AUSTRALIAN PRODUCT INFORMATION

MITOCIN® (MITOMYCIN) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

Mitomycin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mitocin injection is available in single use vials. Each vial contains 20 mg of mitomycin.

One vial of Mitocin 20 mg powder for injection/infusion or intravesical use contains 20 mg of mitomycin. After reconstitution with 40 mL water for injections 1 mL of solution for injection/infusion contains 0.5 mg mitomycin. After reconstitution with 20 ml solvent 1 mL of solution for intravesical use contains 1 mg mitomycin.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Powder for injection/infusion or intravesical use

Mitocin is an antibiotic isolated from the broth of *Streptomyces caespitosus* which has been shown to have anti-tumour activity. Mitomycin is a blue-violet crystalline powder slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol, slightly soluble in acetone.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mitomycin is indicated in the palliative treatment of carcinoma of the stomach, pancreas, colon, lung (non-small cell), breast, cervix, head and neck, liver and bladder.

4.2 Dose and method of administration

Mitocin is administered by slow intravenous infusion. Mitocin should not be given by rapid intravenous injection.

Mitocin is for single use in one patient only. Discard any unused portion.

Mitocin 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 mitomycin 20 mg. To administer add Sterile Water for injection 20 mL to 20 mg vials. Shake to dissolve. The reconstituted solution is then added immediately as a single dose through a running intravenous infusion of 5 % Glucose, 0.9% Sodium Chloride or Sodium Lactate Injection IV infusion, for the treatment of all tumours other than bladder tumours. Shake until the reconstituted solution becomes clear and free of particles.

For the treatment of bladder tumours the reconstituted 20 mg dose is further diluted to 50 mL with sterile Water for Injection and immediately instilled directly into the bladder via a catheter and retained in the bladder as long as possible.

After full haematological recovery (see guide to dosage adjustment) from any previous chemotherapy, either of the following dosage schedules may be used at 6 to 8 week intervals. Because of cumulative myelosuppression, patients should be fully re-evaluated after each course of Mitocin and the dose reduced if the patient has experienced any toxicities. Doses greater than 20 mg/m^2 have not been shown to be more effective, and are more toxic than lower doses. Dosage reduction should be considered in cases with prior extensive bone marrow irradiation or renal dysfunction.

1. 20 mg/m^2 intravenously as a single dose via a functioning intravenous catheter.

2. 2mg/m^2/day intravenously for 5 days. After a drug-free interval of 2 days, 2mg/m^2/day for 5 days, thus making the total initial dose 20 mg/m^2 given over 10 days. The following schedule (Table 1) is suggested as a guide to dosage adjustment.

Table 1: Guide to dosage adjustment

NADIR AFTER PRIOR DOSE		Percentage of Prior Dose go be Given
Leucocytes	Platelets	
>4,000	>100,000	100%
3,000-3,999	75,000-99,999	100%
2,000-2,999	25,000-74,999	70%
<2,000	<25,000	50%

No repeat dosage should be given until leucocyte count has returned to 3,000 and platelet count to 75,000.

Renal and hepatic dysfunction also usually require dosage reduction and may be an indication for interrupting treatment. When Mitocin is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues

to progress after two courses of Mitocin, the drug should be stopped since chances of response are minimal.

Guidelines for proper handling and disposal of anticancer drugs.
Care must be taken whenever handling anticancer products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

4.3 Contraindications

Pancytopenia or isolated leucopoenia/thrombopenia, haemorrhagic diathesis and acute infections are absolute contraindications.

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breastfeeding
- Mitomycin is contraindicated in patients with coagulation disorder.

Systemic therapy
Restrictive or obstructive disturbances to pulmonary ventilation, renal function, liver function and/or a poor general state of health are relative contraindications. Temporal connection with radiotherapy or other cytostatic may be a further contraindication.

Intravesical therapy
Perforation of the bladder wall is an absolute contraindication.
Cystitis is a relative contraindication

4.4 Special warnings and precautions for use

Mitomycin should not be administered orally, intrathecally or into the tissues (such as intramuscularly or subcutaneously).

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 diagnostic and treatment facilities are readily available.

Mitomycin should only be used when appropriate access to haematological and pathological services is available. Haematological screening is required during therapy and for at least 7 weeks after treatment.

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 leucopenia. Thrombocytopenia may contribute to hemorrhage and leucopenia to overwhelming infections in already compromised patient (see **section 4.8 Adverse effects (undesirable effects)**). Therefore, the following studies should be obtained repeatedly during therapy and for at least 7 weeks following therapy: platelet count, white blood cell count, differential and haemoglobin. The occurrence of a platelet count below 100,000 or a WBC below 4,000, or a progressive decline in either is an indication for interruption of therapy.

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

Dose adjustment according to nadir count may be required. Therefore, the following studies should be obtained repeatedly during therapy and for at least 8 weeks following therapy: white blood cell (WBC) and platelet counts, 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.

Hemolytic Uremic Syndrome (HUS), a serious complication of chemotherapy, consisting primarily of microangiopathic haemolytic 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 >60 mg of mitomycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome. The incidence of the syndrome has not been defined (See section **4.8 Adverse effects (undesirable effects)**).

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 has occurred within minutes to hours after the vinca alkaloid injection. The total number of doses for each drug has varied considerably. Bronchodilators, corticosteroids and/or oxygen have produced symptomatic relief (see **section 4.8 Adverse effects (undesirable effects)**).

A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapeutic agents who were being maintained perioperatively at FiO_2 concentrations greater than 50% (See **section 4.8 Adverse effects (undesirable effects)**). Therefore, caution should be exercised, and only enough oxygen to provide adequate arterial saturation should be used since oxygen itself can be toxic to the lungs. Careful attention should be paid to fluid balance, and overhydration should be avoided.

Reports of bladder fibrosis/contraction, following intravesicular administration, which in rare cases have required cystectomy, have been received post marketing. Bladder necrosis and penile necrosis have also been reported (See **section 4.8 Adverse effects (undesirable effects)**).

Injection site reactions may occur during the administration of mitomycin (See **section 4.8 Adverse effects (undesirable effects)**). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Use in the elderly
No data available.

Paediatric use
The safety and efficacy of mitomycin in children have not been established.

Effects on laboratory tests
No data available.

4.5 Interactions with other medicines and other forms of interactions

No data available.

4.6 Fertility, pregnancy and lactation

Effects on fertility
The effect of mitomycin on fertility is unknown.

Use in Pregnancy
Pregnancy Category D - Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies.

Use in lactation
It is not known if mitomycin is excreted in human milk. Because many drugs are excreted in milk, it is recommended that women receiving mitomycin not breast feed because of the potential for serious adverse reactions from mitomycin in nursing infants.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (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 leucopenia 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 leucopenia 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. The most important dermatologic event is 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 cases. Stomatitis and alopecia also occurred frequently. Rashes are rarely reported. Amputations subsequent to extravasation of mitomycin have occurred (See **section 4.4 Special warnings and precautions for use**).

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. Dyspnoea with a non-productive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin induced pulmonary toxicity. If other aetiologies 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 chemo-therapeutic agents and who were maintained at FiO_2 concentrations greater than 50% perioperatively (See section **4.4 Special warnings and precautions for use**).

Haemolytic Uremic Syndrome (HUS): This serious complication of chemotherapy, consisting primarily of microangiopathic haemolytic anemia (haematocrit ≤ 25%), thrombocytopenia (≤100,000/mm3), and irreversible renal failure (serum creatinine ≥1.6mg/dL or ≥140 µmol/L) has been reported in patients receiving systemic mitomycin. Microangiopathic haemolysis with fragmented red blood cells seen 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. The incidence of the syndrome has not been defined. A high mortality rate (52%) has been associated with this syndrome (See section **4.4 Special warnings and precautions for use**).

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 ≥60mg of mitomycin should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombocytopenia, and decreased renal function.

Hepatic Toxicity: Hepatic dysfunction has been reported in approximately 5% of cases.

Cardiac: Congestive heart failure, often responding to conventional therapy, has been reported rarely. 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 undesirable side effects that have been reporting during mitomycin therapy have been headache, blurring of vision, confusion, drowsiness, syncope, fatigue, oedema, thrombophlebitis, haematemesis, diarrhoea 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.

Intravesical Administration: Genitourinary irritation, including dysuria, cystitis, nocturia, increased frequency of micturition, hematuria, and other symptoms of local irritation, rash and pruritus on hands and genital area. Reports of bladder fibrosis/contraction, which in rare cases have required cystectomy, have been received postmarketing (see also See section **4.4 Special warnings and precautions for use**). Bladder necrosis and penile necrosis have been reported following intravesical administration of mitomycin. (See **section 4.4 Special warnings and precautions for use)**

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No specific antidote for mitomycin is known. Management of overdose should include general supportive measures to sustain the patient through any period of toxicity that may occur.
For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mitomycin is an antibiotic isolated from *Streptomyces caespitosus* with anti-neoplastic effect. It is present in an inactive form. Activation to a trifunctional alkylating agent is rapid, either at physiological pH in the presence of NADPH in serum or intracellularly in virtually all cells of the body with the exception of the cerebrum, as the blood-brain barrier is not overcome by mitomycin. The 3 alkylating radicals all stem from a quinone, an aziridine and a urethane group.

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

Clinical trials
No data available

5.2 Pharmacokinetic properties

Absorption
After injection of 30 mg, 20 mg or 10 mg IV, the maximal serum concentrations were 2.4 microgram/mL, 1.7 microgram/mL and 0.52 microgram/mL respectively.

Distribution
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.

Metabolism
Clearance is affected primarily by metabolism in the liver, but metabolism occurs in other issues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought of saturation of the degradative pathways.

Excretion
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

Genotoxicity
Mitomycin toxicity is consistent in all species studied to date. In laboratory animals, the LD_{50} varies from 1.0-2.5 mg/kg, which corresponds with severe toxicity in humans. In mice, rats, cats, dogs and monkeys, death from poisoning was delayed with the animals characteristically progressively losing weight and showing gastro-intestinal disturbances. Frequently, death was associated with fever and leucopenia. In animals, oral toxicity was similar to intravenous toxicity at doses 8-12 times the intravenous doses. The LD50 of multiple low intravenous doses in dogs was approximately equivalent to the LD50 a single large intravenous dose.

Carcinotoxicity
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 tumour incidence in male Sprague-Dawley rats, and a greater than 50 per cent increase in tumour incidence in female Swiss mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol

6.2 Incompatibilities

Incompatibilities occur with highly acidic or alkaline substances. The optimum pH of the ready-to-use mitomycin solution is 7.0.

6.3 Shelf life
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted solution

Only clear solutions may be used.
The contents of the vials are intended for single use only.
Unused solutions must be discarded.
The chemical and physical stability at room temperature and during exposure to light of a reconstituted solution is
1 hour with Water for Injections
2 hours with sodium chloride 9 mg/ml (0.9%) solution

All reconstituted solutions are intended for immediate use.

6.4 Special precautions for storage

Store between 15°C-25°C. Store the vial in the outer carton in order to protect from light. For storage conditions after reconstitution of the medicinal product, see **section 6.3 Shelf Life.**

6.5 Nature and contents of container

Each 20 mg vial contains 20 mg mitomycin and 40 mg mannitol. Each pack contains 1 vial.

The power is stored in a 50 ml amber glass vial (glass type I Ph. Eur.), closed with a grey bromobutyl stopper and sealed with a white flip-off aluminium seal

6.6 Special precautions for disposal

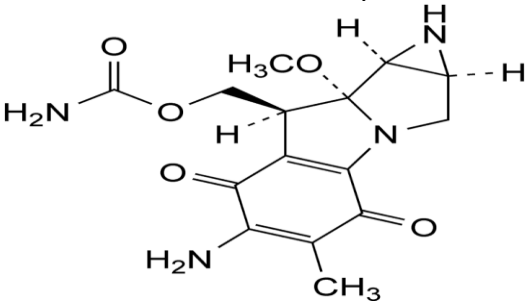
Special precautions for the preparation and the disposal of unused cytotoxic medicinal products should be complied with.

The reconstituted solution should be stored away from light in the refrigerator.

Before the ready-to-use solution is used it should be warmed up to room or body temperature.

6.7 Physicochemical properties

The CAS number for Mitomycin is 50-07-7. The structure is:



[(1aS,8S,8aR,8bS)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-
,1a,2,4,7,8,8a,8boctahydroazirino [2',3':3,4] pyrrolo[1,2-a]-indol-8-yl]methyl carbamate
Molecular weight: 334.3 Molecular formula: $C_{15}H_{18}N_4O_5$

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4– Prescription Only Medicine

8. SPONSOR

Echo Therapeutics Pty Ltd
ABN 9628 298 699
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Lindfield NSW 2070
Email: customerservice@echotherapeutics.net

9. DATE OF FIRST APPROVAL

25 July 2022

10. DATE OF REVISION

Not applicable

Summary table of changes

Section changed	Summary of New Information