SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 1 mg/ml powder for solution for injection/infusion or intravesical use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of <invented name> contains 2 mg mitomycin.
Each vial of <invented name> contains 10 mg mitomycin.
Each vial of <invented name> contains 20 mg mitomycin.
Each vial of <invented name> contains 40 mg mitomycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion or intravesical use.

Grey to grey blue powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous use

Mitomycin is used in palliative tumour therapy.

Intravenous use of mitomycin is indicated as monochemotherapy or in combined cytostatic chemotherapy in adults with:

- advanced colorectal carcinoma
- advanced gastric carcinoma
- advanced and/or metastatic breast carcinoma
- advanced oesophageal carcinoma
- advanced cervical carcinoma
- non-small-cell bronchial carcinoma
- advanced pancreatic carcinoma
- advanced tumours of the head and neck

Intravesical use

Mitomycin is indicated as **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 intravenously. 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 doses are 10 - 20 mg/m² body surface area every 6 – 8 weeks, 8 - 12 mg/m² body surface area every 3 - 4 weeks, or 5 - 10 mg/m² of body surface area every 3 – 6 weeks, depending on the therapeutic scheme used.
In combination therapy, the dose is considerably lower. Because of the risk of additive myelotoxicity, proven treatment protocols may not be deviated from without a specific reason.

Intravesical administration

There are many intravesical mitomycin regimens, varying in the dose of mitomycin used, the frequency of instillation and the duration of therapy.

Unless otherwise specified, the dose of mitomycin is 40 mg instilled into the bladder once weekly.
Regimens with instillations every 2 weeks, every month or 3 monthly can also be used.
The specialist should decide on the optimum regimen, frequency and duration of therapy on an individual patient basis.

Special populations
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).

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

Renal or hepatic impairment
The medicinal product should be used with caution in patients with renal or hepatic impairment.

Paediatric population
The safety and efficacy of <invented name> in children have not been established.
No data are available.

Method of administration

Mitomycin is only intended for 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
- <Invented name> 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 intravenously.

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 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, isolated leukopenia or 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
Bladder wall perforation, cystitis

4.4 Special warnings and precautions for use

Extravasation following systemic administration

It is essential that the injection is administered intravenously. If the medicinal product is injected perivasally, extensive necrosis occurs in the concerned area. To avoid necrosis, the following recommendations apply:
- Always inject into large veins in the arms.
- Do not directly inject intravenously, but rather into the line of a secure, well-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, and bone marrow depression, which may be protracted, so administer mitomycin with special caution in this population while closely monitoring the patient's condition.

Bone marrow toxicity
Due to the toxic effects of mitomycin on the bone marrow, 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 patients concomitantly treated intravenously with mitomycin and other antineoplastic agents.

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 intravenous doses of > 30 mg of mitomycin/m² 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.

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

Before the start of treatment
- Full 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 the treatment
- Regular monitoring of the blood count
- Close monitoring of renal function

4.5 Interaction with other medicinal products and other forms of interaction

Possible interaction under systemic therapy

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-uraemic syndrome has been reported in patients receiving concomitant administration of intravenous mitomycin and 5-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 as this may result in an increased risk of infection by the live vaccine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Mitomycin is genotoxic and can adversely affect the development of an embryo (see section 5.3). <Invented name> should not be used during pregnancy. If treatment of a pregnant patient is vitally indicated, medical counselling should be provided regarding the risk of harmful effects on the child associated with the treatment.

Breast-feeding

Mitomycin is excreted in human milk. Due to its proven mutagenic, teratogenic and carcinogenic effects, breast-feeding must be discontinued during treatment with <invented name> (see section 4.3).

Fertility

Women must not become pregnant during treatment with mitomycin. In the event of pregnancy during treatment, genetic counselling must be provided. Women of childbearing potential have to use effective contraception or practise sexual abstinence during chemotherapy and for 6 months afterwards.

Mitomycin is genotoxic. Men treated with mitomycin are therefore advised not to father a child during treatment and for 6 months afterwards and to seek advice on sperm conservation before starting the therapy due to the possibility of irreversible infertility caused by mitomycin therapy.

4.7 Effects on ability to drive and use machines

Even when used in accordance with instructions this medicinal product may cause nausea and vomiting and thereby reduce reaction times to such an extent that the ability to drive and use machines is impaired. This applies even more if alcohol is consumed at the same time.

4.8 Undesirable effects

Adverse reactions 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 adverse reactions under systemic therapy

The most common adverse reactions of systemically administered mitomycin are gastrointestinal symptoms, such as nausea and vomiting, and bone marrow suppression with leukopenia and generally dominant thrombocytopenia. 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 lymphatic system disorders	Very common Bone marrow suppression, leukopenia, 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
Hepatobiliary disorders	Rare Hepatic dysfunction, transaminases increased, icterus, veno-occlusive liver disease (VOD)
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, serum creatinine increased, 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 adverse reactions 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 Rare Generalised exanthema
Renal and urinary disorders	Common Cystitis (possibly haemorrhagic), dysuria, nocturia, pollakiuria, haematuria, local irritation of the bladder wall Very rare Necrotising 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 national reporting system listed in Appendix V.

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 leukocytes 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.

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

As no effective antidote is available, the utmost caution should be exercised at each administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, cytotoxic antibiotics and related substances, other cytotoxic antibiotics, ATC code: L01DC03

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

Mechanism of action

Mitomycin is an antibiotic with an antineoplastic effect which is isolated from *Streptomyces caespitosus*. It is present in an inactive form. Activation to a trifunctional alkylating agent takes place rapidly, 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 three alkylating radicals all stem from a quinone, an aziridine and a urethane group. The mechanism of action is based predominantly on DNA (to a lesser extent RNA) alkylation, 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 cells. As with other alkylating agents, proliferating cells are damaged to a greater extent than those 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 adverse reactions.

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 intravenous administration of 10 - 20 mg/m² mitomycin, peak plasma levels of 0.4 - 3.2 µg/ml have been measured.

Distribution

The biological half life is short, between 40 and 50 minutes. The serum level falls biexponentially, steeply within the first 45 minutes and more slowly thereafter.
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.

5.3 Preclinical safety data

In animal studies mitomycin has a toxic effect on all proliferating tissues, in particular on the cells of the bone marrow and the gastrointestinal mucosa, and spermatogenesis is inhibited.
Mitomycin has mutagenic, carcinogenic and teratogenic properties, which can be demonstrated in appropriate experimental models.

If injected outside a vein, or in the event of extravasation into surrounding tissue, mitomycin causes severe necrosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Urea

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

<Invented name>, vials with 2 mg (10 mg, 20 mg, 40 mg) mitomycin
2 years

After reconstitution the medicinal product should be used immediately.

6.4 Special precautions for storage

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

<Invented name> 2 mg
Packs of 1, 5 and 10 6 ml clear glass vials (type I) with fluoropolymer coated bromobutyl rubber stopper and a flip off aluminium seal

<Invented name> 10 mg
Packs of 1, 5 and 10 10 ml clear glass vials (type I) with fluoropolymer coated bromobutyl rubber stopper and a flip off aluminium seal

<Invented name> 20 mg
Packs of 1, 5 and 10 20 ml clear glass vials (type I) with fluoropolymer coated bromobutyl rubber stopper and a flip off aluminium seal

<Invented name> 40 mg
Packs of 1, 5 and 10 50 ml clear glass vials (type I) with fluoropolymer coated bromobutyl rubber stopper and a flip off aluminium seal

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of solution for injection or infusion ready for use

Mitomycin 2 mg
Dissolve the contents of one 2 mg vial of <invented name> in 2 ml water for injections by inverting the vial.
If the powder does not dissolve immediately, leave to stand at room temperature until fully dissolved.
The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 10 mg
Dissolve the contents of one 10 mg vial of <invented name> in 10 ml water for injections by inverting the vial.
If the powder does not dissolve immediately, leave to stand at room temperature until fully dissolved.
The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 20 mg
Dissolve the contents of one 20 mg vial of <invented name> in 20 ml water for injections by inverting the vial.
If the powder does not dissolve immediately, leave to stand at room temperature until fully dissolved.
The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 40 mg
Dissolve the contents of one 40 mg vial of <invented name> in 40 ml water for injections by inverting the vial.
If the powder does not dissolve immediately, leave to stand at room temperature until fully dissolved.
The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

<Invented name> must not be used in mixed injections. Other solutions for injection or infusion must be administered separately.
It is essential that extravasation is avoided in case of intravenous administration.

Reconstitution of solution for intravesical use ready for use

Mitomycin 2 mg
Dissolve the contents of 10 - 20 vials of <invented name> 2 mg (equivalent to 20 - 40 mg mitomycin) in 20 - 40 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 10 mg
Dissolve the contents of 2 - 4 vials of <invented name> 10 mg (equivalent to 20 - 40 mg mitomycin) in 20 - 40 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 20 mg
Dissolve the contents of 1 - 2 vials of <invented name> 20 mg (equivalent to 20 - 40 mg mitomycin) in 20 - 40 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Mitomycin 40 mg
Dissolve the contents of one vial of <invented name> 40 mg (equivalent to 40 mg mitomycin) in 40 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. The contents of the vial must dissolve to form a blue-purple clear solution within 2 minutes.

Only clear solutions may be used.

The content of the vials is intended for single use/single entry only. Unused solution must be discarded.

Protect the reconstituted solution from light.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD month YYYY
Date of latest renewal: DD month YYYY

10. DATE OF REVISION OF THE TEXT