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 count 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 septicemia as a resullt of leukopenia due to the drug.

Patients receiving Mitomycin injection IP should be observed for evidence of renal toxicity. Mitomycin injection IP should not be given to patients with a serum creatinine greater than 1.7mg percents.

Usage in Pregnancy
Pregancy Category D.Safe use of Mitomycin Injection IP in pregent woman has not been established. Teratological changes have been noted in animal studies. The effect of Mitomycin Injection IP on fertility is unknown.

Nursing Mothers
It is not known if mitomycin is excreted in human milk. Because many drugs excreted in human milk and because of the potenial for serious adverse reactions in nursing infants fromymitomycin, it is recommended that nursing be discontinued when receving mitomycin therapy.

PRECAUTIONS
Acute shotness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received Mitomycin Injection IP. The onset of this acute respiratory distress occured 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 Injection IP 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 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.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

STORAGE
Store between 15°C to 30°C .
Protect from light.

PRESENTATION
Mitomycin Injection IP is available in a vial containing Mitomycin IP 2mg / 10mg / 40mg.

Marketed by:

RMPL
RMPL PHARMA LLP
7,New Marine Lines.
Mumbai - 400020 India
ISO 9001:2015 & 45001:2018, GDP &
WHO-GMP Certified Company

Manufactured by:
Admac Life Sciences
(Dedicated Oncology Facility)
Plot No.107 A & B, EPIP Phase-I,
Jharmajri, Baddi, Dist - Solan, (174103 (H.P)
(A WHO-GMP CERTIFIED COMPANY)

For the use of a Registered Medical Practioner or a Hospital or a Laboratory only

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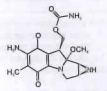
Mitomycin Injection I.P. 2mg/10mg/40mg

WARNING
Mitomycin Injection IP should be administered under the supervison 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, 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 Injection IP.
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 systematic Mitomycin Injection IP. The syndrome may occur at any time during systemic therapy with Mitomycin Injection IP as a single agent or in combination with other cytotoxic drugs, however , most cases occur at doses > 60 mg of Mitomycin Injection IP. Blood product transfusion may exacerbate the symptoms associated with this syndrome.
The incidence of the syndroma has not been defined.

COMPOSITION
Each vial contains :

Mitomycin IP	2 mg / 10 mg / 40 mg
Mannitol IP	q.s

DESCRIPTION
Mitomycin injection is a sterile bluish violet lyophilised mass. It contains mannitol, sodium hydroxide, water for injection as excipients. Mitomycin is an antibiotic isolated from the broth of Streptomyces caespitosus which has been shown to have antitumor activity. The molecular formula is C15-H18-N4-05 and its molecular weight is 334.33. Its structural formula is



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

Pharmacokinetics
In humans , Mitomycin Injection IP is rapidly cleared from the serum after intravenous adminsitration. 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 maximum serum concentrations 2.4 µg / ml , 1.7 µg / ml ,
and 0.52 µg / 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 maximum serum concentration because, it is thought , of satisfaction of the degradative pathways.

Approximately 10% of a dose of Mitomycin injection IP is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses , the percent of dose excreted in Urine increases with increasing dose. In children, excretion of intravenously administered Mitomycin injection IP is similar.

INDICATIONS
Mitomycin is not recommended as a 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.

CONTRAINDICATIONS
Mitomycin Injection IP is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.
Mitomycin Injection IP is contraindicated in patients with thrombocytopenia , coagulation disorder , or an increase in bleeding tendency due to other causes.

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

After full hematological recovery (see guide to dosage adjustment) from any previous chemotherapy , the following dosage schedule may be used at 6 to 8 week intervals: 20mg/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 Injection, IP and the dose reduced if the patient has experienced any toxicities. Doses greater than 20mg/m2 have not been shown to be more effective, and are more toxic than lower doses.

Guide to dosage adjustment :

Nadir after prior dose Leucocyte/mm3	Platelets / mm3	Percentage of prior dose to be given
> 4000	> 100,000	100%
3000-3999	75,000-99999	100%
2000-2999	75,000-99999	70%
<2000	< 25000	50%

No repeat dosage should be given until leucocyte count has returned to 4000/mm3 and a platelet count to 100,000/mm3 . When Mitomycin Injection IP 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 Injection IP, the drug should be stopped since chances of response are minimal.
Reconstitution :
Each vial contains Mitomycin 2mg , 10mg , 40mg . To administer, add Sterile Water for Injection, 4ml, 20ml, and 80ml respectively. Shake to dissolve. If product does not dissolve immediately , allow to stand at room temperature until solution is obtained.

Sability
1. Unreconstituted Mitomycin Injection IP 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 Injection IP 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
5% Dextrose Injection	3 hours
0.9% Sodium Chloride Injection	12 hours
Sodium Lactate Injection	24 hours

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

Overdosage
No data is available

ADVERSE REACTIONS
Bone Marrow Toxicity
This was the most common and most serious toxicity. 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. Mitomycin Injection IP produces cumulative myelosuppression.

Integument and Mucous Membrane Toxicity
This had occured in approximately 4% of patients treated with Mitomycin Injection IP. 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 result 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.

Renal Toxicity
Rise in creatinine.

Pulmonary Toxicity
This has occured infrequently but can be severe and may be life threatning. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative or Mitomycin Injection IP -induced pulmonary toxicity. If other etiologies are eliminated, Mitomycin Injection IP therapy should be discontinued. Steroids have been employed as treatment of this toxicity, but the therapeutic value has not been determined .

Hemolytic Uremic Syndrome (HUS)
This serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia (hematocrit, < 25%) , thrombocytopenia (< 100,000/mm3), and irreversible renal failure (serum creatinine > 1.6 mg/dL) has been reported in patients receiving systematic Mitomycin Injection IP.Microangiopathic hemolysis with fragmented red blood cells on peripheral blood smears has occured.

Other less frequent complications on the syndrome may include pulmonary edema, neurologic abnormalities and hypertension. Exacerbation of the symptoms associated with HUS has been reported in some patients receiving blood product transfusions. A high mortality rate has been associated with this syndrome.

The syndrome may occur at any time during systematic therapy with Mitomycin injection IP 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 injection IP. Patients developes the syndrome at total doses exceeding 60mg of Mitomycin injection IP. Consequently, patients receiving > 60mg of Mitomycin injection IP 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. Acute side effects due to Mitomycin Injection IP were fever, anorexia , nausea, and vomiting.

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.

WARNINGS
Patients being treated with Mitomycin Injection IP must be observed carefully and frequently during and after theraphy.
The use of mitomycin injection IP results in a high incidence of bone marrow suppression , particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtainde repeatedly during therapy , platelet count , white blood cell count, differential,and