SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mitomycin 2 mg powder for solution for injection/infusion or intravesical use

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Mitomycin 2 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion or intravesical use

Blue-violet cake or 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 adults with:

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

Furthermore mitomycin is administered **intravenously** in combined chemotherapy in adults with:

- non-small cell bronchial carcinoma
- advanced pancreatic carcinoma

Intravesical administration for relapse prevention in adults with 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, in case of intravenous use, with continual monitoring of the haematological parameters.

Intravenous administration
It is essential that the injection is administered intravenous. If the medicinal product is injected perivasally, extensive necrosis occurs in the concerned area.

Unless otherwise prescribed, mitomycin is dosed as follows:

In cytostatic monochemotherapy, mitomycin is usually administered intravenously as a bolus injection. The recommended dosage is 10 - 20 mg/m^2 of body surface area every 6 - 8 weeks, 8 - 12 mg/m^2 of body surface area every 3 - 4 weeks or 5-10 mg/m^2 of body surface area every 1-6 weeks, depending on the therapeutic scheme used.

Mitomycin 2 mg, powder for solution for injection/infusion may not be reconstituted in water.

A dose greater than 20 mg/m^2 gives more toxic manifestations without therapeutic benefits. The maximum cumulative dose of mitomycin is 60 mg/m^2.

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 in 20 - 40 ml of phosphate buffer pH 7.4 or sodium chloride (0.9%) solution or Water for Injection (WFI), is instilled weekly into the bladder. The treatment period is 8 to 12 weeks. 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. The solution should be retained in the bladder for 1-2 hours.

Special population
The dose must be reduced in patients who have undergone extensive previous cytostatic therapy, in case of myelosuppression or in elderly patients (only valid for intravenous use of mitomycin).

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

Renal or hepatic impairment

The product should be used with caution in patients with renal or hepatic impairment (see section 4.3).

Paediatric population
The safety and efficacy of mitomycin in children aged from 0 to 17 years have not been established.

No data are available

Method of administration

Mitomycin is only intended for intravenous injection or infusion into a blood vessel (intravenous use) or for intravesical instillation after being dissolved. Partial use is applicable only valid for intravenous use of mitomycin).

Intravenous administration
Precautions to be taken before handling or administering the medicinal product

- Mitomycin 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.

Intravesical administration

It is advised to use this medicinal product at its optimal pH (urinary pH > 6) and to maintain the concentration of mitomycin by reducing fluid intake before, during and after instillation. The bladder must be emptied before instillation. Mitomycin is introduced into the bladder by means of a catheter and at low pressure. The length of individual instillation should be 1 – 2 hours. During this period the solution should have sufficient contact with the entire mucosal surface of the bladder. Therefore the patient should be mobilised as much as possible. After 2 hours the patient should void the instilled solution, preferably in a sitting position.

For instructions on reconstitution 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 (see section 4.6)

Systemic therapy
Pancytopenia, isolated leucopoenia/thrombocytopenia, haemorrhagic diathesis and acute infections are absolute contraindications.

Restrictive or obstructive disturbances to pulmonary ventilation, renal dysfunction, hepatic dysfunction and/or a poor general state of health are relative contraindications. Temporal connection with radiotherapy or other cytostatics 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

Extravasation following systemic administration

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, immediate topical use of dimethylsulfoxide (DMSO 99%), repeated every 4-8 hours as well as the use of dry, cold compresses is recommended. A (plastic) surgeon should be consulted at an early stage (within 72 hours). A systemic injection of 200 mg of Vitamin B6 may be of some value in promoting the regrowth of tissues that have been damaged.

Extravasation following intravesical administration

Symptoms of extravasation after intravesical mitomycin administration might present straight after the application or weeks or months later. It can be unclear if the extravasation occurred due to unnoticed perforation, a thinned muscularis propria or if the medicinal product was not administered correctly. First symptoms present as pelvic or abdominal pain that are refractory to simple analgesia. (Fat) tissue necrosis in the surrounding area as a consequence of the extravasation was observed in most cases. Bladder perforation or development of fistula and/or abscess has also been reported (see section 4.8).

Therefore, physicians should consider the possibility that extravasation occurred if the patient complains about pelvic or abdominal pain to prevent serious consequences.

General hygiene for the patient following instillation
It is recommended to wash hands and genital area after micturition. This applies especially to the first micturitions following mitomycin administration. Mitomycin is a mutagenic and potentially carcinogenic substance in humans. Contact with the skin and mucous membranes is to be avoided. If cystitis does occur, symptomatic treatment with local anti-inflammatories and analgesics should be given. In most cases the mitomycin therapy can be continued, if necessary at a reduced dose. Isolated cases of allergic (eosinophilic) cystitis have been reported which necessitated discontinuation of therapy (see section 4.8).

Elderly

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.

Bone marrow toxicity

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.
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.

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.

Particular caution is required when possible occurrence or aggravation of infectious disease and bleeding tendency.

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). The occurrence of a haemolytic-uraemic syndrome (HUS: irreversible renal failure, microangiopathic haemolytic anaemia [MAHA syndrome] and
thrombocytopenia) is commonly fatal.

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. No cases of MAHA
have been observed so far after intravesical use of mitomycin.

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 immunoadsorption with staphylococcal protein A columns.

Immunisation with live virus vaccines (e.g. yellow fever vaccination) increases the risk of infection and other adverse reactions such as vaccinia gangrenosa and generalized vaccinia, in patients with reduced immunocompetence, such as during treatment with mitomycin. Therefore, live virus vaccines should not be administered during therapy. It is advised to use live virus vaccines with caution after stopping chemotherapy, and vaccinate not sooner than 3 months after the last dose of chemotherapy (see section 4.5).

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 as this may result in an increased risk of infection by the live vaccine (see section 4.4).

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 should not be administered during breastfeeding. Breastfeeding women must first discontinue breastfeeding before initiating treatment with mitomycin.

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.
As the effect in prolonged use is cumulative, bone marrow suppression is often dose limiting.

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 Haemolytic anaemia, thrombotic microangiopathy (TMA), incl. thrombotic thrombocytopenic purpura (TTP) Not known Anaemia
Infections and infestations	Rare Life-threatening infection, sepsis Not known Infection
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
Hepato-biliary 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 erythrodysaesthesia (PPE) 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

Adverse reactions may result either from the solution for intravesical instillation or after deep
resection.

The most common adverse reactions of intravesically administered mitomycin are allergic skin
reactions in the form of local exanthema (e.g. contact dermatitis, also in the form of palmar and plantar erythema), and cystitis.

Skin and subcutaneous tissue disorders	Common Pruritus, allergic skin rash, contact dermatitis, palmar plantar erythema (PPE) 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, bladder perforation. Not known *In case of extravasation:* bladder perforation, (fat) tissue necrosis of the surrounding area, vesical fistula, abscesses

After intravesical administration, only minor amounts of mitomycin reach the systemic circulation. Nevertheless, in very rare cases the following systemic adverse reactions have been reported:

Possible systemic adverse reactions occurring **very rarely** following intravesical administration:

Blood and lymphatic system disorders	Leukocytopenia, thrombocytopenia
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Gastrointestinal disorders	Nausea, vomiting, diarrhoea
Hepatobiliary disorders	Transaminases increased
Skin and subcutaneous tissue disorders	Alopecia
Renal and urinary disorders	Renal dysfunction
General disorders and administration site conditions	Fever

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
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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.

However, up until now, no cases of overdose of intravesical administration of mitomycin have been reported.

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 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

Absorption

Following intravesical administration only a small proportion of mitomycin reaches the serum. Maximum peak plasma levels of 0.05 µg/mL 40 minutes after intravesical instillation of 40 mg mitomycin have been measured. This is well below the level of 0.4 µg/mL of mitomycin in serum which is known to be myelosuppressive. Nevertheless, a systemic effect cannot be completely excluded.

In comparison, following the intravenous administration of 10 - 20 mg/m^2 of mitomycin, maximum plasma levels of 0.4 - 3.2 µg/ml have been measured.

Distribution
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.

Biotransformation and elimination
The main location for metabolism and elimination after systemic application 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 E421

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened vial: 2 years

The reconstituted product should be used immediately.

The contents of the vials are intended for single use only. Unused solutions must be discarded.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Mitomycin is contained within a amber colored, type I glass vial with a bromo butyl rubber stopper and an aluminium seal.

The 2 mg vials are packaged into cartons containing 1, 5 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Intravenous use:

Mitomycin 2 mg, powder for solution for injection/infusion may not be reconstituted in water.

The contents of the vial should be reconstituted with saline or 20% glucose solution in a ration of:

2 ml for the 2 mg of mitomycin.

Reconstitution/ Dilution Fluid	Concentration	pH range	Osmolality
Saline	1.0mg/mL, (Reconstitution) 0.1 mg/mL (Dilution)	4.5 – 7.5	Approx. 290 mOsm/Kg
20% glucose solution	1.0mg/mL, (Reconstitution) 0.1 mg/mL (Dilution)	3.5 – 7.0	Approx. 1100 mOsm/Kg

Intravesical use:

The contents of the vial should be reconstituted with saline or phosphate buffer 7.4 or water for injection in a ration of:

2 ml for the 2 mg of mitomycin.

Reconstitution Fluid	Concentration	pH range	Osmolality
Saline	1.0 mg/mL	4.5 – 7.5	Approx. 290 mOsm/Kg
Phosphate Buffer pH 7.4	1.0 mg/mL	6.0 – 8.5	Approx. 185 mOsm/Kg

Water for Injection	1.0 mg/mL	5.0 - 7.5	5 to 15 mOsm/kg

Pregnant healthcare personnel should not handle and/or administer drug product. 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.

The reconstituted solution is clear blue-violet colour free from visible particulate matter.
Any unused product or waste material should be disposed of in accordance with local requirements.

Waste material should be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

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