

Package leaflet: Information for the user

BCG-medac 2 x 10⁸ – 1.5 x 10⁹ cfu Powder and solvent for intravesical suspension

(Bacillus Calmette-Guérin)

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 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 BCG-medac is and what it is used for
2. What you need to know before you use BCG-medac
3. How to use BCG-medac
4. Possible side effects
5. How to store BCG-medac
6. Contents of the pack and other information

1. What BCG-medac is and what it is used for

The full name of this medicine is BCG-medac 2 x 10⁸ – 1.5 x 10⁹ cfu Powder and solvent for intravesical suspension. It will be referred to as BCG-medac in the rest of this leaflet.

BCG-medac contains weakened (attenuated) *Mycobacterium bovis* bacteria with low infectious potential.

BCG-medac stimulates the immune system and is used to treat bladder cancer and to prevent bladder cancer from coming back after bladder surgery.

BCG-medac is administered directly into the bladder through a tube.

2. What you need to know before you use BCG-medac

Do not use BCG-medac if

- if you are allergic to viable BCG (Bacillus Calmette-Guérin) bacteria or any of the other ingredients of this medicine, especially polysorbate 80 and polygeline (listed in section 6.).
- you are HIV-positive. You may need to have a blood test for HIV.
- you have problems with your immune system caused by illness (e.g. leukaemia, lymphoma) or other medicines you are taking (e.g. immunosuppressive therapy, such as chemotherapy or corticosteroids).
- you have or think you have TB (tuberculosis).
- you have had radiotherapy to the bladder or adjacent regions.
- you are breast-feeding or pregnant.
- you have had surgery through the urethra (TUR; transurethral resection), a sample of your bladder tissue (bladder biopsy) was taken or you suffered injury by catheter (traumatic catheterisation) during the previous 2 – 3 weeks.
- you have bladder perforation.
- there is visible blood in your urine (macrohaematuria).
- you have a urinary tract infection (UTI) or cystitis (inflammation of the bladder). This must be treated first.

BCG-medac must not be used for administration under or into the skin, into the muscle or vein or for vaccination. It must be administered directly into the bladder by instillation.

Warnings and precautions

Your doctor will give you a patient alert card, which you should always carry with you (see also section 4).

Talk to your doctor or pharmacist before using BCG-medac

- if you have a fever or presence of blood in the urine. Treatment with BCG-medac should be postponed.
- if you have a low bladder capacity as it may decrease even more after the treatment.
- if you are HLA-B27 (human leukocyte antigen B27) positive as the risk of inflammation of the joints could be increased (reactional arthritis).
- if you have arthritis with inflammation of the skin, eyes, and the urinary tract (Reiter's syndrome).
- if you have a localised dilatation of a blood vessel (aneurysm) or prosthesis. You may get an infection of implants or grafts.
- if you have liver problems or take drugs which may affect the liver. This is particularly important if anti-tuberculosis drugs are considered.

General hygiene

After intravesical instillation sit down to urinate to prevent spray of urine to avoid contamination of surrounding area with BCG bacteria.

It is recommended to wash your hands and genital area after urinating. This applies especially to the first urination following BCG treatment. If skin lesions are contaminated, an appropriate disinfectant should be used (ask your doctor or pharmacist).

Detection of Bacillus Calmette-Guérin

The detection of BCG bacteria is generally difficult. A negative test result does not rule out an infection with BCG outside the bladder.

Patients with contact to immunosuppressed persons

If you are treated with BCG-medac you must comply with general hygienic standards as stated above. This is of utmost importance if you are in contact with immunosuppressed persons, as BCG bacteria can be harmful to patients with a weak immune system. However, man-to-man transmission of the bacteria has not been reported yet.

Sexual transmission

Sexual intercourse should be avoided or a condom should be used for one week after BCG therapy to prevent sexual transmission of BCG bacteria.

Other medicines and BCG-medac

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

This is especially important with the following medicines:

- medicines for TB (e.g. ethambutol, streptomycin, p-aminosalicylic acid (PAS), isoniazid (INH) and rifampicin);
- antibiotics (fluoroquinolones, doxycycline or gentamicin);
- medicines which affect the immune system (immune-suppressants);
- chemotherapy or radiotherapy.

Pregnancy, breast-feeding and fertility

Pregnancy

You should not have BCG-medac if you are pregnant or you think you might be pregnant.

Breast-feeding

You should not have BCG-medac when you are breast-feeding.

Fertility

BCG may affect sperm production. Men should seek advice about the possibility of sperm preservation before starting BCG-medac.

Driving and using machines

This medicine could have an effect on your ability to drive or operate machines. Do not drive or operate machinery until you know what effect BCG-medac has on you.

Talk to your doctor, nurse or pharmacist if you are unsure about anything.

3. How to use BCG-medac

Dosage

You will be given BCG-medac by a doctor or nurse.

Administration

Before BCG-medac is given

Do not drink any liquid for 4 hours before the treatment

You will be asked to urinate immediately before BCG-medac is given to you.

Being given your medicine

A small flexible tube (catheter) will be passed into your bladder. This will remove any urine that is still in your bladder.

BCG-medac is then run into your bladder through this tube.

The tube will then be removed.

After it has been given

BCG-medac will be left in your bladder for 2 hours.

During this time you should move around a little. This makes sure that treatment is spread around your entire bladder wall.

Do not drink any liquid for 2 hours after you have been given BCG-medac.

After 2 hours you should empty your bladder in a sitting position to avoid splashing your urine around the toilet.

During the next 6 - 48 hours

If you need to urinate again, also do this while sitting down.

Every time you urinate, add two cups of household bleach to the toilet.

Leave the bleach and urine to stand in the toilet for 15 minutes before flushing

Drink plenty of fluid for 48 hours after each BCG-medac treatment.

How often BCG-medac is given

BCG-medac is given once a week for 6 weeks (induction therapy). After this some people have 'maintenance therapy', where you may be given more doses. Your doctor will talk to you about this.

If you use more BCG-medac than you should

Overdose is unlikely to occur as one vial of BCG-medac corresponds to one dose instilled into the bladder. There are no data indicating that an overdose may lead to any other symptoms than the described side effects (see section 4).

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them. The side effects of BCG treatment are frequent but generally mild and temporary. Adverse reactions usually increase with the number of BCG treatments.

Show your patient alert card to your treating physicians.

The most serious side effect is a severe systemic BCG infection. Tell your doctor immediately if you experience the following symptoms which can occur at any time and are sometimes delayed, and may develop weeks, months or even years after your last dose:

- Fever above 39.5 °C during at least 12 hours or fever above 38 °C lasting for weeks; night sweats
- Weight loss of unknown origin
- Feeling increasingly unwell (e.g. tired, weak or exhausted)
- Signs of inflammation that may present as
 - breathing difficulties, chest pain or a cough,
 - liver problems: a feeling of pressure in right upper abdomen or, liver function test abnormalities (especially an enzyme called alkaline phosphatase), or
 - pain and redness of the eye, vision problems or blurry vision
- swelling of your lymph glands

Systemic BCG infection/reaction

If the bladder is accidentally injured during treatment with BCG or BCG is administered into a muscle or vein this can result in a severe general infection with BCG. Severe systemic BCG infection can lead to BCG sepsis. BCG sepsis is a life-threatening situation. Talk immediately to your physician if you experience a symptom or sign that worries you.

It is importance to carry the alert card with you and show it to the doctors and nurses treating you to ensure appropriate treatment should a delayed BCG infection occur.

Below is a complete list of side effects of BCG-medac:

Very common: may affect more than 1 in 10 people

- Feeling sick (nausea)
- Bladder inflammation (cystitis), inflammatory reactions (granulomata) of the bladder. These side effects may be an essential part of the anti-tumour activity.
- Frequent urination with discomfort and pain. This may affect up to 90% of the patients.
- Inflammatory reactions of the prostate gland (asymptomatic granulomatous prostatitis)
- Temporary systemic BCG reactions such as fever below 38.5 °C, flu-like symptoms (malaise, fever, chills) and general discomfort
- Fatigue

Common: may affect up to 1 in 10 people

- Fever higher than 38.5 °C

- Muscle pain (myalgia)
- Diarrhoea
- Abdominal pain
- Incontinence

Uncommon: may affect up to 1 in 100 people

- Severe systemic BCG reaction/infection, BCG sepsis (see below for more detailed information)
- Deficiency of cells in the blood (cytopenia)
- Anaemia (decrease in haemoglobin in the blood)
- Reiter's syndrome (arthritis with inflammation of the skin, eyes, and the urinary tract)
- Inflammation of the lungs (miliary pneumonitis)
- Inflammatory reactions of the lung (pulmonary granuloma)
- Inflammation of the liver (hepatitis)
- Skin abscess
- Skin rash, joint inflammation (arthritis), joint pain (arthralgia). In most cases, these side effects are signs of an allergic (hypersensitivity) reaction to BCG. In some cases it may be necessary to discontinue treatment.
- Urinary tract infection, presence of blood in the urine (macroscopic haematuria)
- Abnormally small bladder (bladder retraction), abnormally low urine flow (urinary obstruction), bladder contracture
- Inflammation of the testes (orchitis)
- Inflammation of the epididymis (epididymitis)
- Inflammatory reaction of the prostate gland (symptomatic granulomatous prostatitis)
- Low blood pressure (hypotension)
- Abnormal liver function test

Rare: may affect up to 1 in 1,000 people

- Vascular infection (e.g. infected localised dilatation of a blood vessel)
- Kidney abscess

Very rare: may affect up to 1 in 10,000 people

- BCG infection of implants and surrounding tissue (e.g. aortic graft infection, cardiac defibrillator, hip or knee arthroplasty)
- Inflammation of the lymph nodes of the neck (cervical lymphadenitis), regional lymph node infection
- Allergic (hypersensitivity) reaction (e.g. oedema of eyelids, cough)
- Inner eye inflammation (chorioretinitis)
- Conjunctivitis ("pinkeye"), uveitis (inflammation of the uvea of the eye)
- Vascular fistula
- Vomiting, intestinal fistula, inflammation of the peritoneum (peritonitis)
- Infection of bone and bone marrow by bacteria (osteomyelitis)
- Bone marrow infection
- Psoas abscess (abscess of the muscle of the loin)
- Inflammation of the testes (orchitis) or epididymis (epididymitis) resistant to antituberculous therapy
- Infection of the glans penis
- Swelling in your arms or legs

Not known: frequency cannot be estimated from the available data

- Inflammation of the blood vessels (possibly in the brain)
- Genital disorders (e.g. vaginal pain)
- Painful sexual intercourse (dyspareunia)
- Severe immunologic reaction with fever, enlarged liver, spleen and lymph nodes, jaundice and rash (haemophagocytic syndrome)
- Renal failure, inflammation of the kidney tissue, chambers, pelvis (pyelonephritis, nephritis [including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis])
- Absence or low level of sperm in semen (azoospermia, oligospermia)

- Elevation of Prostatic specific antigen (PSA, a prostate laboratory test)

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 Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store BCG-medac

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

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

After reconstitution the product should be used immediately.

6. Contents of the pack and other information

What BCG-medac contains

The active ingredient is viable BCG (Bacillus Calmette-Guérin) bacteria (seed RIVM derived from seed 1173-P2).

After reconstitution one vial contains:

BCG seed RIVM derived from seed 1173-P2, viable units 2×10^8 to 1.5×10^9

The other ingredients of the powder are: polygeline, glucose anhydrous and polysorbate 80.

The other ingredients of the solvent are: sodium chloride and water for injections.

What BCG-medac looks like and contents of the pack

BCG-medac consists of a white or almost white powder or porous cake with shades of yellow and grey and a colourless, clear solution used as solvent. There are packages of 1 or 3 or 5 or 6 vials with or without catheter(s) and connector(s) [conical to Luer Lock]. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

medac

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This leaflet was last revised in 05/2024.

The following information is intended for healthcare professionals only:

Treatment of symptoms, signs and syndrome

Symptoms, signs or syndrome	Treatment
1. Symptoms of vesical irritation lasting less than 48 hours	Symptomatic treatment
2. Symptom of vesical irritation lasting more or equal to 48 hours	Discontinue therapy with BCG-medac and start treatment with quinolones. If after 10 days no complete resolution is observed, administer isoniazid (INH)* for 3 months. In case of antituberculous treatment, therapy with BCG-medac should definitively be discontinued.
3. Concomitant bacterial infection of urinary tract	Postpone BCG-medac therapy until the urinalysis is normalised and treatment with antibiotics is completed
4. Other genitourinary undesirable effects: symptomatic granulomatous prostatitis, epididymitis and orchitis, urethral obstruction and renal abscess	Discontinue therapy with BCG-medac. Consider a consultation with a specialist for infectious diseases. Administer isoniazid (INH)* and rifampicin*, for 3 to 6 months according to severity. In case of antituberculous treatment, therapy with BCG-medac should definitively be discontinued.
5. Fever less than 38.5 °C lasting less than 48 hours	Symptomatic treatment with paracetamol.
6. Cutaneous eruption, arthralgias or arthritis or Reiter's syndrome	Discontinue therapy with BCG-medac. Consider a consultation with a specialist for infectious diseases. Administer antihistaminic or non-steroidal anti-inflammatory drugs. Cortisone therapy should be considered in case of an immune-mediated reaction. If no response, administer isoniazid* for 3 months. In case of antituberculous treatment, therapy with BCG-medac should definitively be discontinued.
7. Systemic BCG reaction/infection** without septic shock signs **see definition systemic BCG reaction	Definitely discontinue treatment with BCG-medac. Consider a consultation with a specialist for infectious diseases. Administer a triple drug antituberculous therapy* for 6 months and low dose corticosteroid therapy.
8. Systemic BCG reaction/infection with septic shock signs	Definitely discontinue treatment with BCG-medac. Administer immediately a triple antituberculous therapy* combined with high-dose, quick-acting corticosteroids. Seek the opinion of a specialist for infectious diseases.

***Caution:** BCG bacteria are sensitive to all antituberculous medicinal products currently used, except for pyrazinamide. If a triple antituberculous therapy is necessary, the combination usually recommended is isoniazid (INH), rifampicin and ethambutol.

Instructions for use/handling

BCG-medac should be administered in the conditions required for intravesical endoscopy.

Handling precautions

BCG-medac should not be handled either in the same room or by the same personnel preparing cytotoxic medicinal products for intravenous administration. BCG-medac should not be handled by a person who presents well-known immunodeficiency.

Spillage of BCG-medac

Spillage of BCG-medac suspension should be treated with a disinfectant with proven activity against mycobacteria, such as household bleach. Spillage on the skin should be treated with an appropriate disinfectant.

Tuberculin cutaneous tests

The intravesical treatment to BCG-medac could induce sensitivity to tuberculin and complicate subsequent interpretation to tuberculin cutaneous tests for mycobacterial infection diagnosis. Therefore, reactivity to tuberculin could be performed before administration of BCG-medac.

Preparation

Administration of the catheter should be done carefully to avoid injuries of the epithelium which may lead to development of systemic BCG infection. Use of a lubricant is recommended to minimize the risk of traumatic catheterisation and to make the procedure more comfortable. Females might need less lubricant than males. It has not been observed that a possible antiseptic effect of the lubricant may influence the efficacy of the product. A draining of the bladder after catheterisation reduces residual lubricant before BCG is applied.

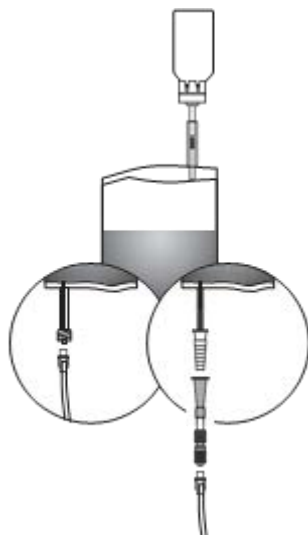
Before use the product has to be resuspended under aseptic conditions with sterile 0.9 % sodium chloride solution (see below). Remix the suspension before use by rotating gently. Avoid skin contact with BCG-medac. The use of gloves is recommended.

Visible macroscopic particles do not affect the efficacy and safety of the product.

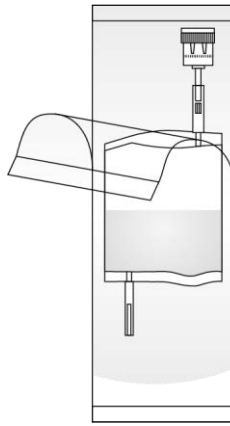
The following handling instructions are used for the system with conical or Luer-Lock adapter. The Luer-Lock adapter may only be used for intravesical instillation (see section 4.4. of the SmPC).

For further information regarding the catheter please see the corresponding instructions for use.

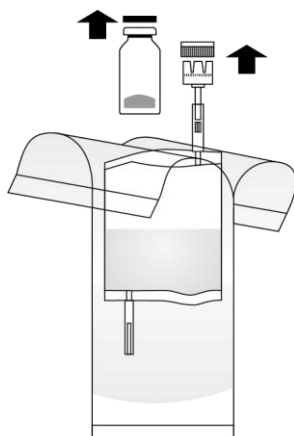
The following instructions apply for the powder and solvent for intravesical solution (instillation set)



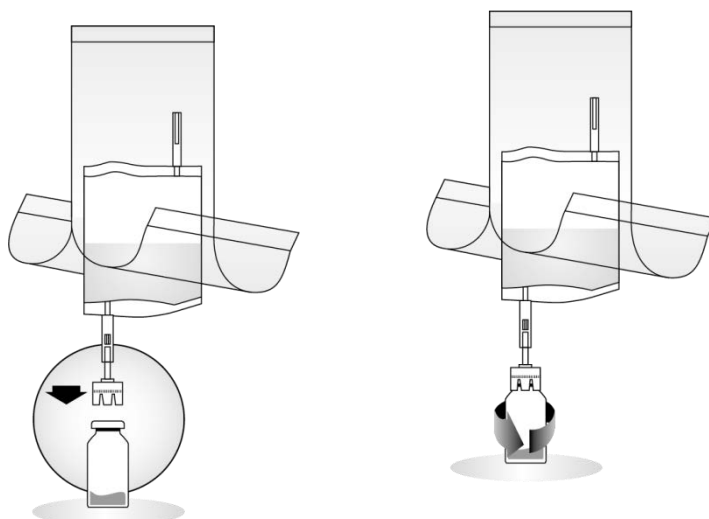
1. Tear open the protective bag but do not remove it completely! This will protect the tip of the instillation system from contamination up to the last minute.



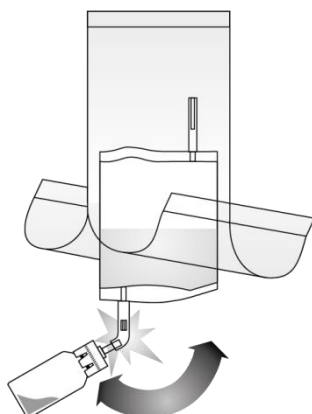
2. Remove the caps of the vial and instillation system. Lay out a disposal bag.



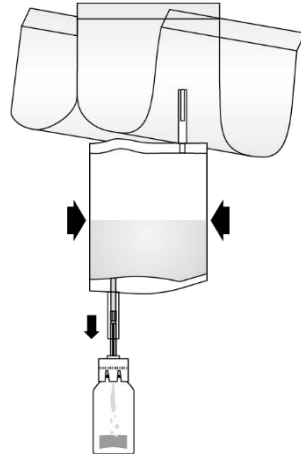
3. Place the BCG-medac vial on a solid surface (e.g. table) and press the vial connector of the instillation system upright and firmly onto the BCG-medac vial. Turn the vial 2 times completely in the same direction.



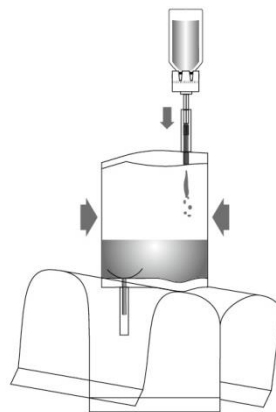
4. Break open the mechanism in the tube of the vial connector by repeated bending backwards and forwards. This establishes the connection. Please hold the tube – and not the vial – during this process!



5. Pump the liquid into the vial, but do not fill the vial completely. If flow is not possible, turn the vial again 2 times in the same direction to assure that the septum is completely penetrated. Repeat this step until flow is possible.



6. Invert the entire system; Pump air from the instillation system into the vial at the top and draw the reconstituted BCG-medac into the instillation system. Do not remove the vial.



7. Keep the instillation system in an upright position. Now remove the protective bag completely. Connect the catheter (and a connector [conical to Luer Lock]) to the instillation system. Now break the sealing mechanism in the tube section bending it back and forth and instil the BCG-medac suspension into the patient's bladder. 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.

