

DATA SHEET

Name of Medicine

Mitomycin-C Kyowa®

Mitomycin C

2mg
10mg
20mg

Presentation

MITOMYCIN-C KYOWA® is an antibiotic isolated from the broth of *Streptomyces caespitosus* which has been shown to have anti-tumour activity. **Mitomycin C** is a blue-purple crystalline powder slightly soluble in water or ethanol and insoluble in ether. The CAS number for **Mitomycin C** is 50-07-7.

MITOMYCIN-C KYOWA® injection is available in single use vials. Each vial contains either 2mg, 10mg or 20mg of **mitomycin C**. In addition each vial contains 48mg, 240mg or 480mg respectively of sodium chloride.

Uses**Actions**

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. In humans, **mitomycin** is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30mg bolus injection is 17 minutes. After injection of 30mg, 20mg or 10mg IV, the maximal serum concentrations were 2.4 microgram/mL, 1.7 microgram/mL and 0.52 microgram/mL respectively. Clearance is effected 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. 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.

Animal Toxicology

Mitomycin toxicity is consistent in all species studied to date. In laboratory animals, the LD₅₀ 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 leukopenia. 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. **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.

Indications

MITOMYCIN-C KYOWA[®] is indicated for: Metastatic breast cancer; Locally advanced or metastatic non-small cell lung cancer; Primary treatment of carcinoma of the anal canal in combination with radiation; Primary treatment of oesophageal and head and neck cancers in combination with radiation; Intravesical use for superficial bladder cancer following transurethral resection.

Dosage And Administration

MITOMYCIN-C KYOWA[®] is administered by slow intravenous infusion.

MITOMYCIN-C KYOWA[®] should not be given by rapid intravenous injection.

MITOMYCIN-C KYOWA[®] should be given intravenously only, using care to avoid extravastion of the compound. If extravastion occurs, cellulitis, ulceration and slough may result. Each vial contains either **mitomycin** 2 mg, **mitomycin** 10mg or **mitomycin** 20mg. To administer add Sterile Water for injection 4mL to the 2mg vial, or 20mL to the 10mg and 20mg 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 fusion, for the treatment of all tumours other than bladder tumours. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

For the treatment of bladder tumours the reconstituted 20mg dose is further diluted to 50mL 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 MITOMYCIN-C KYOWA[®] 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. Dosage reduction should be considered in cases with prior extensive bone marrow irradiation or renal dysfunction.

1. 20mg/m² intravenously as a single dose via a functioning intravenous catheter.
2. 2mg/m²/day intravenously for 5 days. After a drug-free interval of 2 days, 2mg/m²/day for 5 days, thus making the total initial dose 20 mg/m² given over 10 days. The following schedule is suggested as a guide to dosage adjustment.

NADIR AFTER PRIOR DOSE		Percentage of Prior Dose to be Given
Leukocytes	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 leukocyte count has returned to 3000 and platelet count to 75,000.

Renal and hepatic dysfunction also usually require dosage reduction and may be an indication for interrupting treatment. When MITOMYCIN-C KYOWA[®] 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-C KYOWA[®], 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.

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.

Contraindications

MITOMYCIN-C KYOWA[®] is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

MITOMYCIN-C KYOWA[®] is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

Warnings And Precautions

General

MITOMYCIN-C KYOWA[®] should not be administered orally, intrathecally or into the tissues (such as intramuscularly or subcutaneously).

MITOMYCIN-C KYOWA[®] 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-C KYOWA[®] 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-C KYOWA[®] must be observed carefully and frequently during and after therapy.

The use of MITOMYCIN-C KYOWA[®] results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Thrombocytopenia may contribute to hemorrhage and leukopenia to overwhelming infections in an already compromised patient (see ADVERSE REACTIONS/EVENTS). 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 leukopenia 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 hemolytic anemia, thrombocytopenia, and irreversible renal failure has been reported in patients receiving systemic MITOMYCIN-C KYOWA[®]. The syndrome may occur at any time during sytemic therapy with MITOMYCIN-C KYOWA[®] as a single agent or in combination with other cytotoxic drugs, however, most cases occur at doses >60 mg of MITOMYCIN-C KYOWA[®]. Blood product transfusion may exacerbate the symptoms

associated with this syndrome. The incidence of the syndrome has not been defined. (See ADVERSE EFFECTS).

Patients receiving MITOMYCIN-C KYOWA[®] should be observed for evidence of renal toxicity. MITOMYCIN-C KYOWA[®] should not be given to patients with a serum creatinine greater than 1.7mg 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-C KYOWA[®]. 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 ADVERSE EFFECTS.)

A few cases of adult respiratory distress syndrome have been reported in patients receiving MITOMYCIN-C KYOWA[®] in combination with other chemotherapeutic agents who were being maintained perioperatively at FiO₂ concentrations greater than 50%. (See ADVERSE 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 postmarketing. Bladder necrosis and penile necrosis have also been reported. (See ADVERSE EFFECTS.)

Injection site reactions may occur during the administration of MITOMYCIN-C KYOWA[®]. (See ADVERSE 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 Pregnancy

Pregnancy Category D - Safe use of MITOMYCIN-C KYOWA[®] in pregnant women has not been established. Teratological changes have been noted in animal studies. The effect of MITOMYCIN-C KYOWA[®] on fertility is unknown.

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.

Adverse 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 leukopenia or thrombocytopenic episodes did not recover. MITOMYCIN-C KYOWA[®] produces cumulative myelosuppression.

Integument and Mucous Membrane Toxicity : This has occurred in approximately 4% of patients treated with MITOMYCIN-C KYOWA[®]. 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-C KYOWA[®], 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-C KYOWA[®] have occurred. (See PRECAUTIONS).

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-C KYOWA[®] induced pulmonary toxicity. If other aetiologies are eliminated, MITOMYCIN-C KYOWA[®] 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-C KYOWA[®] in combination with other chemo-therapeutic agents and who were maintained at FiO₂ concentrations greater than 50% perioperatively. (See PRECAUTIONS.)

Haemolytic 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 \geq 1.6mg/dL or \geq 140 Φ mol/L) has been reported in patients receiving systemic MITOMYCIN-C KYOWA[®]. Microangiopathic hemolysis 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 WARNINGS/PRECAUTIONS).

The syndrome may occur at any time during systemic therapy with MITOMYCIN-C KYOWA[®] 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-C KYOWA[®]. Of 83 patients studied, 72 developed the syndrome at total doses exceeding 60 mg of MITOMYCIN-C KYOWA[®]. Consequently, patients receiving ≥ 60 mg of MITOMYCIN-C KYOWA[®] should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombo-cytopenia, 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-C KYOWA[®] 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-C KYOWA[®] 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 **PRECAUTIONS**). Bladder necrosis and penile necrosis have been reported following intravesical administration of MITOMYCIN-C KYOWA[®]. (See **PRECAUTIONS**.)

Pharmaceutical Precautions

1. Dry crystalline MITOMYCIN-C KYOWA[®] is stable for up to 4 years at less than 25°C.
2. Reconstituted with sterile distilled water (**mitomycin** concentration 0.5mg/mL), it is stable for 1 day at less than 5°C, pH 5.5-7. However, as the solution does not contain any preservative agent, to reduce the microbiological hazard, the reconstituted solution should be used as soon as possible. If storage is required, store between 2-8°C (refrigerate, do not freeze) and use within 8 hours). It is not stable in human serum.
Note : The solution contains no bacteriostal.
3. Stability in IV fluids at room temperature.

5% Glucose	should be used immediately.
0.9% Sodium Chloride	use within 8 hours.
Sodium Lactate Injection	use within 8 hours.

Medicine Classification

Prescription Medicine.

Package Quantities

Each 2mg vial contains 2mg **mitomycin** and 48mg sodium chloride. Each 10mg vial contains 10mg **mitomycin** and 240mg sodium chloride. Each 20mg vial contains 20mg **mitomycin** and 480mg sodium chloride.

Further Information

Nil.

Name And Address

Bristol-Myers Squibb (N.Z.) Company
Auckland
New Zealand

Date Of Preparation

January 2003
Safety Amendment: August 2010