SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MITOCIN 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mitomycin 20mg/Vial

For the full list of excipients, see section 6.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion

Mitocin is a grey, lyophilised powder

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Intravenous, intra-arterial (hepatic artery), and local (intraserosal) administration for the treatment of adenocarcinomas of the stomach, pancreas, colon, rectum, breast, and their metastases.

Intravesical administration for the prevention of recurrence in superficial cancer of bladder after transurethral resection.

4.2. Posology and method of administration

Posology and administration

Routes of administration

- Direct intravenous route into the infusion tube or continuous infusion.
- Any extravasation or accidental subcutaneous injection can lead to necrotic complications.
- Intra-arterial route (hepatic artery).
- Local route (intraserosal).
- Intravesical route.

Mode of Administration

A change in solution colour from violet to pink may indicate molecule denaturation. This denaturation can be observed at a pH lower than 6 or in the presence of oxidizing and reducing agents. For this reason, the use of plastic pouch for infusion is discouraged, as well as the combination with other drugs in the infusion vial.

Reconstitution volumes

Injection/infusion administration:

- 40 mL of solvent for 1 vial of 20 mg.
- Concentration: 0.5 mg/mL.
- Solvents: water for injectable preparations.

Intravesical administration:

- 20 mL of solvent for 1 vial of 20 mg.
- Concentration: 1 mg/mL.
- Solvents: 0.9% NaCl solution.

Posology

Administration by injection

Dosages vary depending on the indications and protocols for use.

In endovascular use, the mean total dose per course is 10 to 15 mg/m^2.

The interval between each course is 4 to 8 weeks, with a total dose of 80 mg/m^2.

These mean doses can be increased depending on tolerability and progression.

The frequency of administration varies depending on the nature of the conditions being treated.

In the event of extravasation, the infusion must be discontinued immediately.

Intravesical administration

For intravesical treatment, instillation of 20 to 40 mg mitomycin in sodium chloride solution (0.9%), once weekly, into the bladder.

If administered intravesically, urine pH must be above 6.

Another dosage recommendation in the prevention of recurrent superficial bladder cancer is 4 to 10 mg (0.06 to 0.15 mg/kg body weight) instilled into the bladder through a urethral catheter 1 or 3 times per week.

Paediatric population

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

4.3. Contraindications

This medicinal product is contraindicated in cases of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

This medicinal product is contraindicated:
- in pregnant or breast-feeding women (see section 4.6)
- in combination with:
  - live-attenuated vaccines (see section 4.5)
- in the case of intravesical administration:
  - in patients with perforation of the bladder wall
  - cystitis is a contraindication.

This medicinal product is GENERALLY not recommended in cases of impaired renal function: serum creatinine twice the normal value (see section 4.8) and in combination with phenytoin and olaparib.

4.4. Special warnings and precautions for use

Special warnings

Due to the toxic effects of mitomycin on the bone marrow, other myelotoxic treatments (in particular, other cytostatics, radiotherapy) should be administered with particular caution to minimize the risk of additive myelosuppression.

Handle with care, avoiding contact with skin (see section 6.6).

Traumatic probing of the urethra, even minor, exposes the patient to passage of mitomycin into the periurethral tissues and the risk of necrosis, particularly of the erectile bodies.

In intravesical use, this medicinal product must be administered with caution due to the risk of bladder perforation, which may occur immediately or weeks after injection of the product.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Precautions for use

Systemic use

Regular monitoring of the complete blood count during and after treatment, as well as renal function.

4.5. Interaction with other medicinal products and other forms of interaction

Due to the increased thrombotic risk in tumour disease, anticoagulant treatment is commonly used. The large intra-individual variability of clotting ability during these conditions, combined with the possibility of an interaction between oral anticoagulants and cancer chemotherapy, requires an increase in the frequency of INR monitoring if a decision is made to treat the patient with oral anticoagulants.

Contraindicated combinations

Live-attenuated vaccines

Risk of generalised vaccine disease, potentially fatal.

CONTRAINDICATED during chemotherapy and for 6 months after its discontinuation..

Combinations not recommended

Olaparib

Risk of increased myelosuppressive effect of the cytotoxic agent.

Phenytoin (and, by extrapolation, fosphenytoin)

Risk of seizure occurrence due to decreased gastrointestinal absorption of phenytoin alone by the cytotoxic agent, or a risk of increased toxicity or loss of efficacy of the cytotoxic agent, due to an increase in its hepatic metabolism via phenytoin or fosphenytoin.

Combinations requiring precautions for use

Vitamin K antagonists

Increased thrombotic and haemorrhagic risk in tumour disease. In addition, possible interaction between vitamin K antagonists and chemotherapy.

More frequent INR monitoring.

Combinations to be taken into consideration

Flucytosine

Risk of increased haematological toxicity.

Immunosuppressants

Excessive immunosuppression with risk of lymphoproliferative disorders.

Cytotoxic vinca alkaloids

Risk of increased pulmonary toxicity from mitomycin and vinca alkaloids.

Interactions with other treatment methods which are toxic to bone marrow (particularly other cytotoxic agents and radiotherapy) are possible.

4.6. Fertility, pregnancy and lactation

Contraception in women of childbearing age and in men

Female patients of childbearing age must use a method of contraception during treatment with mitomycin and for up to 6 months after the end of treatment. Men being treated with mitomycin are advised to use a contraception method during treatment and for up to 3 months after the end of treatment.

Pregnancy

There is no data on the use of mitomycin in pregnant women. Animal studies have shown toxicity on reproductive functions (see Section 5.3). Mitomycin has a mutagenic, teratogenic and carcinogenic effect and may therefore harm the development of the fetus. Mitomycin is contraindicated during pregnancy (see Section 4.3). In case of a vital indication for the treatment

of a pregnant patient, a medical consultation must be conducted regarding the risks of harmful effects of the treatment on the unborn child.

Breast-feeding

The data suggests that mitomycin is excreted in breast milk. Due to its mutagenic, teratogenic and carcinogenic effects, mitomycin is contraindicated during breastfeeding (see Section 4.3). Women who are breastfeeding should discontinue breastfeeding before starting treatment with mitomycin.

Fertility

Because of the possibility of irreversible sterility due to mitomycin treatment (see Section 5.3), men should be advised before treatment to consider sperm preservation.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Adverse reactions are listed below according to the MedDRA classification by system organ class. The following terminology is used to classify adverse reactions according to their frequency:

- 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),
- Not known (cannot be estimated from the available data).

Systemic use

Blood and lymphatic system disorders

All 3 lines may be affected, but the platelet line is most often affected. This toxicity is dose-dependent and cumulative. It can manifest either very early during treatment or later on (up to 8 weeks after the last injection). Recovery generally occurs within 6 to 8 weeks.

Very common: myelosuppression, leukopenia, thrombocytopenia.

Gastrointestinal disorders

Common: nausea, vomiting, anorexia, diarrhoea, stomatitis.

These effects are generally moderate.

Skin and subcutaneous tissue disorders

Not known: alopecia, desquamation, pruritus, rash, local necrosis in the event of extravasation, generally occurring a few days after the infusion.

Respiratory, thoracic and mediastinal disorders

Common: diffuse interstitial lung disease, which may progress to fibrosis, must be suspected systematically in the presence of dyspnoea, dry cough or hypoxia.

Very rare: exceptional case of pulmonary arterial hypertension.

Cardiac disorders

Rare: a few rare cases of heart failure have been reported, usually in patients receiving or having received doxorubicin.

Hepatobiliary disorders

Very rare: exceptional cases of hepatic veno-occlusive disease have been reported after administration of high-dose mitomycin, usually followed by autologous bone marrow transplantation.

Not known: elevated liver enzymes, generally moderate.

Renal and urinary disorders

Not known: moderate renal failure or in the context of haemolytic-uremic syndrome (renal failure, haemolytic anaemia, thrombocytopenia, microangiopathy, etc.).

Reproductive system and breast disorders

Not known: azoospermia, amenorrhoea.

Intravesical use

Skin and subcutaneous tissue disorders

Common: pruritus, allergic skin rash, contact dermatitis, exanthema, palmar-plantar erythema,

Rare: exanthema generalised.

Renal and urinary disorders

Common: cystitis (potentially haemorrhagic), dysuria, nocturia, pollakiuria, haematuria, localised irritation of the bladder wall.

Very rare: necrotising cystitis, allergic (eosinophilic) cystitis, lower urinary tract stenosis, reduced bladder capacity, calcification of the bladder wall, fibrosis of the bladder wall, necrosis of the glans and erectile bodies, generally after traumatic probing of the urethra, which can lead to genitourinary sequelae and perforation of the bladder (see section 4.4).

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9. Overdose

In the event of overdose, exaggerated side effects can be expected.

Renal function and complete blood counts must therefore be monitored very closely.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: **other cytotoxic antibiotic,**

(L: Antineoplastic and immunomodulating agents),

ATC code: **L01DC03**.

Cytostatic antineoplastic agent of the antibiotic class, isolated from *Streptomyces caespitosus*.

It has an alkylating effect: DNA adduct formation and particularly marked action in phases G1 and S.

5.2. Pharmacokinetic properties

The decline in blood concentration is relatively rapid (elimination half-life of approximately one hour). Mitomycin is catabolised by the liver.

Its active form is the result of enzymatic reduction; 20% maximum of the dose is found in the urine.

During intravesical treatment, the rate of mitomycin absorption is very limited (1 to 5% of the dose). Nevertheless, a systemic effect cannot be completely excluded.

5.3. Preclinical safety data

In animal studies, mitomycin is toxic to all proliferating tissues, including bone marrow cells and the mucosa of the gastrointestinal tract. Furthermore, it can lead to inhibition of spermatogenesis.

Mitomycin has mutagenic, carcinogenic and teratogenic effects that have been demonstrated in appropriate experimental models.

Local tolerance

Mitomycin causes severe necrosis if injected perivenously or extravasated into surrounding tissues.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol, hydrochloric acid, concentrated and sodium hydroxide for pH adjustment.

6.2. Incompatibilities

To avoid any degradation of mitomycin, do not combine in the infusion bottle with 20% glucose solution, glucose solution containing chlorides of potassium or calcium, FAD, vitamins B1, B6, B12, C and K1, glutathione, adriamycin, ampicillin, cysteine, cystine, L-asparaginase, chromomycin A3, cyclophosphamide, cefalotin, glucuronolactone, gentamycin sulphate, cefaloridine, tetracycline hydrochloride, deslanoside or phytonadione.

Avoid mixing with medicinal substances likely to raise (> 10) or lower (< 5.6) the pH of the resulting solution due to the risk of precipitation, or with substances characterised by the presence of a or several thiol groups.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution, in-use physicochemical stability has been demonstrated at room temperature and upon exposure to light for:

- 1 hour with water for injections
- 2 hours with sodium chloride solution 9 mg/mL (0.9%)

From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Do not store above 25°C.

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

6.5. Nature and contents of container

50 mL amber glass vial, type I, closed with a bromobutyl stopper.

Box of 1 or 5 vials.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

The product must be handled with caution due to the risk of local toxic lesions and allergic reactions.

Handling of this cytotoxic agent by nursing or medical staff requires every precaution to ensure the protection of the handler and his/her environment.

Reconstituted solution:

Shake until the reconstituted solution becomes clear and free of particles.

Use only clear solutions.

The vial contents are for single use.

Unused solutions must be discarded.

Volumes for reconstitution

Injection/infusion use:

- 40 mL solvent per 1 x 20 mg vial.
- Concentration: 0.5 mg/mL.
- Solvents: water for injections.

Intravesical use:

- 20 mL solvent per 1 x 20 mg vial.
- Concentration: 1 mg/mL.
- Solvents: NaCl solution 0.9%.

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

7. MARKETING AUTHORIZATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel.

8. MARKETING AUTHORIZATION NUMBER(S)

175-89-37070-99

Revised in August 2025 according to MOH guidelines