SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mitomycin 40 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial of Mitomycin 40 mg powder for solution for injection/infusion contains 40 mg of mitomycin. After reconstitution with 80 ml solvent each ml of solution contains 0.5 mg mitomycin.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion
Blue – violet lyophilized powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mitomycin is used in palliative tumour therapy.

Mitomycin is administered intravenously as monochemotherapy or in combined cytostatic chemotherapy in the case of:

- advanced metastatic gastric carcinoma
- advanced and/or metastatic breast cancer

Furthermore mitomycin is administered intravenously in combined chemotherapy in the case of:

- non-small cell bronchial carcinoma
4.2 Posology and method of administration

Posology

Mitomycin should only be used by doctors experienced in this therapy if there is a strict indication and with continual monitoring of the haematological parameters. It is essential that the injection is administered intravenous. If the medicinal product is injected perivascularly, extensive necrosis occurs in the area concerned.

Unless otherwise prescribed, mitomycin is dosed as follows:

Intravenous administration
In cytostatic monochemotherapy mitomycin is usually administered intravenously as a bolus injection. The recommended dosage is 10 - 20 mg/m² of body surface every 6 - 8 weeks, 8 - 12 mg/m² of body surface every 3 - 4 weeks or 5-10 mg/m² of body surface every 1-6 weeks, depending on the therapeutic scheme used.

In combination therapy the dosage is considerably lower. Because of the risk of additive myelotoxicity, proven treatment protocols may not be deviated from without a specific reason.

Special population
The dose must be reduced in patients who have undergone extensive previous cytostatic therapy, in case of myelosuppression or in elderly patients.

Insufficient data from clinical studies are available concerning the use of mitomycin in patients ≥65 years of age.

The product should not be used in patients with renal impairment (see section 4.3)

The product is not recommended in patients with hepatic impairment due to lack efficacy and safety data in this group of patients.

Paediatric population
The safety and efficacy of mitomycin in children have not been established.

Method of administration
Mitomycin is intended for intravenous injection or infusion after being dissolved. Partial use is applicable.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
  - Breastfeeding

Systemic therapy

Pancytopenia or isolated leucopenia/thrombopenia, haemorrhagic diathesis and acute infections are absolute contraindications.

Restrictive or obstructive disturbances to pulmonary ventilation, renal function, liver function and/or a poor general state of health are relative contraindications. Temporal connection with radiotherapy or other cytostatic may be a further contraindication.

4.4 Special warnings and precautions for use

Due to the toxic effects on the bone marrow of mitomycin, other myelotoxic therapy modalities (in particular other cytostatics, radiation) must be administered with particular caution in order to minimise the risk of additive myelosuppression.

It is essential that the injection is administered intravenous. If the medicinal product is injected perivasally, extensive necrosis occurs in the area concerned. To avoid necrosis following recommendations apply:
  - Always inject into large veins in the arms.
  - Do not directly inject intravenously, but rather into the tube of a good and securely running infusion.
  - Before removing the cannula after central venous administration, flush it through for a few minutes using the infusion in order to release any residual mitomycin.

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.
Long-term therapy may result in cumulative bone marrow toxicity. Bone marrow suppression may only manifest itself after a delay, being expressed most strongly after 4 - 6 weeks, accumulating after prolonged use and therefore often requiring an individual dose adjustment.

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

Mitomycin is a mutagenic and potentially carcinogenic substance in humans. Contact with the skin and mucous membranes is to be avoided.

In the case of pulmonary symptoms, which cannot be attributed to the underlying disease, therapy should be stopped immediately. Pulmonary toxicity can be well treated with steroids.

Therapy should be stopped immediately also if there are symptoms of haemolysis or indications of renal dysfunction (nephrotoxicity).

At doses of > 30 mg of mitomycin/m2 of body surface microangiopathic-haemolytic anaemia has been observed. Close monitoring of renal function is recommended.

New findings suggest a therapeutic trial may be appropriate for the removal of immune complexes that seem to play a significant role in the onset of symptoms by means of staphylococcal protein A.

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

Recommended check-ups and safety measures in the case of intravenous administration:

**Before the start of treatment**
- Complete blood count
- Pulmonary function test if pre-existing lung dysfunction is suspected
- Renal function test in order to exclude renal insufficiency
- Liver function test in order to exclude liver insufficiency

**During therapy**
- Regular checks of the blood count
- Close monitoring of renal function
4.5 Interaction with other medicinal products and other forms of interaction

Myelotoxic interactions with other bone marrow-toxic treatment modalities (especially other cytotoxic medicinal products, radiation) are possible.

Combination with vinca alkaloids or bleomycin may reinforce pulmonary toxicity.

An increased risk of haemolytic-uremic syndrome has been reported in patients receiving a concomitant administration of mitomycin and fluorouracil or tamoxifen.

In animal experiments, pyridoxine hydrochloride (vitamin B₆) resulted in the loss of effect of mitomycin.

No injections with live vaccines should be carried out in connection with mitomycin treatment.

The cardiotoxicity of Adriamycin (doxorubicin) may be reinforced by mitomycin.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from the use of mitomycin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Mitomycin has a mutagenic, teratogenic and carcinogenic effect and therefore may impair the development of an embryo. Mitomycin should not be used during pregnancy. In the case of a vital indication for the treatment of a pregnant patient a medical consultation should be carried out with respect to the risk of the harmful effects on the child, which are associated with the treatment.

Breastfeeding

It is suggested that mitomycin is excreted in breast milk. Due to its proven mutagenic, teratogenic and carcinogenic effects, mitomycin may not be administered during breastfeeding and therefore Mitomycin is contraindicated during breastfeeding (see section 4.3).

Fertility/ Contraception in males and females

Female patients of a sexually mature age should take contraceptive measures during and up to 6 months after the end of chemotherapy or refrain from sexual intercourse.

Mitomycin has a genetically harmful effect. Men who are being treated with mitomycin are therefore advised not to father a child during treatment and up to 6
months thereafter and to seek advice on the preservation of sperm before the start of therapy due to the possibility of irreversible infertility caused by the therapy with mitomycin.

4.7  **Effects on ability to drive and use machines**

Even when used in accordance with instructions these medicinal products may cause nausea and vomiting and thereby reduce reaction times to such an extent that the ability to drive a motor vehicle or operate machinery is impaired. This applies even more in connection with alcohol.

4.8  **Undesirable effects**

Undesirable effects are listed below by system organ class and frequency. Frequencies below are defined as:

- Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).

**Possible side-effects under systemic therapy**

The most common side effects of mitomycin administered systemically are gastrointestinal symptoms like nausea and vomiting and bone marrow suppression with leukopenia and mostly dominant thrombocytopenia. This bone marrow suppression occurs in up to 65% of patients.

In up to 10% of patients serious organ toxicity in the form of interstitial pneumonia or nephrotoxicity must be expected.

Mitomycin is potentially hepatotoxic.

<table>
<thead>
<tr>
<th>Blood and the lymphatic system disorders</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow suppression, leucopenia thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Life-threatening infection, sepsis, haemolytic anaemia</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe allergic reaction</td>
<td></td>
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</tbody>
</table>

<p>| Cardiac disorders                     | Rare      |</p>
<table>
<thead>
<tr>
<th><strong>Heart failure after previous therapy with anthracyclines</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Interstitial pneumonia, dyspnoe, cough, shortness of breath</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Pulmonary hypertension, <em>pulmonary veno-occlusive disease (PVOD)</em></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Very common</td>
</tr>
<tr>
<td><em>Nausea, vomiting,</em></td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Mucositis, stomatitis, diarrhoea, anorexia</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Liver dysfunction, increased transaminases, jaundice, veno-occlusive disease (VOD) of the liver</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Exantherma, allergic skin rash, contact dermatitis, palmar-plantar erythema</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Generalised exantherma</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Renal dysfunction, increase in serum creatinine, glomerulopathy, Nephrotoxicity</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome (HUS) (commonly fatal), microangiopathic-haemolytic anaemia (MAHA syndrome)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Following Extravasation: Cellulitis, tissue necrosis</td>
</tr>
<tr>
<td>Uncommon</td>
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<tr>
<td>Fever</td>
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**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 at agency’s website: www.mhra.gov.uk/yellowcard.

4.9 **Overdose**

In case of overdose severe myelotoxicity or even myelophthisis must be expected, with the full-blown clinical effect only appearing after approximately 2 weeks.

The period until which the number of leucocytes falls to the lowest value may be 4 weeks. Prolonged close haematological monitoring therefore also has to be carried out if an overdose is suspected.

As there are no effective antidotes available, the greatest level of caution is required during each application.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agent, Other cytotoxic antibiotics

ATC code: L01DC03

The antibiotic mitomycin is a cytostatic medicinal product from the group of alkylating agents.

Mitomycin is an antibiotic isolated from Streptomyces caespitosus with antineoplastic effect. It is present in an inactive form. Activation to a trifunctional alkylating agent is rapid, either at physiological pH in the presence of NADPH in serum or intracellularly in virtually all cells of the body with the exception of the cerebrum, as the blood-brain barrier is not overcome by mitomycin. The 3 alkylating radicals all stem from a quinone, an aziridine and a urethane group. The mechanism of action is based predominantly on the alkylation of DNA (RNA to a lesser extent) with the corresponding inhibition of DNA synthesis. The degree of DNA damage correlates with the clinical effect and is lower in resistant cells than in sensitive ones. As with other alkylating agents, proliferating cells are damaged to a greater extent than those that are in the resting phase (G0) of the cell cycle. Additionally, free peroxide radicals are released, particularly in the case of higher doses, which result in DNA breaks. The release of peroxide radicals is associated with the organ-specific pattern of side-effects.
5.2 Pharmacokinetic properties

After the intravenous administration of 10 - 20 mg/m² of mitomycin, maximum plasma levels of 0.4 - 3.2 µg/ml have been measured. The biological half-life is short and is between 40 and 50 minutes. The serum level falls biexponentially, steeply at first within the first 45 minutes, and then more slowly.

After approximately 3 hours the serum levels are usually below the detection limit. The main location for metabolism and elimination is the liver. Accordingly, high concentrations of mitomycin have been found in the gall bladder. Renal excretion plays only a minor role with respect to the elimination.

5.3 Preclinical safety data

In animals, mitomycin is toxic to all proliferating tissues, particularly the cells of the bone marrow and the mucous membrane of the gastrointestinal tract, resulting in the inhibition of spermiogenesis.

Mitomycin has mutagenic, carcinogenic and teratogenic effects which can be demonstrated in corresponding experimental systems.

Local tolerance
Mitomycin causes severe necrosis in the case of paravenous injection or leakage from the blood vessel into surrounding tissue.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

6.2 Incompatibilities

Not known
6.3 **Shelf life**

Powder: 2 years

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours in the recommended diluents stored at 25°C and 2-8°C.

Diluted solution: After dilution, the solution should be used immediately

6.4 **Special precautions for storage**

Do not refrigerate or freeze.

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

6.5 **Nature and contents of container**

Mitomycin is contained within a Type I 100 ml amber moulded glass vials with dark grey bromobutyl lyo stopper and a violet flip off aluminium seal.

The vials are packaged into cartons containing 1, 5 or 10 vials.
Not all pack size may be marketed.

6.6 **Special precautions for disposal**

Preparation of ready-to-use solution for injection or infusion

The contents of the vial should be reconstituted with water for injection or 0.9\% sodium chloride solution, to a concentration of 0.5 mg/ml.

Preparation of Reconstituted solution
The contents of one vial of Mitomycin 40 mg are dissolved in 80 ml of water for injections or 0.9% sodium chloride solution. After reconstitution with 80 ml solvent each ml of solution contains 0.5 mg mitomycin.

If the powder does not dissolve immediately, allow it to stand at room temperature until it has completely dissolved. The contents of the vial must dissolve to form a clear solution within 2 minutes.

For intravenous infusion the solution of Mitomycin 40 mg is further diluted with 0.9% Sodium chloride solution or Sodium Lactate Injection to a concentration of 20 or 40 micrograms of mitomycin/ml.

Notes

- Mitomycin 40 mg must not be used in mixed injections.
- Other injection solutions or infusion solutions must be administered separately.
- It is essential that the injection is administered intravenous.

For storage conditions of the reconstituted/ diluted medicinal product, see sections 6.3.

Mitomycin 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL
8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1552

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/05/2014

10 DATE OF REVISION OF THE TEXT

14/11/2014