₆) resulted in the loss of effect of mitomycin.

No injections with live vaccines should be carried out in connection with mitomycin treatment.

The cardiotoxicity of Adriamycin (doxorubicin) may be reinforced by mitomycin.

4.6 Fertility, pregnancy and lactation

Fertility

The effect of mitomycin on fertility is unknown.

Pregnancy

Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies.

Lactation

It is not known if mitomycin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mitomycin, it is recommended that nursing be discontinued when receiving mitomycin therapy.

4.7 Effects on ability to drive and use machines

Even when used in accordance with instructions these medicinal products may cause nausea and vomiting and thereby reduce reaction times to such an extent that the ability to drive a motor vehicle or operate machinery is impaired. This applies even more in connection with alcohol.

4.8 Undesirable effects

Bone Marrow Toxicity

This was the most common and most serious toxicity, occurring in 605 of 937 patients (64.4%). Thrombocytopenia and/or leukopenia may occur anytime within 8 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenic or thrombocytopenic episodes did not recover. 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. Elderly patients may be more susceptible than younger patients to injection site reactions (see section 4.4 Special warnings and precautions for use: Elderly).

Renal Toxicity

2% of 1,281 patients demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between total dose administered or duration of therapy and the degree of renal impairment.

Pulmonary Toxicity

This has occurred infrequently but can be severe and may be life threatening. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin-induced pulmonary toxicity. If other etiologies are eliminated, mitomycin therapy should be discontinued. Steroids have been employed as treatment of this toxicity, but the therapeutic value has not been determined. A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO₂ concentrations greater than 50% perioperatively.

Hemolytic Uremic Syndrome (HUS)

This serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia (hematocrit $\leq 25\%$), thrombocytopenia ($\leq 100,000/\text{mm}^3$), and irreversible renal failure (serum creatinine $\geq 1.6 \text{ mg/dL}$) has been reported in patients receiving systemic mitomycin. Microangiopathic hemolysis with fragmented red blood cells on peripheral blood smears has occurred in 98% of patients with the syndrome. Other less frequent complications of the syndrome may include pulmonary edema (65%), neurologic abnormalities (16%), and hypertension. Exacerbation of the symptoms associated with HUS has been reported in some patients receiving blood product transfusions. A high mortality rate (52%) has been associated with this syndrome.

The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs. Less frequently, HUS has also been reported in patients receiving combinations of cytotoxic drugs not including mitomycin. Of 83 patients studied, 72 developed the syndrome at total doses exceeding 60 mg of mitomycin. Consequently, patients receiving $\geq 60 \text{ mg}$ of mitomycin should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombocytopenia, and decreased renal function.

The incidence of the syndrome has not been defined.

Therapy for the syndrome is investigational.

Cardiac Toxicity

Congestive heart failure, often treated effectively with diuretics and cardiac glycosides, has rarely been reported. Almost all patients who experienced this side effect had received prior doxorubicin therapy.

Acute side effects due to Mitomycin were fever, anorexia, nausea, and vomiting. They occurred in about 14% of 1,281 patients.

Other

Headache, blurring of vision, confusion, drowsiness, syncope, fatigue, edema, thrombophlebitis, hematemesis, diarrhea, and pain. These did not appear to be dose related and were not unequivocally drug related. They may have been due to the primary or metastatic disease processes. Malaise and asthenia have been reported as part of postmarketing surveillance. Bladder fibrosis/contraction has been reported with intravesical administration (see section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

In case of overdose severe myelotoxicity or even myelophthisis must be expected, with the full-blown clinical effect only appearing after approximately 2 weeks.

The period until which the number of leucocytes falls to the lowest value may be 4 weeks. Prolonged close haematological monitoring therefore also has to be carried out if an overdose is suspected.

As there are no effective antidotes available, the greatest level of caution is required during each application

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

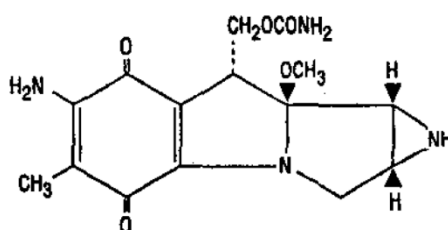
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, Other cytotoxic antibiotics, ATC Code: L01DC03

Mitomycin (also known as mitomycin and/or mitomycin-C) is an antibiotic isolated from the broth of *Streptomyces caespitosus* which has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

Mitomycin for Injection is a sterile dry mixture of mitomycin and mannitol, which when reconstituted with Sterile Water for Injection provides a solution for intravenous administration. Each vial contains mitomycin 5 mg and mannitol 10 mg. Each mL of reconstituted solution will contain 0.5 mg mitomycin and have a pH between 6.0 and 8.0.

Mitomycin is a blue-violet crystalline powder with the molecular formula of $C_{15}H_{18}N_4O_5$, and a molecular weight of 334.33. Its chemical name is 7-amino-9 α -methoxymitosane and it has the following structural formula;



Mitomycin selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

5.2 Pharmacokinetic properties

In humans, mitomycin is rapidly cleared from the serum after intravenous administration. 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 I.V., the maximal serum concentrations were 2.4 mcg/mL, 1.7 mcg/mL, and 0.52 mcg/mL, respectively. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradative pathways.

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

5.3 Preclinical safety data

Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in man, it produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol E421

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened vial: 2 years

After reconstitution: 14 days. Store at 2-8°C. Refrigerate, do not freeze. Protect from light.
7 days. Store at or below 25°C.

6.4 Special precautions for storage

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Mitomycin 5 mg/vial powder for injection is contained within a amber coloured, type I glass vial with a bromo butyl rubber stopper and an aluminium seal.

Each vial is individually packed in single carton.

6.6 Special precautions for disposal and handling

1. Unreconstituted mitomycin stored at room temperature is stable for the lot life indicated on the package. Avoid excessive heat (over 40°C, 104°F).
2. Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg per mL, mitomycin is stable for 14 days refrigerated or 7 days at room temperature.
3. Diluted in various I.V. fluids at room temperature, to a concentration of 20 to 40 micrograms per mL:

I.V. Fluid	Stability
0.9% Sodium Chloride Injection	12 hours
Sodium Lactate Injection	24 hours

The combination of mitomycin (5 mg to 15 mg) and heparin (1,000 units to 10,000 units) in 30 mL of 0.9% Sodium Chloride Injection is stable for 48 hours at room temperature.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

This medicine has been given a provisional consent under Section 23 of the Medicines Act. This consent is valid until 28 October 2020.

10. DATE OF REVISION OF THE TEXT

1 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format