Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mitomycin-C Kyowa 10 mg, Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of Mitomycin-C.

Each vial also contains 240mg of sodium chloride (equivalent to 4.1 mmol sodium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection)
Blue/purple powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mitomycin C must be used under supervision of an Oncologist.

1. As a single agent in the treatment of superficial bladder cancer. In addition it has been shown that post-operative instillations of Mitomycin-C Kyowa can reduce recurrence rates in newly diagnosed patients with superficial bladder cancer.

2. As a single agent or as part of combination therapy in the treatment of adenocarcinoma of the breast.

3. As part of combination therapy in the treatment of adenocarcinomas of the stomach and oesophagus.

4. Small studies have suggested it may be useful as part of combination therapy in the treatment of adenocarcinomas of the pancreas and biliary tract.

5. As part of combination therapy with other cytotoxic drugs and radiotherapy in the treatment of squamous cell carcinoma of the anus.

6. Small studies have suggested that it may be useful as part of combination therapy in the treatment of non small cell lung cancer.

7. Limited studies suggest it may be useful as part of combination therapy in the treatment of adenocarcinoma of the colon and rectum.

4.2 Posology and method of administration

Paediatric population
The safety and efficacy of Mitomycin C in children has not yet been established. No data are available.For parenteral use.Intravenously, the dose should be given with great care in order to avoid extravasation.The usual dose is in the range of 4-10 mg (0.06-0.15 mg/kg) given at 1-6 weekly intervals depending on whether other drugs are given in combination and on bone marrow recovery.In a number of combination schedules, the dose is 10 mg/m^2 of body surface area, the course being repeated at intervals. A course ranging from 40-80 mg (0.58-1.2 mg/kg) is often required for a satisfactory response when used alone or in combination.

Because of cumulative myelosuppression, patients should be fully re-evaluated after each course and the dose reduced if the patient has experienced any toxic effects. Doses greater than 0.6 mg/kg have not been shown to be more effective and are more toxic than lower doses.

Treatment of superficial bladder tumours: In the treatment of superficial bladder tumours the usual dose is 20-40 mg dissolved in 20-40 ml of diluent, instilled into the bladder through a urethral catheter, weekly or three times a week for a total of 20 doses. The dose should be retained by the patient for a minimum of one hour. During this one hour period the patient should be rotated every 15 minutes to ensure that the Mitomycin-C Kyowa comes into contact with all areas of the bladder urothelium. When the bladder is emptied in the voiding process, care must be taken to ensure that no contamination occurs locally in the groin and genitalia areas. In the prevention of recurrent superficial bladder tumours, various doses have been used. These include 20 mg in 20 ml of diluent every two weeks and 40 mg in 40 ml of diluent monthly or three monthly. The dose is instilled into the bladder through a urethral catheter. In both cases, the dose should be adjusted in accordance with the age and condition of the patient.

4.3 Contraindications

Patients who have demonstrated a hypersensitive or idiosyncratic reaction to any components of Mitomycin-C Kyowa in the past. Hepatic disorders, renal disorders, thrombocytopenia, coagulation disorders and increased bleeding tendency.

4.4 Special warnings and precautions for use

Mitomycin-C Kyowa should be administered under the supervision of a physician experienced in cytotoxic cancer chemotherapy. Local ulceration and cellulitis may be caused by tissue extravasation during intravenous injection. Since vascular pain, phlebitis, thrombus, injection site induration and necrosis may occur, Mitomycin-C should be injected as slowly as possible, paying careful attention to the site and method of administration (please see Section 4.8).
Extravascular leakage may cause induration or necrosis at the injection site.

Intraarterial administration can cause skin disorders such as induration, pain, redness, erythema, blisters, erosion and ulceration which may lead to skin/muscle necrosis. Administration should be discontinued and appropriate measures should be taken, if any such symptoms develop. In particular, parenchymatous liver disorder, biloma, cholangitis (also sclerosing), and bile duct necrosis may occur after hepatic arterial administration of the drug (please see Section 4.8).

Since the influx of the drug solution into other sites than the targeted site in the administration to the hepatic artery may cause gastroduodenal ulcer, haemorrhage, perforation, etc, the location of the end of the catheter and drug distribution area should be confirmed photographically or by other means, paying attention to possible deviation or shift of the catheter and infusion rate. Administration should be discontinued and appropriate measures should be taken, if any of such symptoms develop.

Following the intravesical use of Mitomycin-C Kyowa, cases of bladder wall fibrosis have been reported, some of which may have led to renal failure. Mitomycin-C should be carefully injected since calcinosis, contracted bladder and cystitis associated with dysuria and pollakiuria, bladder perforation, bladder necrosis and penile necrosis may occur (please see Section 4.8).

The person administering the injection of Mitomycin-C Kyowa should not allow the solution to come into contact with his or her skin.

Patients should be carefully monitored with frequent laboratory testing (haematological test, liver function test, renal function test, etc) because serious adverse reactions such as bone marrow depression may occur. If any abnormality is observed, appropriate measures such as reduction of the dose and suspension of administration should be taken. Additionally, Mitomycin-C Injection should be administered with care because long-term use of the product may cause enhanced adverse reactions, which may be protracted.

Careful consideration should be given before administration: to patients with hepatic or renal dysfunction since adverse reaction may be enhanced; to patients with bone marrow depression since bone marrow depression may be exacerbated; to patients complicated with infection since infection may be aggravated due to bone marrow depression and to patients with varicella since fatal systemic disorders may occur.

Special precautions are required due to the possible manifestation of infectious disease, and bone marrow depression. In case of administration in children or patients with reproductive possibility, potential effects on gonad should be considered. The safety of Mitomycin-C injection in children has not been established. Special attention should be paid to the manifestation of adverse reactions when administered in children.

Because elderly patients often have reduced physiological function, bone marrow depression, which may be protracted, and renal disorder are likely to occur. Administer Mitomycin-C Kyowa with caution in this population while closely monitoring patient's condition and paying special attention to the dose and dosing interval.

The occurrence of acute leukaemia and myelodysplastic syndrome (MDS) has been reported in patients treated concomitantly with other antineoplastic agents (please see Section 4.8).
This medicinal product contains up to 4.1 mmol (or 95 mg) sodium per dose. This should be taken into consideration when patients are on a sodium-controlled diet.

4.5 Interaction with other medicinal products and other forms of interactions

Due to the dependence on drug metabolism in the pharmacology of Mitomycin-C Kyowa, there is a potential for a positive or a negative effect on the drug with any treatment which alters the activity of drug-metabolising enzymes.

There have been reports that the drug interacts with doxorubicin in potentiating the cardiotoxicity of the latter. Adverse reactions such as bone marrow depression may be enhanced with other antineoplastic agents or irradiation. Shortness of breath and bronchospasm may occur in combination with Vinca alkaloid antineoplastic agents such as Vindesine sulphate.

4.6 Fertility, pregnancy and lactation

Mitomycin-C Kyowa should not be administered to patients who are pregnant or to mothers who are breast feeding.

Teratological changes have been observed in animal studies including developmental inhibition, cleft palate, hypoplastic tail, hypoplasic jaws and ectrodactyly. Nursing mothers should discontinue breast feeding during treatment since the safety of Mitomycin-C injection in nursing mothers has not been established.

4.7 Effects on ability to drive and use machines

Generalised weakness and lethargy have been reported on rare occasions. If affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

1. The main adverse reactions collected from the literature are leucopenia (40.2%), thrombocytopenia (24.7%), anorexia (21.8%), nausea/vomiting (15.4%), malaise (5.6%), weight loss (5.5%), bleeding tendency (3.6%) and anaemia (3.0%).

Thrombocytopenia and leucopenia resulting from myelosuppression, which is delayed and cumulative, are known side-effects. Patients should be monitored closely during each course of treatment, paying particular attention to peripheral blood count including platelet count.

No repeated dose should be given unless the leucocyte count is above 3.0×10^9/L or more and the platelet count is 90×10^9/L or more. The nadir is usually around four weeks after treatment and toxicity is usually cumulative, with increasing risk after each course of treatment. If disease progression continues after two courses of treatment, the drug should be stopped since the chances of response are then minimal.

2. Haemolytic uraemic syndrome and microangiopathic haemolytic anaemia. Patients should be carefully observed with periodical testing, and, if symptoms such as anaemia with fragmented red blood cells, thrombocytopenia and renal dysfunction are observed, appropriate measures such as discontinuing treatment should be taken.

3. Serious nephropathy such as acute renal failure may occur. Patients should be carefully observed, and, if any abnormal change is noted in BUN, creatinine, creatinine clearance etc appropriate measures such as discontinuing treatment should be taken. Mucosal inflammation has been reported following intravesical instillation.

Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before starting treatment and again after each course. Nausea and vomiting are sometimes experienced immediately after treatment, but these are usually mild and of short duration.

4. Pulmonary toxicity, interstitial pneumonia, pulmonary fibrosis (accompanied by fever, coughing, dyspnoea, abnormal findings on chest X-ray and eosinophilia), pulmonary hypertension and pulmonary veno-occlusive disease (PVOD) may occur. If signs of these conditions are observed, discontinue treatment and take appropriate measures.

5. Anaphylactic shock or anaphylactoid reaction may occur, patients should be carefully observed. If symptoms such as itching, rash, hot flush, sweating, dyspnoea and decreased blood pressure occur, treatment should be immediately discontinued and appropriate measures taken.

6. Cystitis, atrophy of the bladder, contracted bladder (pollakiuria, dysuria), calcinosis, bladder necrosis, bladder perforation and penile necrosis have been reported when given by intravesical instillation.

7. Administration to the hepatic artery may cause liver and biliary tract disorders such as cholecystitis, cholangitis (also sclerosing), biloma, bile duct necrosis and parenchymatous liver disorder. Drug distribution area should be confirmed photographically or by other means and treatment should be discontinued and appropriate measures should be taken if any abnormal signs are noted.

8. Skin toxicity may occur in a small proportion of patients, with side-effects such as alopecia (although this is less frequent and less severe than with certain other cytotoxic agents). Palmar-plantar erythrodysaesthesia (PPE), bleeding, rashes and mouth ulcers have been reported.

9. Other reported effects, **not already described in the text above,** include:

Infections and Infestations	
	Bacterial, viral or fungal infections (at different anatomical sites, mild to moderate in nature, and usually reversible with appropriate treatment), sepsis and septic shock
Blood and lymphatic system disorders	
	Acute leukaemia, acute myeloid leukaemia or myelodysplastic syndrome, pancytopenia, neutropenia, granulocytopenia, febrile neutropenia, haemorrhage, erythropenia, microangiopathic haemolytic anaemia, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura.
Immune system disorders	
	Hypersensitivity
Vascular disorders	
	Hypertension
Respiratory, thoracic and mediastinal disorders	
	Bronchospasm
Gastrointestinal disorders	
	Diarrhoea, constipation, abdominal discomfort, stomatitis
Hepatobiliary disorders	
	Hepatic damage, jaundice
Skin and subcutaneous tissue disorders	
	Erythema, pruritus, rash, alopecia
Renal and urinary disorders	
	Renal disorder, cystitis, haematuria, proteinuria, serious nephropathy, albuminuria, oedema
General disorders	
	Pyrexia, chills, injection site phlebitis, oedema, generalised weakness and lethargy on rare occasions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971

Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie

4.9 Overdose

In the unlikely event of accidental overdosage then an increase in the more common side-effects should be expected, such as fever, nausea, vomiting and myelosuppression. Appropriate supportive measures should be instituted.

If extravasation occurs, it is recommended that the area is immediately infiltrated with sodium bicarbonate 8.4% solution, followed by an injection of 4 mg dexamethasone. A systemic injection of 200 mg of Vitamin B6 may be of some value in promoting the regrowth of tissues that have been damaged.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mitomycin-C Kyowa is an antitumour antibiotic that is activated in the tissues to an alkylating agent which disrupts deoxyribonucleic acid (DNA) in cancer cells by forming a complex with DNA and also acts by inhibiting division of cancer cells by interfering with the biosynthesis of DNA.

5.2 Pharmacokinetic properties

In vivo, Mitomycin-C Kyowa is rapidly cleared from the serum after intravenous administration. The 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 intravenously, the maximal serum concentrations were 2.4 micrograms/ml, 1.7 micrograms/ml and 0.52 micrograms/ml respectively. Clearance is affected 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-C Kyowa is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percentage dose excreted in the urine increases with increasing dose. In children, the excretion of intravenously administered Mitomycin-C Kyowa is similar to that in adults.

5.3 Preclinical safety data

Acute toxicity has been studied in mice and rats. LD_{50} values in mice were 4.3 mg/kg for males and 6.7 mg/kg for females, following i.p. administration. In rats, LD_{50} values were 3.1 mg/kg for males and 2.5 mg/kg for females after i.v. administration and 5.0 mg/kg for males and 4.7 mg/kg for females after i.p. administration.

Chronic toxicity has been studied in rats, treated six times a week i.p. for a total period of six months with a series of different doses ranging from 0.4 micrograms/kg to 100 micrograms/kg, the latter being approximately 100th the typical therapeutic dose in man. On the whole, toxicity was only observed at the top two doses studied (33 micrograms/kg and 100 micrograms/kg), but not at doses less than 11 micrograms/kg. All animals suffered from myelosuppression, which is the main toxic event in man.

Genesis of various types of tumours has been reported in experiments with mice by subcutaneous administration and with rats by intraperitoneal or intravenous administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

6.2 Incompatibilities

Data from compatibility studies is available from the Marketing Authorisation Holder. The mixing of Mitomycin-C Kyowa with other products is the responsibility of the treating physician/user.

6.3 Shelf life

Four years from the date of manufacture.

After reconstitution, the solution should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.

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

6.5 Nature and contents of container

Mitomycin-C Kyowa is contained within a colourless, Type I glass vial with a rubber stopper and an aluminium cap with a coloured lid.

The following colours of lid are used to distinguish between the different strengths of the product.

Strength	Size of vial	Colour of lid
2 mg	10 ml	Purple
10 mg	30 ml	Purple
20 mg	30 ml	Violet
40 mg	50 ml	Lavender

The vials are packaged into cardboard cartons containing 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The contents of the vial should be reconstituted with Water for Injections or saline, at least 10 ml for the 10 mg vial.

Since the potency of Mitomycin C may be reduced when a low pH solution (lower than pH 7.0) is used for recontitution. It is recommended to use the solution immediately after reconstitution. In addition, it is recommended to avoid mixing with other low pH injectable solutions.

For single use only. Discard any unused contents.

Mitomycin-C Kyowa should not be allowed to come into contact with the skin. If it does, it should be washed thoroughly with soap and plenty of water. Hand creams and emollients should not be used as they may assist the penetration of the drug into the epidermal tissue.

In the event of contact with the eye, it should be rinsed several times with saline solution. It should then be observed for several days for evidence of corneal damage. If necessary, appropriate treatment should be instituted.

If spillage occurs, wear an approved respirator and chemically compatible gloves. Vacuum or sweep up the spillage, avoid dust. Place the spillage in an appropriate container for waste disposal. Wash contaminated clothing before re-use.

For disposal, waste should be treated with alkali or strong acid, and then neutralized with acid or alkali.

Mitomycin-C Kyowa should be prepared and administered by trained personnel in line with local cytotoxic guidelines.

Cytotoxics should not be handled by pregnant personnel.

7 MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2288/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2003

Date of last renewal: 12 December 2008

10 DATE OF REVISION OF THE TEXT

February 2019