

Package leaflet: Information for the user

BCG-medac, 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, 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 several types of cancer in the urinary bladder. It is effective if the cancer is limited to the cells lining the inside of the bladder (urothelium) and has not invaded the inner tissues of the bladder.

BCG-medac is administered directly into the bladder by instillation.

For the flat lesion form of bladder cancer (carcinoma *in situ*) BCG-medac is used to cure the disease confined to the bladder lining. There are different grades of cancer that can affect the lining of the bladder and the layer of cells next to the lining (lamina propria).

BCG-medac is also used to prevent the cancer coming back (prophylactic treatment).

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

Do not use BCG-medac

- if you are allergic to viable BCG (Bacillus Calmette-Guérin) bacteria or any of the other ingredients of this medicine (listed in section 6.).
- if the activity of your immune system is reduced or you suffer from immune deficiencies, whether due to simultaneous disease (e.g. positive HIV serology, leukaemia, lymphoma), cancer therapy (e.g. cytostatic medicines, radiation) or immunosuppressive therapy (e.g. corticosteroids).
- if you are suffering from active tuberculosis.
- if your bladder or adjacent regions have been treated by radiotherapy before.
- if you are breast-feeding.

- if 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.
- if you have bladder perforation.
- if there is visible blood in your urine (macrohematuria).
- if you suffer from an acute infection of the urinary tract.

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 hands over to 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. Then, 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 you could have an increase of the occurrence of inflammation of the joints (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 triple antibiotic therapy with so-called anti-tuberculosis drugs is considered.

General hygiene

After instillation sit down before urinating to prevent sprinkling of the urine and to avoid contamination of the 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.

Urinary tract infection

Your doctor should determine that you do not have an acute urinary tract infection before each bladder treatment with BCG. If an acute urinary tract infection is diagnosed during BCG-therapy, treatment should be interrupted until the urinalysis is normalised and therapy with antibiotics is completed.

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, a man-to-man transmission of the bacteria has not been reported yet.

Sexual transmission

You should use a condom during sexual intercourse for one week after BCG-therapy to be sure that no sexual transmission of BCG-bacteria happens.

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, as BCG-bacteria are sensitive to:

- antituberculous agents (e.g. ethambutol, streptomycine, p-aminosalicylic acid (PAS), isoniazid (INH) and rifampicin);
- antibiotics (fluoroquinolones, doxycycline or gentamicin);
- antiseptics;
- lubricants.

BCG-bacteria are resistant to pyrazinamide and cycloserine.

Pregnancy, breast-feeding and fertility

Pregnancy

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

Breast-feeding

Do not take BCG-medac when you are breast-feeding.

Fertility

BCG was found to adversely affect the production of sperm and might cause low concentration or absence of sperm in semen. This effect was reversible in animals. However, men should seek advice about the possibility of sperm preservation before starting therapy.

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

BCG-medac is prepared and administered by trained healthcare personnel only. The content of one vial is required for one bladder treatment.

Administration

BCG-medac is introduced into the bladder at low pressure by means of a catheter.

The medicine should remain in the bladder for a period of 2 hours if possible. To allow this, you should not drink over a period of 4 hours before the treatment and for 2 hours after the treatment.

While the suspension 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.

Unless you are on a restricted fluid regimen, you are advised to drink abundantly for 48 hours after each treatment.

Use in children

Safety and efficacy in children have not been established for BCG-medac.

Use in the elderly

There are no special instructions for use in the elderly. However, liver function should be considered before BCG is administered.

Duration of treatment

As a standard treatment schedule (induction therapy) you will receive one intravesical treatment with BCG-medac per week for 6 consecutive weeks. After a period of 4 weeks without treatment you may receive an additional intravesical administration called maintenance therapy for at least one year as described below. Your doctor will talk to you about this.

Induction therapy

- BCG-therapy should begin about 2 – 3 weeks after surgery through the urethra (TUR; transurethral resection) or taking of a bladder tissue sample (bladder biopsy) and without injury by catheter (traumatic catheterisation). It will be repeated at weekly intervals for 6 weeks.
- After this many people get maintenance therapy, where you may be given more doses.

Maintenance therapy

- Maintenance therapy consists of 3 treatments at weekly intervals given for a minimum of 1 year up to 3 years, at month 3, 6, 12, 18, 24, 30, and 36. With this scheme you will receive a total of 15 to 27 treatments during a period of 1 to 3 years.

Your doctor will discuss with you the need for maintenance therapy every 6 months beyond the first year of treatment, if necessary.

Although maintenance therapy reduces the possibility of the cancer coming back and may reduce its ability to progress, the side effects and discomfort of the treatment may outweigh the benefits for some patients. Thus, it is important that your doctor discusses the draw-backs of the treatment and your own preferences with you before beginning or continuing maintenance treatment.

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.

However, the most serious side effect is a severe systemic 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.

Show your patient alert card to your treating physicians.

- 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 poorly
- Signs of inflammation may differ and present as
 - breathing difficulties or a cough that do not feel like a normal cold (miliary pneumonia)
 - 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; “pink eye”
- A so-called granulomatous inflammation which has been shown in a biopsy.

Systemic BCG-infection/reaction

If the bladder is accidentally injured during treatment with BCG medac or BCG medac 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 worry you or contact a physician specialised in infectious diseases! However, the infection is not virulent. Your doctor will prescribe you medicine for your side effects and BCG-treatment may be interrupted.

In contrast to a BCG-infection, a BCG-reaction often presents with low-grade fever, flu-like symptoms and general discomfort for 24 – 48 hours as a starting immune reaction. You doctor may prescribe some medicine to treat the symptoms. Talk to your doctor, if the symptoms worsen.

Delayed BCG-infection

In single cases BCG-bacteria may remain in the body for years. This infection might present at any time and sometimes the symptoms and signs of an infection occur lately, even years after the last dose of BCG medac has been administered. Signs of inflammation could be similar to a severe BCG-infection/reaction like mentioned above. Problems with your implant or graft may also be a side effect of BCG-treatment and require urgent treatment.

Therefore, it is of utmost importance to take your personal alert card with you and hand it over to every doctor treating you to ensure appropriate treatment in case of an occurrence of a delayed BCG-infection. The doctor will also be able to assess if the symptoms are a side effect of your BCG-therapy or not.

In the following, please find a complete list of side effects that may occur:

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

Common: may affect up to 1 in 10 people

- Fever higher than 38.5 °C
- Muscle pain (myalgia)
- Diarrhoea

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)

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

Not known: frequency cannot be estimated from the available data

- 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)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRAs Pharmacovigilance, website: www.hpra.ie. 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.....2 x 10⁸ to 3 x 10⁹ viable units

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 powder and a colourless, clear solution used as solvent. There are packages of 1 or 3 or 5 or 6 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in 05/2020.

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 resolvment 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.

Symptoms, signs or syndrome	Treatment
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 solution should be treated with a disinfectant with proven activity against mycobacteria. 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

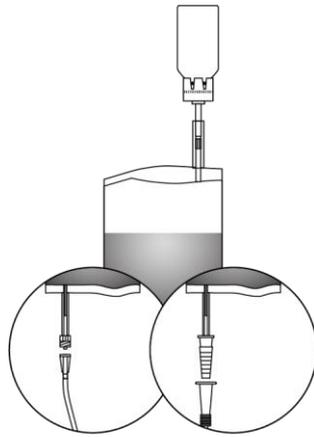
Administration of the catheter should be done carefully to avoid injuries of the epithelium which may lead to development of systemic BCG-infection. Use of a lubricant is recommended to minimise the risk of traumatic catheterisation and to make the procedure more comfortable. Females might need less 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.

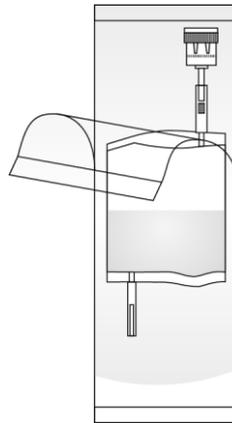
Visible macroscopic particles do not affect the efficacy and safety of the product.

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).

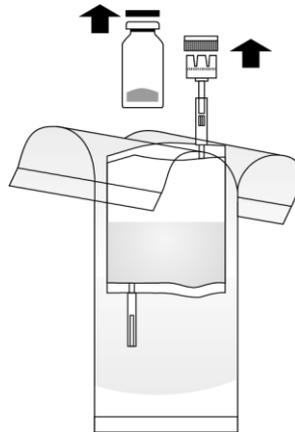
Instructions for use for the solvent for intravesical solution (instillation set)



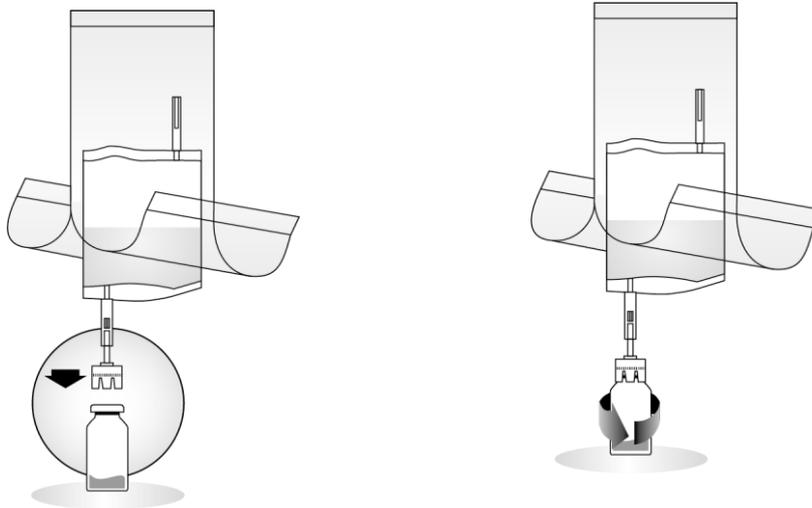
1. Tear open the protective bag but do not remove it completely! This will protect the tip of the instillation system from contamination up to the last minute.



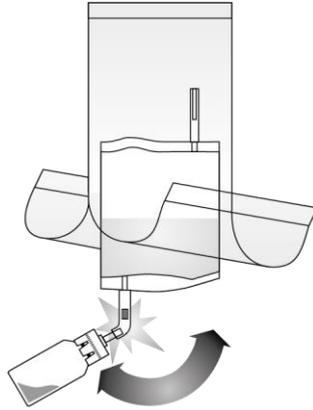
2. Remove the caps from the vial and instillation system. Lay out a disposal bag.



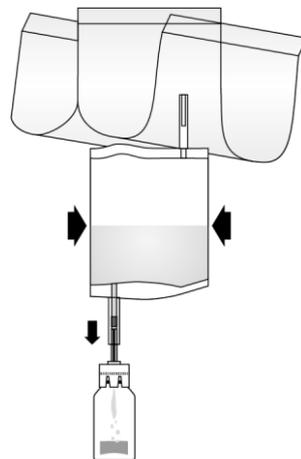
3. Place the BCG-medac vial on a solid surface (e.g. table) and press the adapter of the instillation system upright and firmly onto the BCG-medac vial. Turn the vial 2 times completely in the same direction.



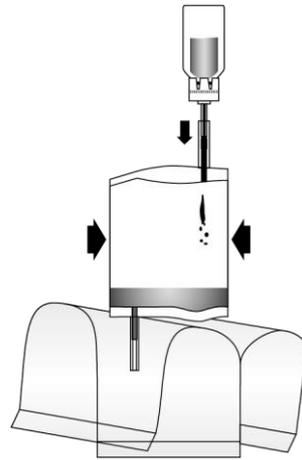
4. Break open the mechanism in the tube of the adapter by repeated bending backwards and forwards. This establishes the connection. Please hold the tube – and not the vial – during this process!



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 completely in the same direction to assure that the septum is completely penetrated. Repeat this step until flow is possible.



- 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.



- Keep the instillation system in an upright position. Now remove the protective bag completely. Connect the catheter to the instillation system. Now break the sealing mechanism in the tube section by bending it back and forth and instil the BCG-medac suspension into the patient's bladder. At the end of the instillation free the catheter by pressing air through. Keep the instillation system squeezed and place it together with the catheter into the disposal bag.

