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

Mitomycin C 10 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Blue-purple powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Antimitotic and Cytotoxic
Recommended for certain types of cancer in combination with other drugs or after primary therapy has failed. It has been successfully used to improve subjective and objective symptoms in a wide range of neoplastic conditions.

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 can reduce recurrence rates in newly diagnosed patients with superficial bladder cancer.

2. As a single agent and in combination with other drugs in metastatic breast cancer.

3. In combination with other agents in advanced squamous cell carcinoma of the uterine cervix.

4. It shows a degree of activity as part of combination therapy in carcinoma of the stomach, pancreas and lung (particularly non-small cell).

5. It shows a degree of activity as a single agent and in combination in liver cancer when given by the intra-arterial route.
6. It has a possible role in combination with other cytotoxic drugs in colorectal cancer.
7. It shows a degree of activity as a single agent or part of combination therapy in cancer of the head and neck.
8. It shows a degree of activity as a single agent in cancer of the prostate.
9. It has a possible role in skin cancer.
10. It has a degree of activity in leukaemia and non-solid tumours.
11. It has a possible role in sarcomas.
12. It has been successfully used in combination with surgery, pre-operatively (oesophageal squamous cell carcinoma) and post-operatively (gastric cancer).
13. It has been shown to be effective when used in combination with radiotherapy.

4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Mitomycin C in children has not been established. No data are available.

Intravenous administration

Intravenously, the dose should be given as slowly as possible and 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 for as long as required. 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. A higher dosage course may be given when used alone or as part of a particular combination schedule and total cumulative doses exceeding 2 mg/kg have been given.

Intra-arterial administration

For administration into specific tissues, Mitomycin-C Kyowa can be given by the intra-arterial route directly into the tumours.

Dose reductions

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.

Disease progression

If disease progression continues after two courses of treatment, the drug should be stopped since the chances of response are minimal.

Use in patients with 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 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 Mitomycin-C Kyowa or any of the components of the product in the past. 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 and utmost care should be taken in administration. 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.

Patients should be carefully monitored with frequent laboratory testing (haematological test, liver function test, renal function test, etc.) paying particular attention to peripheral blood count including platelet count. No repeat dose should be given unless the leucocyte count is above 3.0 x 10^9/L or more and the platelet count is 90 x 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. 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.

Extravascular leakage may cause induration or necrosis at the injection site. Intraarterial administration may cause skin disorders such as pain, redness, erythema, blisters, erosion and ulceration which may lead to skin/muscle necrosis. 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 develops.

Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before starting treatment and again after each course.
Mitomycin-C Kyowa should be administered with care in children and patients with the following:

- Hepatic or renal dysfunction as adverse reactions may be enhanced
- Bone marrow depression and bleeding tendency as these may be exacerbated
- Infections as these may be aggravated due to bone marrow depression
- Varicella as fatal systemic disorders may occur

In case administration of this drug is required 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.

Occurrence of acute leukaemia (in some cases following preleukaemic phase) and myelodysplastic syndrome has been reported in the patients treated with Mitomycin-C Kyowa concomitantly with other antineoplastic agents.

4.5 Interaction with other medicinal products and other forms of interaction

Mitomycin-C Kyowa should be administered with care when it is coadministered with other antineoplastic agents or irradiation. The adverse reactions of each drug may be enhanced, for example bone marrow depression. With vinca alkaloids adverse reactions of shortness of breath and bronchospasm may be enhanced.

4.6 Fertility, Pregnancy and lactation

Mitomycin-C Kyowa should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Teratological changes have been noted in animal studies.

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
The main adverse reactions collected from literature were leucopenia in 130 (40.2%) of 323 patients, thrombocytopenia in 75 (24.7%) of 304 patients, anorexia in 58 (21.8%) of 266 patients, nausea/vomiting in 41 (15.4%) of 266 patients, malaise in 15 (5.6%) of 266 patients, weight loss in 18 (5.5%) of 329 patients, bleeding tendency in 12 (3.6%) of 329 patients and anaemia in 10 (3.0%) of 329 patients.

Nausea and vomiting are sometimes experienced immediately after treatment, but these are usually mild and of short duration. Pulmonary toxicities such as pulmonary oedema, interstitial pneumonia and pulmonary fibrosis (accompanied by fever, coughing, dyspnoea, abnormal x-ray findings and eosinophilia) pulmonary hypertension and pulmonary veno-occlusive disease (PVOD) have been reported. If signs of these conditions are observed, discontinue treatment and take appropriate measures.

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.

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 should be taken.

Administration related Undesirable Effects
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.

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 taken if any abnormal signs are noted.

The following administration related adverse reactions have also been reported: vascular pain, phlebitis, thrombus, induration or necrosis at the injection site, pain, redness erythema, blisters, erosion and ulceration which may lead to skin/muscle necrosis.

Other reported effects, not already described in the text above, include the following:

<table>
<thead>
<tr>
<th>Infections and Infestations</th>
<th>Bacterial, viral or fungal infections, sepsis and septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms benign and malignant</td>
<td>Myelodysplastic syndrome, acute myeloid leukaemia, acute leukaemia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Bone marrow depression, pancytopenia, neutropenia,</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Flushing, hypertension</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory disorders such as interstitial lung disease, bronchospasm, pneumonitis</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, constipation, abdominal discomfort, stomatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Parenchymatous liver disorder, cholecystitis, jaundice</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash, pruritus</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Acute renal failure, renal disorder, cystitis, haematuria, proteinuria, serious nephropathy, albuminuria</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia, chills, malaise, injection site phlebitis, oedema, generalised weakness and lethargy</td>
<td></td>
</tr>
</tbody>
</table>

**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 the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

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.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
ATC Code: L01D

Pharmacotherapeutic group: Other cytotoxic antibiotics

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 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-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

There are no preclinical data of relevance to the prescriber which are additional to that already included elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride Ph.Eur.

6.2 Incompatibilities
Not known.

6.3 Shelf life
Four years from the date of manufacture.

After reconstitution, the solution is chemically and physically stable for
24 hours when protected from light and stored in a cool place. Do not refrigerate.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Store in the original package.

The reconstituted solution should be protected from light and stored in a cool place (See Section 6.3).

6.5 Nature and contents of container
Mitomycin-C Kyowa is contained within a colourless, type III glass vial with a rubber stopper and an aluminium seal.

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

6.6 Special precautions for disposal

The contents of the vial should be reconstituted with Water for Injection or saline, at least 10 ml for the 10 mg vial. If possible, avoid mixing with injectable solutions which have a low pH.

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.
7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Limited
Galabank Business Park
Galashiels
TD1 1QH
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 16508/0043

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 1992
Date of latest renewal: 29 June 2006

10 DATE OF REVISION OF THE TEXT

06/06/2017