Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <invented name> is and what it is used for

<Invented name> is a medicine for the treatment of cancer, i.e. a medicine which prevents or considerably delays the division of active cells by influencing their metabolism in various ways (cytostatic). The therapeutic use of cytostatics in cancer therapy is based on the fact that one way in which cancer cells differ from normal cells in the body is that the rate of cell division is increased due to a lack of control of their growth.

Therapeutic indications
<Invented name> is used in cancer therapy for the relief of symptoms (palliative cancer therapy).

Intravenous application
When given as an injection or infusion into a vein (intravenous administration), this medicine is used either alone or in combination with other cytostatic medicines. This medicine is effective in the case of the following tumours:
- advanced bowel cancer (colorectal carcinoma)
- advanced stomach cancer (gastric carcinoma)
- advanced and/or metastatic breast cancer (breast carcinoma)
- advanced cancer of the oesophagus (oesophageal carcinoma)
- advanced cancer of the cervix (cervical carcinoma)
- non-small-cell lung cancer (bronchial carcinoma)
- advanced cancer of the pancreas (pancreatic carcinoma)
- advanced tumours of the head and neck.

Intravesical application
This medicine is introduced into the urinary bladder (intravesical application) to prevent recurrence of superficial urinary bladder cancer after the tissue affected by the cancer has been removed through the urethra (transurethral resection).

2. What you need to know before you use <invented name>

Mitomycin may only be administered if strictly indicated, with continuous monitoring of the blood count when administered intravenously, and by doctors experienced in this type of therapy.

Do not use <invented name>
- if you are allergic to mitomycin or any of the other ingredients of this medicine (listed in section 6),
- while breast-feeding: you must not breast-feed during treatment with mitomycin.
- in the case of **intravenous** administration (injection or infusion into a blood vessel):
  - if you suffer from a major reduction in the number of all types of blood cells (including red and white blood cells as well as platelets [pancytopenia]), or an isolated reduction of white blood cells (leukopenia) or blood platelets (thrombocytopenia),
  - if you suffer from a tendency to bleed (haemorrhagic diathesis),
  - in acute infections (disease caused by pathogens).
- in the case of **intravesical** administration (application in the urinary bladder):
  - if you have a perforation of the bladder wall,
  - if you suffer from an inflammation of the urinary bladder (cystitis).

Warnings and precautions
Talk to your doctor or pharmacist before using <invented name>.

Particular caution is required when using <invented name>
- if you are in poor general health,
- if you are suffering from impaired lung, kidney or liver function,
- if you are undergoing radiation therapy,
- if you are being treated with other cytostatics (substances which inhibit cell growth/cell division),
- if you have been told that you have bone marrow depression (your bone marrow is not able to make the blood cells that you need). It may become worse (especially in the elderly and during long term treatment with mitomycin); infection may get worse due to low blood count and may lead to fatal conditions,
- if you are of child-bearing age as mitomycin may affect your ability to have children in the future.

Mitomycin is a substance that can cause significant hereditary changes in genetic material, and can potentially cause cancer in humans.

Intravesical administration
If you experience abdominal pain or pain in the pelvic region that occurs straight after or weeks or months after the application of <invented name> in the bladder, inform your doctor immediately. It can be necessary that your doctor performs an ultrasound of the abdominal to clarify the cause of your pain.

Avoid contact with the skin and mucous membranes.
Please read the general hygiene instructions after an intravesical instillation into the bladder:
It is recommended to sit down for urinating to avoid spillage of the urine and to wash hands and genital area after urinating. This applies especially to the first urination following mitomycin administration.

Children and adolescents
The use of this medicine in children and adolescents is not recommended.

Other medicines and <invented name>

No interactions with other medicines are known if mitomycin is given in the bladder (intravesical administration)

Possible interaction during injection or infusion in a blood vessel (intravenous administration)

Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

If other forms of treatment (in particular other anti-cancer medicines, radiation) which also have a harmful effect on the bone marrow are used at the same time, it is possible that the harmful effect of <invented name> on the bone marrow will be intensified.

Combination with vinca alkaloids or bleomycin (medicines belonging to the group of cytostatics) can intensify the harmful effect on the lungs.

An increased risk of a particular form of kidney disease (haemolytic-uraemic syndrome) has been reported in patients receiving a concomitant administration of intravenous mitomycin and 5-fluorouracil or tamoxifen.

There are reports from animal experiments that the effect of mitomycin gets lost, if administered together with vitamin B_6.

You should not get vaccinated with live vaccines during mitomycin treatment because this may put you at an increased risk to get infected by the live vaccine.

The harmful effect on the heart of Adriamycin (doxorubicin, a medicine belonging to the group of cytostatics) can be intensified by mitomycin.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Mitomycin can cause inherited genetic damage and can adversely affect the development of an embryo. You must not become pregnant during treatment with mitomycin. If you become pregnant, genetic counselling must be provided.
You should not use mitomycin during pregnancy. Your doctor has to evaluate the benefit against the risk of harmful effects on your child if mitomycin treatment during pregnancy is necessary

Breast-feeding
Mitomycin probably passes into breast milk. Breast-feeding must be discontinued during treatment with <invented name>.

Fertility/Contraception in males and females
As a sexually mature patient you must take contraceptive measures or practise sexual abstinence during chemotherapy and for 6 months afterwards.

Mitomycin can cause inherited genetic damage. As a man treated with mitomycin you are therefore advised not to father a child during treatment and for 6 months afterwards, and to seek advice on sperm conservation before starting treatment due to the possibility of irreversible infertility caused by mitomycin therapy.

Driving and using machines

Even when used in accordance with instructions this medicine may cause nausea and vomiting and thereby reduce your reaction times to such an extent that the ability to drive a motor vehicle or use machines is impaired. This applies in particular if you consume alcohol at the same time.

3. How to use <invented name>

<Invented name> is administered by trained healthcare personnel only.
This medicine is intended to be used for injection or infusion into a blood vessel (intravenous use) or for introduction into the urinary bladder (intravesical instillation) after being dissolved.

Your doctor will prescribe a dose and treatment regimen that is right for you.

Intravenous administration

Before you receive <invented name> as injection or infusion a blood test, check of lung, kidney and liver function is recommended to exclude any diseases that could worsen during mitomycin therapy.

The needle must remain in the blood vessel while <invented name> is being given. If the needle comes out or becomes loose, or the medicine is leaking into the tissue outside the vein (you may feel discomfort or pain) tell the doctor or nurse immediately.

Intravesical administration

<Invented name> is introduced into the bladder at low pressure by means of a catheter. You must empty your bladder before the treatment. The medicine should remain in the bladder for a period of 1 - 2 hours. To allow this, you should not drink too much liquid before, during and after the treatment. While the solution remains in your bladder, it should have sufficient contact with the entire mucosal surface, moving around supports the treatment. After 2 hours you should empty your bladder in a sitting position to avoid spillage.

If you use more <invented name> than you should

If you have been accidentally given a higher dose you may experience symptoms such as fever, nausea, vomiting and blood disorders. Your doctor may give you supportive treatment for any symptoms that may occur.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible side effects following injection or infusion into a blood vessel (intravenous administration)

Severe allergic reaction (symptoms may include faintness, skin rash or hives, itching, swelling of lips, face and airway with difficulty in breathing, loss of consciousness (may affect up to 1 in 10,000 people) may occur.

Severe lung disease presenting as shortness of breath, dry cough and crackles when breathing-in (interstitial pneumonia) as well as severe renal dysfunction (kidney disease where you pass little or no urine) may occur.

If you notice any of the above reactions please inform your doctor immediately because mitomycin therapy must be stopped.

Very common: may affect more than 1 in 10 people
- inhibition of blood cell production in the bone marrow (bone marrow suppression)
- decreased number of white blood cells (leukopenia) increasing the risk of infections
- decreased number of platelets (thrombocytopenia) causing bruises and bleeding
- feeling sick (nausea) and being sick (vomiting)

Common: may affect up to 1 in 10 people
- lung disorder presenting as shortness of breath, dry cough and crackling sounds when breathing in (interstitial pneumonia)
- difficulties breathing (dyspnoea), cough, shortness of breath
- skin rash (exanthema)
- allergic skin rash
- skin rash caused by contact with mitomycin (contact dermatitis)
- numbness, swelling and painful redness of palms and soles (palmar-plantar erythema)
- kidney disorders (renal dysfunction, nephrotoxicity, glomerulopathy, increased levels of creatinine in the blood) where you pass little or no urine

In the event of injection or leakage of mitomycin into the surrounding tissue (extravasation)
- inflammation of connective tissue (cellulitis)
- death of tissue (tissue necrosis)

Uncommon: may affect up to 1 in 100 people
- inflammation of the mucous membranes (mucositis)
- inflammation of the mucous membranes in the mouth (stomatitis)
- diarrhoea
- hair loss (alopecia)
- fever
- loss of appetite

Rare: may affect up to1 in 1,000 people
- life-threatening infection
- blood poisoning (sepsis)
- decrease in number of red blood cells due to an abnormal breakdown of these cells (haemolytic anaemia)
- bruises (purpura) and red and purple dots (petechiae) on the skin (thrombotic thrombocytopenic purpura)
- heart failure (cardiac insufficiency) after previous therapy with anti-cancer medicines (anthracyclines)
- raised blood pressure in the lungs, e,g. leading to shortness of breath, dizziness and fainting (pulmonary hypertension)
- disease involving obstruction of the veins in the lungs (pulmonary veno-occlusive disease, PVOD)
- liver disease (liver dysfunction)
- increased levels of liver enzymes (transaminases)
- yellowing of the skin and whites of the eyes (icterus)
- disease involving obstruction of the veins in the liver (veno-occlusive liver disease, VOD)
- rash over the whole body (generalised exanthema)
- a particular form of kidney failure (haemolytic uraemic syndrome, HUS) characterised by destruction of red blood cells that outpaces your bone marrow’s production (haemolytic anaemia), acute kidney failure, and a low platelet count
- a type of haemolytic anaemia caused by factors in the small blood vessels (microangiopathic haemolytic anaemia, MAHA)

Very rare: may affect up to 1 in 10,000 people
- severe allergic reaction (symptoms may include faintness, skin rash or hives, itching, swelling of lips, face and airway with difficulty in breathing, loss of consciousness)

Not known: frequency cannot be estimated from the available data
- infections
- reduced blood cell count (anaemia)

Possible side effects following instillation in the bladder (intravesical use)

Please inform your doctor immediately if you notice any of the following reactions (which have been observed very rarely following instillation in the bladder), because mitomycin therapy will have to be stopped:
- severe allergic reaction, with symptoms such as faintness, skin rash or hives, itching, swelling of lips, face and airway with difficulty in breathing, loss of consciousness.
- severe lung disease presenting as shortness of breath, dry cough and crackling sounds when breathing in (interstitial pneumonia)
- severe renal dysfunction: kidney disease where you pass little or no urine.

Common: may affect up to 1 in 10 people
- bladder inflammation (cystitis) which may be accompanied by blood in the bladder/urine
- painful urination (dysuria)
- frequent urination at night (nocturia)
- excessive frequent urination (pollakiuria)
- blood in the urine (haematuria)
- local irritation of the bladder wall
- localised skin rash (local exanthema)
- allergic skin rash
- skin rash caused by contact with mitomycin (contact dermatitis)
- numbness, swelling and painful redness of palms and soles (palmar-plantar erythema)

Rare: may affect up to1 in 1,000 people
- rash over the whole body (generalised exanthema)

Very rare: may affect up to 1 in 10,000 people
- bladder inflammation with damage of the bladder tissue (necrotising cystitis)
- allergic (eosinophilic) bladder inflammation (cystitis)
- narrowing (stenoses) of the urinary tract
- reduced bladder capacity
- calcium deposits in the bladder wall (bladder wall calcification)
- partial conversion of bladder wall tissue into connective tissue (bladder wall fibrosis)
- decreased number of white blood cells (leukopenia) increasing the risk of infections
- decreased number of platelets (thrombocytopenia) causing bruises and bleeding
- systemic allergic reactions
- lung disorder presenting as shortness of breath, dry cough and crackling sounds when breathing in (interstitial lung disease)
- increased levels of liver enzymes (transaminases increased)
- hair loss (alopecia)
- feeling sick (nausea) and being sick (vomiting)
- diarrhoea
- kidney disease (renal dysfunction) where you pass little or no urine
- fever

Not known: frequency cannot be estimated from the available data

If mitomycin reaches other regions than the bladder by accident:
- bladder damage
- pocket of pus in the abdomen (abscess)
- death of (fat) tissue (necrosis) of the surrounding area
- vesical fistula

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <invented name>

Keep this medicine out of the sight and reach of children.

Store the vial in the outer carton in order to protect from light.

Do not use this medicine after the expiry date which is stated on the label and carton after "EXP". The expiry date refers to the last day of that month.

After reconstitution this medicine should be used immediately.

Protect the reconstituted solution from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What <invented name> contains
- The active substance is mitomycin.
- The other ingredient is urea.

One vial contains 2 mg (10 mg, 20 mg, 40 mg) mitomycin.

What <invented name> looks like and contents of the pack

<Invented name> is a grey to grey-blue powder for solution for injection or infusion or solution for intravesical use in a vial with a coated rubber stopper and aluminium seal.
Each vial contains 2, 10, 20 or 40 mg of mitomycin.

Each pack of <invented name> contains 1, 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

This medicine is authorised in the Member States of the European Economic Area under the following names:

Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Iceland, Latvia, Lithuania, Norway, Poland, Slovakia:
Mitomycin medac

Italy, Portugal, Spain:
Mitomicina medac

Slovenia:
Mitomicin medac

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

The following information is intended for healthcare professionals only:

Posology

Intravenous administration
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.

It is advised to use this medicinal product at its optimal pH (urinary pH > 6) and to maintain the concentration of mitomycin in the bladder 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.

<u>Reconstitution of the solution for injection or infusion ready for use</u>

Mitomycin 2 mg
Dissolve the contents of one 2 mg vial of <invented name> in 2 ml water for injections by inverting the vial.

Mitomycin 10 mg
Dissolve the contents of one 10 mg vial of <invented name> in 10 ml water for injections by inverting the vial.

Mitomycin 20 mg
Dissolve the contents of one 20 mg vial of <invented name> in 20 ml water for injections by inverting the vial.

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 the 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 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.

Notes
After reconstitution the medicinal product should be used immediately.

Only clear solutions must be used. The content of the vials is for single use/single entry only. Unused solution must be discarded.