SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mitocin 20 mg, powder for solution for injection/infusion or intravesical use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Mitomycin

1 vial of Mitocin 20 mg powder for solution for injection/infusion or intravesical use contains 20 mg of mitomycin. After reconstitution with 40 ml water for injections 1 ml of solution for injection/infusion contains 0.5 mg mitomycin. After reconstitution with 20 ml solvent 1 ml of solution for intravesical use contains 1 mg mitomycin.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion or intravesical use

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
- advanced pancreatic carcinoma

Intravesical administration for relapse prevention in superficial urinary bladder carcinoma after transurethral resection.

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 perivasally, 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/m^2 of body surface every 6 - 8 weeks, 8 - 12 mg/m^2 of body surface every 3 - 4 weeks or 5-10 mg/m^2 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.

Intravesical administration

In intravesical therapy, 20 - 40 mg of mitomycin, corresponding to 1 - 2 vials of Mitocin 20 mg in 20 - 40 ml of water for injections or sodium chloride (0.9%) solution, is instilled weekly into the bladder. In the case of intravesical administration the urine pH should be higher than pH 6.

Alternative dose recommendation in the prevention of recurrent superficial bladder tumours is 4-10 mg (0.06-0.15 mg/kg of body weight) instilled into the bladder though a urethral catheter 1 or 3 times per week.

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 or for intravesical instillation after being dissolved. Partial use is applicable.

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

The contents of one vial of Mitocin 20 mg are dissolved in 40 ml of water for injections by swirling.

Shake until the reconstituted solution becomes clear and free of particles.

For intravenous infusion the solution of Mitocin 20 mg can be diluted in 40 ml of water for injections with isotonic sodium chloride infusion solution down to a concentration of 20 - 40 micrograms of mitomycin/ml.

Preparation of ready-to-use solution for intravesical administration

The contents of 1 - 2 vials of Mitocin 20 mg (equivalent to 20 – 40 mg of mitomycin) are dissolved in 20 – 40 ml of water for injections or sodium chloride (0.9%) solution.

Notes

- Mitocin 20 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

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 leucopoenia/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.

Intravesical therapy

Perforation of the bladder wall is an absolute contraindication.

Cystitis is a relative 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/m^2 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 B_6) 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 Mitocinis 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 impair alertness 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.

Blood and the lymphatic system disorders	Very common Bone marrow suppression, leucopenia thrombocytopenia Rare Life-threatening infection, sepsis, haemolytic anaemia
Immune system disorders	Very rare Severe allergic reaction
Cardiac disorders	Rare Heart failure after previous therapy with anthracyclines
Respiratory, thoracic and mediastinal disorders	Common Interstitial pneumonia,dyspnoe, cough,

	shortness of breath Rare Pulmonary hypertension, *pulmonary veno-occlusive disease (PVOD)*
Gastrointestinal disorders	Very common *Nausea, vomiting,* Uncommon Mucositis, stomatitis, diarrhoea, anorexia
Hepatobiliary disorders	Rare Liver dysfunction, increased transaminases, jaundice, veno-occlusive disease (VOD) of the liver
Skin and subcutaneous tissue disorders	Common Exanthema, allergic skin rash, contact dermatitis, palmar-plantar erythema Uncommon Alopecia Rare Generalised exanthema
Renal and urinary disorders	Common Renal dysfunction, increase in serum creatinine, glomerulopathy, Nephrotoxicity Rare Haemolytic uraemic syndrome (HUS) (commonly fatal), microangiopathic-haemolytic anaemia (MAHA syndrome)
General disorders and administration site conditions	Common Following Extravasation: Cellulitis, tissue necrosis Uncommon Fever

Possible side-effects under intravesical therapy

Skin and subcutaneous tissue disorders	Common Pruritus, allergic skin rash, contact dermatitis, palmar-plantar erythema Rare

	Generalised exanthema
Renal and urinary disorders	Common Cystitis (possibly haemorrhagic), dysuria, nocturia, pollakisuria, hematuria, local irritation of the bladder wall Very rare necrotizing cystitis, allergic (eosinophilic) cystitis, stenosis of the efferent urinary tract, reduction in bladder capacity, bladder wall calcification and bladder wall fibrosis.

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 Yellow Card Scheme, 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: Cytotoxic antibiotics and related substances

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 anti-neoplastic 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 (GO) 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/m^2 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.

During intravesical therapy mitomycin is only absorbed in insignificant doses. Nevertheless, a systemic effect cannot be excluded completely.

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,

36% hydrochloric acid and sodium hydroxide for pH adjustment

6.2 Incompatibilities

Incompatibilities occur with highly acidic or alkaline substances. The optimum pH of the ready-to-use mitomycin solution is 7.0.

6.3 Shelf life

3 years

Reconstituted solution:

Shake until the reconstituted solution becomes clear and free of particles.

The contents of the vials are intended for single use only.

Unused solutions must be discarded.

The chemical and physical stability at room temperature and during exposure to light of a reconstituted solution is

- 1 hour with Water for Injections
- 2 hours with sodium chloride 9 mg/ml (0.9%) solution

All reconstituted solutions are intended for immediate use!

6.4 Special precautions for storage

Do not store above 25ºC. Store the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Packs of 1 amber glass vial (Ph. Eur., type I)

Packs of 5 amber glass vials (Ph. Eur., type I)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Special precautions for the preparation and the disposal of unused cytotoxic medicinal products should be complied with.

The reconstituted solution should be stored away from light in the refrigerator.

Before the ready-to-use solution is used it should be warmed up to room or body temperature.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 47587/0001

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03/2022