Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Mitomycin medac 40 mg powder and solvent for intravesical solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Mitomycin medac contains 40 mg mitomycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for intravesical solution.

Powder: Grey to grey blue powder or cake.
Solvent: Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mitomycin medac is indicated as **intravesical** administration for relapse prevention in adult patients with superficial urinary bladder carcinoma after transurethral resection.

4.2 Posology and method of administration

Mitomycin medac must be administered by physicians experienced in this therapy, only if strictly indicated.

Mitomycin medac is only intended for intravesical use following reconstitution.

Posology

The content of one vial is required for one bladder instillation.

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

Unless otherwise specified, the dose of mitomycin is 40 mg mitomycin 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

Elderly
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.

Paediatric population
The safety and efficacy of Mitomycin medac in children have not been established.
No data are available.

Method of administration

Mitomycin medac is only intended for intravesical instillation after being dissolved.

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(s) or to any of the excipients listed in section 6.1
- Breastfeeding
- Bladder wall perforation
- Cystitis

4.4 Special warnings and precautions for use

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).

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.

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 the 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). The occurrence of a haemolytic-uraemic syndrome (HUS:

irreversible renal failure, microangiopathic haemolytic anaemia [MAHA syndrome] and thrombocytopenia) is commonly fatal.

At intravenous doses > 30 mg of mitomycin/m² of body surface microangiopathic-haemolytic anaemia (MAHA) 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.

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.

4.5 Interaction with other medicinal products and other forms of interactions

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 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.

The cardiotoxicity of 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.
Women must not become pregnant during treatment with mitomycin. In the event of pregnancy during treatment, genetic counselling must be provided.

Breastfeeding
It is suggested that mitomycin is excreted in human milk. Due to its proven mutagenic, teratogenic and carcinogenic effects, breastfeeding must be discontinued during treatment with Mitomycin medac (see section 4.3).

Fertility
Sexually mature patients have to use effective contraception or practise sexual abstinence during chemotherapy and for 6 months afterwards.

Mitomycin is genotoxic. 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 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 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 intravesical therapy

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

The most common undesirable effects 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 Allergic skin rash, contact dermatitis, palmar-plantar erythema, pruritus Rare Generalised exanthema
Renal and urinary disorders	Common Cystitis (possibly haemorrhagic), dysuria, nocturia, pollakiuria, haematuria, local irritation of the bladder wall Very rare or not known Necrotising cystitis, allergic (eosinophilic) cystitis, stenosis of the efferent urinary tract, reduced bladder capacity, bladder wall calcification, bladder wall fibrosis, bladder perforation

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

Possible systemic undesirable effects 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
Hepato-biliary disorders	Transaminases increased
Skin and subcutaneous tissue disorders	Alopecia
Renal and urinary disorders	Renal dysfunction
General disorders and administration site conditions	Fever

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 lymphatic system disorders	Very common Bone marrow suppression, leukopenia, thrombocytopenia Rare Life-threatening infection, sepsis, haemolytic anaemia, thrombotic microangiopathy (TMA), incl. thrombotic thrombocytopenic purpura (TTP)
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, dyspnoea, 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 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

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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 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 microg/ml 40 minutes after intravesical instillation of 40 mg mitomycin have been measured. This is well below the level of 0.4 microg/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 microg/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

Powder for solution for intravesical use: Urea.

Solvent for intravesical solution: Sodium chloride and water for injections.

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

Mitomycin medac, vials with 40 mg mitomycin and instillations set
1 year

After reconstitution the medicinal product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C. 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

Mitomycin medac is contained within clear glass vials (type I) with fluoropolymer coated bromobutyl rubber stopper and a flip off aluminium seal.

Packs of 1 vial (50 ml), 1 PVC bag of 40 ml with 0.9 % sodium chloride solution, catheters.
Packs of 4 vials (50 ml), 4 PVC bags of 40 ml with 0.9 % sodium chloride solution, catheters.
Packs of 5 vials (50 ml), 5 PVC bags of 40 ml with 0.9 % sodium chloride solution, catheters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dissolve the content of one vial of Mitomycin medac (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.

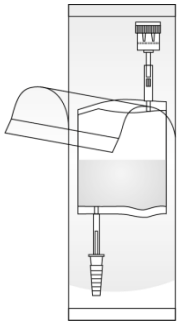
Mitomycin medac must not be used in mixed injections. Other solutions for injection or infusion must be administered separately.

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

<u>Instructions for use for the solvent for intravesical solution (instillation set)</u>

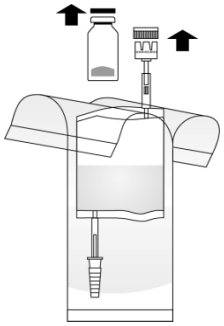
Fig. 1 – 8:

(1)



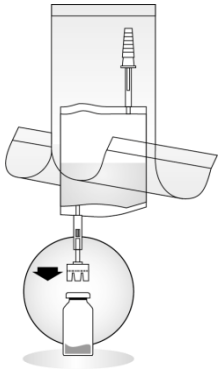
Tear open the protective cover, but do not remove completely! This will protect the tip of the instillation system from contamination up to the last minute.

(2)



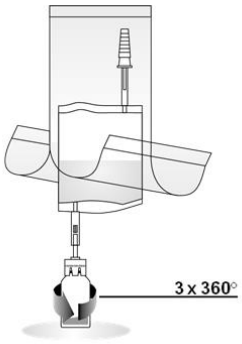
Remove the caps from the vial and instillation system.

(3)



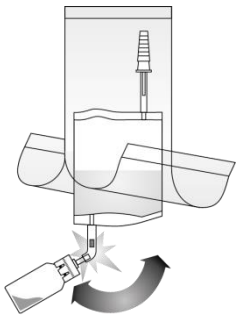
Place the vial on a firm surface and press the connector of the instillation system firmly in a straight manner on to the vial.

(4)



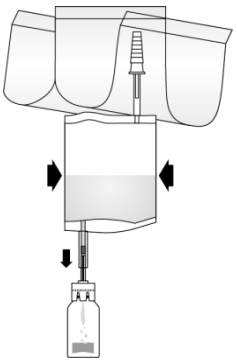
Make sure to turn the vial 3 times completely.

(5)



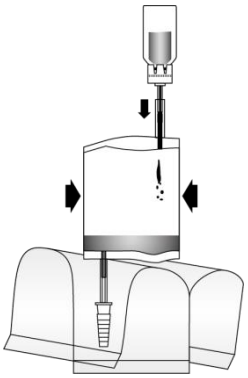
Break open the mechanism in the tube of the connector by repeated bidirectional bending. This establishes the connection. Please hold the tube – and not the vial – during this process!

(6)



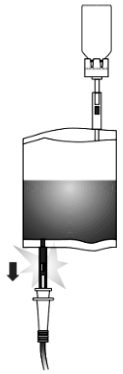
Pump the liquid into the vial, but do not fill the vial completely. If flow is not possible, turn the vial again three times in the other direction to assure that the septum is completely pierced. Repeat this step until flow is possible.

(7)



Invert the entire system. Pump air from the instillation system into the vial at the top. Draw suspended mitomycin into the instillation system. Do not remove the vial.

(8)



Keep the instillation system in an upright position. Now remove the protective cover completely. Connect the catheter to the instillation system. Now break the sealing mechanism in the tube section by bending backwards and forwards and instil the solution. At the end of instillation free the catheter by pressing air through.
Keep the instillation system squeezed and place it together with the catheter into the disposal bag.

7. MARKETING AUTHORISATION HOLDER

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER

PA 0623/016/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2016
Date of last renewal: 28th October 2020

10. DATE OF REVISION OF THE TEXT

April 2020