

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0892/001/003

Case No: 2036657

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Kyowa Hakko UK Limited

258 Bath Road, Slough, Berkshire, SL1 4DX, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Mitomycin-C Kyowa 20 mg, Powder for Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/05/2007** until **12/12/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mitomycin-C Kyowa 20 mg, Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg of Mitomycin-C.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection
Blue/purple crystalline 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

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/m² 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 and utmost care should be taken in administration.

Vascular pain, phlebitis and thrombus may also be caused by intravenous administration.

Extravascular leakage may cause induration or necrosis at the injection site. Intraarterial administration can 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.

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.

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.

Elderly patients often have reduced physiological function, bone marrow depression, which may be protracted, so administer Mitomycin-C Kyowa with caution in this population while closely monitoring patient's condition.

4.5 Interaction with other medicinal products and other forms of interaction

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. The occurrence of acute leukaemia and myelodysplastic syndrome (MDS) has been reported in patients treated concomitantly with other antineoplastic agents.

4.6 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, hypoplastic 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 $3.0 \times 10^9/L$ or more and the platelet count is $90 \times 10^9/L$ 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 pneumonitis, pulmonary fibrosis (accompanied by fever, coughing, dyspnoea, abnormal findings on chest X-ray and eosinophilia), may occur.
5. 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. Cytitis, atrophy of the bladder, contracted bladder (pollakiuria, dysuria), and calcinosis, 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). 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, sepsis and septic shock
Blood and lymphatic system disorders
Bone marrow and depression, pancytopenia, neutropenia, granulocytopenia, febrile neutropenia, haemorrhage, erythropenia, microangiopathic
haemolytic anaemia, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura.
Immune system disorders
Hypersensitivity
Vascular disorders
Hypertension
Gastrointestinal disorders
Diarrhoea, constipation, abdominal discomfort stomatitis (≥0.1% to >5%),
Hepatobiliary disorders
Hepatic damage, jaundice
Skin and subcutaneous tissue disorders
Rash (≥0.1% to >5%), alopecia (≥0.1% to >5%)
Renal and urinary disorders
Renal disorder, cystitis (≥5%), haematuria (≥5%), proteinuria, serious nephropathy, albuminuria (≥0.1% to >5%), oedema

General disorders

Pyrexia, chills, malaise ($\geq 5\%$), injection site phlebitis, oedema, generalised weakness and lethargy on rare occasions.

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. LD₅₀ values in mice were 4.3 mg/kg for males and 6.7 mg/kg for females, following i.p. administration. In rats, LD₅₀ 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

Not known.

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

No special precautions for storage.

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 and are available in packs containing 1 or 5 vials of Mitomycin-C Kyowa 20 mg each.

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 20 ml for the 20 mg vial.

Mitomycin-C Kyowa should not be allowed to come into contact with the skin. If it does, it should be washed several times with 8.4 % sodium bicarbonate solution, followed by soap and 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 Hakko UK Ltd.
258 Bath Road
Slough
Berkshire SL1 4DX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 892/1/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2003

10 DATE OF REVISION OF THE TEXT

May 2007