PACKAGE LEAFLET: INFORMATION FOR THE USER
<Invented Name> 2 mg/10 mg/20 mg 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 or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any of the side effects , talk to your doctor or pharmacist or nurse. 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

Mitomycin 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. The therapeutic application of medicinal products for the treatment of cancer 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
Mitomycin is used in cancer therapy for the relief of symptoms (palliative cancer therapy).

Intravenous application
When administered intravenously it is used in monochemotherapy, i.e. treatment with only one active substance, or in combined cytostatic chemotherapy, i.e. treatment with several active substances. Mitomycin is effective in the case of the following tumours:
- advanced metastatic stomach cancer (stomach carcinoma)
- advanced and/or metastatic breast cancer (breast carcinoma)
- cancer of the respiratory tract (non-small cell bronchial carcinoma)
- advanced cancer of the pancreas (pancreatic carcinoma)

Intravesical application
Application in the urinary bladder (intravesical application) for the prevention of a relapse in the case of superficial urinary bladder cancer after the ablation of tissue through the urethra (transurethral resection).

2. What you need to know before you use <Invented Name>

Do not use <Invented Name> if you:
- are allergic to mitomycin or any of the other ingredients of this medicine (listed in section 6).
- during breastfeeding
- in the case of systemic administration 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 (leucopenia) or blood platelets (thrombocytopenia), a tendency to bleeding (haemorrhagic diathesis) or acute infections (disease caused by pathogens).
- in the case of **intravesical** administration (application in the urinary bladder) if you have perforation of the bladder wall

Warnings and precautions
Talk to your doctor or pharmacist before using <Invented Name>.

- if you are suffering from impaired lung, kidney or liver function.
- if your general state of health is not good.
- if you are undergoing radiation therapy.
- if you are being treated with other cytostatics (substances which inhibit cell growth/cell division).
- if you have inflammation of the urinary bladder (in case of intravesical administration).
- 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 be worse (especially in elderly and during long term treatment with mitomycin); infection may be aggravated due to bone marrow depression and may lead to fatal conditions
- if you are capable to have a baby as mitomycin may affect your ability to have children in the future.
- if you have bleeding tendency and occurrence of infectious disease.
- if you are immunized with live virus vaccine as this increase risk of infection.

You will be given the treatment under the supervision of a healthcare professional who is experienced in this particular branch of medicine to minimise any unwanted side effects in the injection site.

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

Other medicines and <Invented Name>
Tell your doctor if you are taking or have recently taken any other medicines or might take any other medicines.

Through the additional use of other types of therapy (in particular other anti-cancer medicines, radiation) which also have harmful effects on you, it is possible that the adverse effects of mitomycin will be reinforced.

There are reports from animal experiments that the effect of mitomycin lost, if administered together with Vitamin $B_{6.}$

You should not get vaccinated, especially with live vaccines during mitomycin treatment.

Please note that the above also applies to medications used in the recent past.

Pregnancy, breast-feeding and fertility
Mitomycin should not be used 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.

Women of child-bearing age should avoid becoming pregnant. Contraceptive measures must be taken by both male and female patients during and for at least six months after cessation of therapy. Still, if you become pregnant during this period you must immediately inform your doctor.

Breast-feeding must be discontinued before you start to use mitomycin.

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 operate machinery is impaired. This applies in particular in conjunction with alcohol.

3. How to use <Invented Name>

<Invented Name> should only be administered by healthcare professionals experienced in this kind of therapy. <Invented Name> 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.

Before you receive mitomycin as injection or infusion into a vein a blood test, check of lung, kidney and liver function is recommended to exclude any diseases, which could worsen during mitomycin therapy.

The needle must remain in the vein while mitomycin is being given. If the needle comes out or becomes loose, or the medicinal product is going into the tissue outside the vein (you may feel discomfort or pain) - tell the doctor or nurse immediately.

If you are given 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, please 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 administration into a vein

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 – very rare (may affect up to 1 in 10,000 people).
Severe lung disease presenting as shortness of breath, dry cough and crackles during breath-in (interstitial pneumonia) as well as severe renal dysfunction (nephrotoxicity) 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)
- Blood disorders: Inhibition of blood cell production in the bone marrow; decreased number of white blood cells (leucopenia) increasing the risk of infections; decreased number of platelets (thrombocytopenia) causing bruises and bleedings
- Nausea, vomiting

Common (may affect up to 1 in 10 people)
- Lung disorders presenting as shortness of breath, dry cough and inspiratory crackles (interstitial pneumonia)
- Dyspnoea, cough, shortness of breath
- Skin rashes and irritation of the skin
- Numbness, swelling and painful redness on palms and soles (palmar-plantar erythema)
- Kidney disorders (renal dysfunction, nephrotoxicity, glomerulopathy, increased levels of creatinine in the blood) - the kidneys may not be able to work
- Inflammation of connective tissue (cellulitis) and death of tissue (tissue necrosis) following accidental injection into the surrounding tissue (extravasation)

Uncommon (may affect up to 1 in 100 people)
- Inflammation of a mucous membrane (mucositis)
- Inflammation of the mucosa of the mouth (stomatitis)
- Diarrhoea
- Hair loss (alopecia)
- Fever
- Loss of appetite (anorexia)

Rare (may affect up to 1 in 1,000 people)
- Life-threatening infection
- Blood poisoning (sepsis)
- Decrease in number of red blood cells sometimes together with a acute renal dysfunction (haemolytic anaemia, microangiopathic-haemolytic anaemia (MAHA syndrome), Haemolytic uraemic syndrome (HUS))
- Loss of cardiac function (heart failure) after previous therapy with other anti-cancer medicines (anthracyclines)
- Increase in blood pressure in the vasculature of the lungs, e,g, leading to shortness of breath, dizziness and fainting (pulmonary hypertension)
- Obstructive disease of the pulmonary veins (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)
- Blockage of the small veins in the liver (veno-occlusive disease [VOD] of the liver) leading to fluid retention, increased liver size and raised levels of bilirubin in the blood
- Widespread skin rash

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

Possible side effects following installation in the bladder

Common (may affect up to 1 in 10 people)
- Skin rashes (exanthema, allergic skin rash, contact dermatitis)
- Numbness, swelling and painful redness on palms and soles (palmar-plantar erythrodysaesthesia (PPE)/hand-foot syndrome)
- Bladder inflammation (cystitis) - which may be accompanied with blood in the bladder/urine
- Painful urination, excessive frequent urination sometimes over the night (dysuria, pollakisuria, nocturia)
- Blood in urine (hematuria)
- Local irritation of the bladder wall

Rare (may affect up to 1 in 1,000 people)
- Widespread skin rash

Very rare (may affect up to 1 in 10,000 people)
- Severe inflammation of the bladder where portions of the bladder wall may undergo tissue death (allergic cystitis, necrotizing cystitis)
- Stenosis of the efferent urinary tract
- Reduction in bladder capacity
- Hardening of bladder wall (bladder wall calcification, bladder wall fibrosis)

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 <to be completed nationally>. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store <Invented Name>

Keep out of the sight and reach of children.

<Invented Name> does not require any special storage condition.

Use immediately after reconstitution.

Do not use <Invented Name> after the expiry date which is stated on the label after "Exp Date". The expiry date refers to the last day of that month.

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 to protect the environment.

6. Contents of the pack and other information

What <Invented Name> contains

- The active substance is mitomycin
- The other ingredient is mannitol

The 10 and 20 mg vials are packaged into cartons containing 1 or 5 vials. The 2 mg vials are packaged into cartons containing 1, 5 or 10 vials.

What <Invented Name> looks like and contents of the pack
Mitomycin Powder for Solution for Injection is a powder which is mixed before injection. It is packaged in glass vials with a rubber stopper and aluminium seal.

Marketing Authorisation Holder and manufacturer:

Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom

Manufacturer

Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of the Member State	Name of the medicinal product
Austria	Mitomycin Accord 2 mg/10 mg Pulver zur Herstellung einer Injektions- / Infusionslösung oder Lösung zur intravesikalen Anwendung
Belgium	Mitomycin Accord Healthcare 2 mg/10 mg/20 mg, Pulver zur Herstellung einer Injektions- / Infusions oder intravesikalen Anwendung
Bulgaria	Mitomycin Accord 10 mg/20 mg Powder for solution for Injection/Infusion or Intravesical use
Cyprus	Mitomycin Accord 20 mg Powder for solution for Injection/Infusion or Intravesical use
Czech Republic	Mitomycin Accord 2 mg/10 mg/20 mg prášek pro injekční/infuzní nebo intravezikální roztok
Estonia	Mitomycin Accord
Germany	Mitomycin Accord 2 mg/10 mg/20 mg Pulver zur Herstellung einer Injektions- / Infusionslösung oder Lösung zur intravesikalen Anwendung
Finland	Mitomycin Accord 20 mg Injektio-/infuusiokuiva-aine liuosta varten / virtsarakkoon
France	Mitomycin Accord 10 mg/20 mg, Poudre pour solution injectable / perfusion ou utilisation intravésicale
Iceland	Mitomycin Accord 2 mg/10 mg Stungulyfsstofn , lausn / innrennsli eða notkun í þvagblöðru
Italy	Mitomicina Accord
Malta	Mitomycin 10 mg Powder for solution for Injection/Infusion or Intravesical use
The Netherlands	Mitomycin Accord 2 mg/10 mg/20 mg Poeder voor oplossing voor injectie / infusie of intravesicaal gebruik
Portugal	Mitomicina Accord
Poland	Mitomycin Accord
Spain	Mitomicina Accord 2 mg/10 mg/20 mg Polvo para solución para inyección / infusión o uso intravesical EFG
Slovenia	Mitomicin Accord 20 mg prašek za raztopino za injiciranje/infundiranje ali intravezikalno uporabo
Slovak Republic	Mitomycin Accord 2/10/20 mg
United Kingdom	Mitomycin 2 mg/10 mg/20 mg Powder for solution for Injection/Infusion or Intravesical use

The leaflet was last revised in < to be completed nationally >.

The following information is intended for healthcare professionals only

General Information

It is essential that the injection is administered intravenous. If the medicinal product is injected perivasally, extensive necrosis occurs in the area concerned. To avoid necrosis following recommendations apply:

- Always inject into large veins in the arms.
- Do not directly inject intravenously, but rather into the tube of a good and securely running infusion.
- Before removing the cannula after central venous administration, flush it through for a few minutes using the infusion in order to release any residual mitomycin.

If extravasation occurs, it is recommended that the area is immediately infiltrated with sodium bicarbonate 8.4% solution, followed by an injection of 4 mg dexamethasone. A systemic injection of 200 mg of Vitamin B6 may be of some value in promoting the regrowth of tissues that have been damaged.

Contact with the skin and mucous membranes is to be avoided.

Posology and Method of administration

The recommended dose by intravenous administration is 10-20 mg/m^2 of body surface every 6 – 8 week, 8-12 mg/m^2 of body surface every 3-4 weeks or 5-10 mg/m^2 of body surface every 1-6 weeks. 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.
The recommended dose by intravesical administration is 20-40 mg of mitomycin instilled weekly into bladder for 8 to 12 weeks. 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.

Mitomycin is intended for intravenous injection or infusion or for intravesical instillation after being dissolved.

Intravenous use:

<Invented name> 2, 10, 20 mg, powder for solution for injection/infusion or intravesical use 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.
10 ml for the 10 mg of mitomycin.
20 ml for the 20 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:

<Invented name> 2, 10, 20 mg, powder for solution for injection/infusion or intravesical use may not be reconstituted in water.

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

2 ml for the 2 mg of mitomycin.
10 ml for the 10 mg of mitomycin.
20 ml for the 20 mg of mitomycin.

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

Pregnant healthcare personnel should not handle and/or administer drug product. <Invented Name> 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.

The reconstituted product should be used immediately.

Note:

- <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 intravenous.