4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following severe reactions tell your doctor immediately:
- severe breathlessness
- shortness of breath or a cough
- severe allergic reaction – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint.

If you experience any of the following tell your doctor as soon as possible:
- fever on the day of treatment
- loss of appetite and weight loss
- tiredness, weakness and headache
- feeling or being sick (this may shortly disappear during treatment)
- high blood pressure or flushing
- pain, swelling, redness or tenderness at the site of the injection
- sore eyes and mouth and other ulcers
- diarrhoea, abdominal discomfort or constipation
- hardening, thickening, redness, tenderness or swelling of the tips of the fingers and hair loss
- changes in urinating or pain when urinating
- tingling of nails, drifters on pressure points e.g. elbows
- easily pick up infections
- reduced blood flow to the fingers, toes and tip of the nose
- bleeding and bruising
- severe damage and potentially rupture of the wall of the bladder resulting in severe lower abdominal pain, difficulty or inability to pass urine, and possibly blood in the urine
- severe damage to the penis resulting in pain in the penis, abnormal colour of the penis and potential difficulty in passing urine
- increase in blood pressure in the blood vessels of the lungs (pulmonary hypertension), e.g. leading to shortness of breath, dizziness and fainting
- obstructive disease of the pulmonary veins or pulmonary veno-occlusive disease (PVOD). Symptoms may include shortness of breath, tainting and coughing up blood
- numbness, swelling and painful redness on palms of the hands and soles of feet (palmar-plantar erythrodysaesthesia (PPE)/hand-foot syndrome).

Kidney or liver problems have also been reported. Your doctor will monitor your kidney (urine test) and liver (blood test) regularly.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE MITOMYCIN-C KYOWA

Mitomycin-C Kyowa should be kept in its original packaging.

Do not use this medicine after the expiry date which is stated on the label after "Exp Date". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Mitomycin-C Kyowa contains
- The active substance is mitomycin-C.
- The other ingredient is sodium chloride.

What Mitomycin-C Kyowa looks like and contents of the pack
Mitomycin-C Kyowa is a powder which is mixed before injection. It is packaged in glass vials with a rubber stopper and aluminium seal.

Marketing Authorisation Holder
Kyowa Kfin Ltd.
Gatalbank Business Park
Galsohien
TD1 1QH
UK

Manufacturer
Aesica Queniborough

Condensed

This medicinal product is authorised in the Member States of the EEA under the following names:
Mitomycin-C Kyowa.

This leaflet was last revised in 05/2016.
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 myelodysplasia (in some cases following preleukemic phase) and myeloplastic 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 not be administered to patients who are pregnant, who may possibly be pregnant or to mothers who are breast-feeding. Teratogenic 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 to operate machinery.

4.8 Undesirable effects

The main adverse reactions collected from literature were leucopenia in 130 (40.6%) of 323 patients, thrombocytopenia in 75 (24.7%) of 304 patients, anorexia in 58 (18.1%) of 326 patients, nausea/vomiting in 41 (15.4%) of 266 patients, malaise in 15 (5.5%) of 286 patients, weight loss in 18 (5.1%) of 329 patients, bleeding tendency in 12 (3.6%) of 329 patients and anaemia in 10 (3.0%) of 332 patients.

Nausea and vomiting are sometimes experienced immediately after treatment and may persist or become more frequent and of longer duration. Pulmonary toxicities such as pulmonary oedema, interstitial pneumonia and pulmonary fibrosis (accompanied by cough, 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 toxicities have been reported in a small proportion of patients, with side effects such as alopecia (although this is less frequent and less severe than with certain other antineoplastic agents). Palmar plantar erythrodysesthesia (PPE), bleeding, rashes and mouth ulcers have been reported.

Shock or anaphylactoid reaction may occur, patients should be carefully observed. If symptoms such as tachycardia, 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

Cytosis, anemia of the bladder, contracted bladder (polaktyroza, dysuria), tender/bloody urine and pain in the retroperitoneal and perineal regions have been reported when given intravesical injection.

Administration to the nervous system or in analgesia and tract disorders such as cholelithiasis, cholangitis (also ascending), biliary, bile duct necrosis and paralytic ileus and paracentheteric 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 adverse reactions have also been reported: valvular pain, phlebitis, thrombus, irritation or necrosis at the injection site, pain, redness erythema, blisters, erosion and ulceration which may lead to skin necrosis.

- Nausea, vomiting, diarrhea, abdominal pain, tightening, generalised weakness and lethargy.
- Fever, chills, malaise, injection site phlebitis, oedema, generalised weakness and lethargy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01D

Pharmacotherapeutic group: Other cytostatic 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 certain 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 30mg bolus injection is 17 minutes. After injection of 30mg, 20mg or 15mg intravenously, the maximal serum concentrations were 2.4 mg/ml, 1.7 mg/ml and 0.52mg/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 increase in the excretion of unchanged drug is rather low.

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. PHARMACOLOGICAL PARTICULARS

6.1 List of excipients

Sodium Chloride Ph. Eur.

6.2 Incompatibilities

Not known

6.3 Shelf life

Mitomycin-C 2 mg and 10 mg: 4 years

Mitomycin-C 20 mg: 3 years

Mitomycin-C 40 mg: 2 years

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 3.3).

6.5 Nature and contents of container

Mitomycin-C Kyowa is contained within a colourless, type I or III glass vial with a rubber stopper and an aluminium seal.

The 10, 20 and 40 mg vials are packaged into cardboard cartons containing 1 or 5 vials. The 2 mg vials are packaged into cardboard trays with an overwrap containing 10 vials.

6.6 Special precautions for disposal and other handling

6.7 Marketing authorisation holder

Kyowa Kirin Ltd
Galashiels Business Park
Galashiels
TD1 1GH

8. MARKETING AUTHORISATION NUMBER(S)

PL16508/0042-0045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE MARKETING AUTHORISATION

Date of first authorisation: 26th November 1992

10. DATE OF REVISION OF THE TEXT

December 2016

1. WHAT MITOMYCIN-C KYOWA IS AND WHAT IT IS USED FOR

As a single medicine or in a combination with other medicines, Mitomycin-C Kyowa can be used to treat different types of cancers in many different parts of the body as described below:-

- In bladder cancer Mitomycin-C Kyowa can be given by injection or, alternatively introduced directly into the bladder after surgery to reduce the chance of a recurrence of the condition
- Breast cancer and cancer of the neck of the womb (the cervix)
- It shows some activity in cancers of the stomach, pancreas, lung, liver, head and neck, prostate, haematological and certain other types of tumours.
- It has a possible role with other anti-cancer medicines in cancer of the lower bowel, skin cancer and sarcomas (cancers of a particular kind of body tissue called connective tissue).
- It has been used successfully in combination with surgery, before operations (in cases of cancer of the upper digestive tract) and after operations (in cases of cancer of the stomach).

It has been shown to be effective when used in combination with radiotherapy.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE MITOMYCIN-C KYOWA

Do not use Mitomycin-C Kyowa if you:

• are allergic (hypersensitive) to mitomycin or any of the other ingredients of Mitomycin-C Kyowa (listed in section 6).

Take special care with Mitomycin-C Kyowa if you:

• have liver or kidney problems, side effects of mitomycin may be more noticeable
• are capable of child-bearing as mitomycin may affect your ability to have children in the future.
• have been told that you have bone marrow depression (your bone marrow is not able to make the blood cells that you need). It may be made worse (especially in the elderly). infection (including chickenpox) may be aggravated due to bone marrow depression and may lead to fatal complications.

Special attention will be paid if this product is given to the elderly or to children due to the possible side effects in these age groups.

Other medicines and Mitomycin-C Kyowa

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, or been given other treatments (e.g. radiotherapy).

When given together with certain other cancer treatment there have been some reports of problems related to bone marrow and the occurrence of cancer involving various types of blood cells.

Pregnancy and Breast-feeding

You should not be given Mitomycin-C Kyowa if you are pregnant, may be pregnant or if you are breast-feeding. Ask your doctor for advice before taking any medicine.

Driving and using machines

A few people have reported that they feel tired or weak after the treatment. Do not drive or use any tools or machines if you are affected.

3. HOW TO USE MITOMYCIN-C KYOWA

Always use the medicine as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Mitomycin-C Kyowa is usually given by injection or as an infusion (with a drip). However in the treatment or the prevention of the recurrence of bladder cancer, a solution of Mitomycin-C Kyowa will be given directly into the bladder through a type of tube called a catheter. The precise dosage, frequency of dosing and duration of treatment with Mitomycin-C Kyowa will depend on your age, weight, medical condition and whether Mitomycin-C Kyowa is being given in combination with other drug treatment.