1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MITOMYCIN-C 2 mg (powder for injection)

MITOMYCIN-C 10 mg (powder for injection)

COMPOSITION

Each vial of MITOMYCIN-C 2 mg contains 2 mg of crystalline mitomycin-C.

Excipient:

Sodium chloride

Sugar free

Each vial of MITOMYCIN-C 10 mg contains 10 mg of crystalline mitomycin-C.

Excipient:

Sodium chloride

Sugar free

CATEGORY AND CLASS

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mitomycin-C acts as a bifunctional or trifunctional alkylating agent. It inhibits DNA synthesis and cross-links DNA to an extent proportional to its content of guanine and cytosine. Its action is most prominent during the late G1 and early S phases of the cell cycle.

INDICATIONS

MITOMYCIN-C is a broad spectrum cytostatic. Used on its own, MITOMYCIN-C may be effective in the treatment of a wide variety of malignant tumours such as breast cancer and gastrointestinal cancer.

It is, however, very often used in combination with other cytostatics, particularly in the treatment of gastric and pancreatic cancers.

MITOMYCIN-C has also been reported to have an effect in the treatment of bladder cancer, non-small cell lung cancer, head and neck squamous cell cancer and colorectal cancer.

CONTRAINDICATIONS

- MITOMYCIN-C should not be used in patients suffering from an active infection.
- MITOMYCIN-C is contraindicated in pregnancy. Safety during lactation has not been established.
- Patients with a history of hypersensitivity to MITOMYCIN-C.
- Use with caution in patients with hepatic disorder, renal disorder, bone marrow suppression, or in patients with varicella (fatal systemic disorders may occur).

WARNINGS AND SPECIAL PRECAUTIONS

Patients should be carefully monitored with frequent laboratory testing (haematological test, liver function test, renal function test, etc.) because serious adverse effects such as 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 should be administered with care because long-term use of the product may cause enhanced adverse reactions, which may be protracted.

Special precautions are required in the possible manifestation or aggravation of infectious disease and bleeding tendency.

Administration to children and patients with reproductive potential should be carried out with caution considering its potential effects on the gonads.

To avoid necrosis, phlebitis and thrombosis, intravenous administration should be carried out as slowly as possible, paying careful attention to the injection site and method, lest extravasation occur.

Local and tissue necrosis, ulceration and cellulitis may occur following extravasation.

MITOMYCIN-C should be administered cautiously in elderly patients while closely monitoring patient's condition and paying special attention to the dose and dosing interval. Intra-arterial administration may cause skin disorders such as pain, redness, erythema, blisters, erosion and ulceration in the region involved, which may lead to skin/muscle erosion. Administration should be discontinued.

Occurrence of acute leukaemia (in some cases following preleukaemic phase) and

myelodysplastic syndrome (MDS) has been reported in patients treated with MITOMYCIN-C concomitantly with other antineoplastic agents.

INTERACTIONS

The leukopenic and/or thrombocytopenic effects may be increased with concurrent or recent therapy with blood dyscrasia-causing medications (e.g. captopril, carbamazepine, cephalosporins, metronidazole, phenothiazines, sulfamethoxazole and trimethoprim, sulfonamides, thioxanthenes). Dosage adjustments of MITOMYCIN-C, if necessary, should be based on blood counts.

Dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively. Concurrent use with doxorubicin may result in increased cardiotoxicity. The patient's antibody response to vaccine from killed viruses may be decreased because their normal defence mechanism may be suppressed by MITOMYCIN-C therapy. The same response may be experienced with use of vaccines from live viruses, but with additional replication potentiation of the vaccine virus and an increase in its side/adverse effects.

HUMAN REPRODUCTION

It is usually recommended that use of antineoplastics, especially in combination chemotherapy, be avoided whenever possible, especially during the first trimester. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the mutagenicity, teratogenicity and carcinogenic potential of MITOMYCIN-C must be considered.

Other hazards to the foetus include adverse reactions seen in adults. In general, use of a contraceptive is recommended during MITOMYCIN-C therapy.

MITOMYCIN-C is reported to cause teratogenicity in animals.

Although very little information is available regarding distribution of antineoplastic agents such as MITOMYCIN-C into breast milk, breastfeeding is not recommended while MITOMYCIN-C is being administered because of risks to the infant (adverse effects, mutagenicity, carcinogenicity).

DOSAGE AND DIRECTIONS FOR USE

There is limited but increasing evidence and concern that personnel involved in preparation and administration of parenteral antineoplastics such as MITOMYCIN-C may be at some risk because of the potential mutagenicity, teratogenicity, and/or carcinogenicity of these agents, although the actual risk is unknown. Cautious handling both in the preparation and disposal of MITOMYCIN-C is recommended. Precautions include:

- use of a biological containment cabinet during reconstitution and dilution of MITOMYCIN-C and wearing of disposable surgical gloves and masks;
- use of proper technique to prevent contamination of the medication, work area, and operator during transfer between containers (including proper training of personnel in this technique);
- cautious and proper disposal of needles, syringes, vials, ampoules and unused medication.

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

As a single cytostatic:

12 to 14 mg/m^2 once a month or every 35 days by intravenous infusion.

The crystals are dissolved in 200 ml of a 5 % glucose solution, which is then administered over a period of 30 minutes, preferably with Vitamin B compound.

In combination therapy:

MITOMYCIN-C is usually administered along with other agents (e.g. FOAM – 5 FU plus oncovin plus adriamycin plus MITOMYCIN-C; SMF - streptozotocin plus MITOMYCIN-C plus 5 FU; AM - adriamycin plus MITOMYCIN-C; FAM – 5 FU plus adriamycin plus MITOMYCIN-C) in a dosage of 10 mg/m^2 every 6 to 9 weeks. Higher doses have also been given. Although MITOMYCIN-C is primarily administered intravenously other methods of administration have been used.

Intra-arterial injection:

Intra-arterial injection is used only when high concentrations of MITOMYCIN-C are required to attack the tumour. Water, saline or 5 % dextrose/water may be used. The vehicle of choice is saline.

Intravesical infusion:

After catheterization with a Nelaton's catheter, 10 mg to 40 mg, dissolved in 20 ml to 40 ml of sterile distilled water, is injected for the treatment of bladder tumours.

SIDE EFFECTS

Haematologic:

Prolonged depression of the haemogram may occur.

Leucopenia, thrombocytopenia, neutropenia, haemorrhage, anaemia and microangiopathic haemolytic anaemia may occur. Regular full blood counts should be taken, paying special attention to the count of leukocytes and platelets. Treatment should not be repeated until

these counts (leukocytes and platelets) return to normal.

Hepatic:

Hepatic disorders may occur (cholecystitis, bile duct necrosis, parenchymatous liver disorder, etc).

Renal:

Since haemolytic uraemic syndrome and proteinuria, haematuria, oedema and hypertension may occur, monitor the patients carefully by periodical examinations. If any abnormal findings are observed, discontinue administration, or adequate measures should be taken.

Gastrointestinal:

Anorexia, nausea and vomiting and stomatitis may occur.

Hypersensitivity:

Hypersensitivity reactions such as rash may occur.

Urinary:

Cystitis, haematuria, or atrophy of the bladder caused by bladder instillation therapy may occur.

Respiratory:

Interstitial pneumonia and pulmonary fibrosis may occur (accompanied by fever, coughing, dyspnoea, abnormal chest x-rays and eosinophilia).

Others:

Fever, malaise and alopecia may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

See SIDE EFFECTS.

Treatment

Treatment is symptomatic.

IDENTIFICATION

Blue-purple powder.

PRESENTATION

MITOMYCIN-C 2 mg: colourless Type III glass vial with an aluminium seal, butyl rubber stopper and a polypropylene cap containing a blue-purple powder. 1 vial is packed in an outer cardboard carton together with a leaflet.

MITOMYCIN-C 10 mg: Type I colourless 30 ml glass vial and closed with a butyl rubber push in stopper and crimped with an aluminium cap with a polypropylene lid containing a blue-purple powder. 1 vial is packed in an outer cardboard carton together with a leaflet.

Not all packs are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

The product reconstituted with water, saline or 5 % glucose solution is stable at room temperature for 6 hours.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

MITOMYCIN-C 2 mg: H2764 (Act 101/1965)

MITOMYCIN-C 10 mg: R/26/48

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration:

MITOMYCIN-C 2 mg: Old medicine

MITOMYCIN-C 10 mg: 04 April 1986

Date of the most recent amendment to the professional information as approved by the Authority: 25 November 2011

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