**Package leaflet: Information for the user**

**BCG-medac, powder and solvent for suspension for intravesical use**

(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 suspension for intravesical use. It will be referred to as BCG-medac in the rest of this leaflet.

BCG 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 BCG 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 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 suffer from an acute infection of the urinary tract.
- if you have bladder perforation.
• if you are suffering from active tuberculosis.
• if you have been treated by radiotherapy before.
• if you are breast-feeding.

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
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.

Systemic BCG infection/reaction
If the instillation of BCG is performed incorrectly or BCG is administered into a muscle or vein this can result in a severe general infection with BCG. It is possible that this results in shock and even death.

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

Persistence of BCG
In single cases BCG bacteria may remain in the urinary tract for more than 16 months.

Patients with immunodeficiency
BCG bacteria can be harmful to patients with a weak immune system. If you are treated with BCG-medac you must comply with general hygienic standards as stated below, particularly when in contact with other patients. A man-to-man transmission has not been reported yet.

Sexual transmission
Sexual transmission of BCG has not been reported yet, but it is recommended to use a condom during sexual intercourse for one week after BCG therapy.

General hygiene
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).

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, breastfeeding 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 and empty your bladder right before the BCG 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, preferably 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**
BCG-medac should not be used in children as safety and efficacy have not been established.

**Use in older people**
There are no special instructions for the use in older people.
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.

Induction therapy (treatment to prevent recurrence of the cancer)
• 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.
• You should receive a maintenance therapy afterwards.

Maintenance therapy
• One schedule consists of a 12 months therapy with treatments at monthly intervals.
• Another maintenance scheme 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. In this scheme you will receive a total of 15 to 27 treatments during a period of three years.

The specified treatment schedules with different BCG strains have been tested in clinical studies carried out in large numbers of patients. At present it is not possible to state whether one or the other of these regimens is superior to the remaining schedule.

Although maintenance therapy reduces the possibility of the cancer coming back and may reduce its progression, 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. 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.

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 (see below for more detailed information)

Common (may affect up to 1 in 10 people)
• Fever higher than 38.5 °C

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)

**Temporary systemic BCG reactions**
Low grade fever, flu-like symptoms and general discomfort may occur. These symptoms usually subside within 24 – 48 hours and should be managed by standard symptomatic treatment. These reactions are signs of a starting immune reaction. All patients receiving the product should be carefully monitored and advised to report all incidences of fever and other events outside the urinary tract.
Systemic BCG reaction/infection
Systemic adverse reactions/infections are defined as: Fever higher than 39.5 °C for at least 12 hours, fever higher than 38.5 °C for at least 48 hours, inflammation of the lung (miliary pneumonia) due to BCG, inflammatory reaction of the liver (granulomatous hepatitis), liver function test abnormalities, organic dysfunction (other than genito-urinary tract) with granulomatous inflammation at biopsy, Reiter’s syndrome (conjunctivitis [“pinkeye”], asymmetrical oligoarthritis [inflammation of 4 or fewer joints], and cystitis [bladder inflammation]). Severe systemic BCG reaction/infection can lead to BCG-sepsis. BCG-sepsis is a life-threatening situation.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.
Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the carton and label after EXP.
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 09/2015.

The following information is intended for healthcare professionals only:

### Treatment of symptoms, signs and syndrome

<table>
<thead>
<tr>
<th>Symptoms, signs or syndrome</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms of vesical irritation lasting less than 48 hours</td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td>2. Symptom of vesical irritation lasting more or equal to 48 hours</td>
<td>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.</td>
</tr>
<tr>
<td>3. Concomitant bacterial infection of urinary tract</td>
<td>Postpone BCG-medac therapy until the urinalysis is normalised and treatment with antibiotics is completed.</td>
</tr>
<tr>
<td>4. Other genitourinary undesirable effects: symptomatic granulomatous prostatitis, epididymitis and orchitis, urethral obstruction and renal abscess</td>
<td>Discontinue therapy with BCG-medac. 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.</td>
</tr>
<tr>
<td>5. Fever less than 38.5 °C lasting less than 48 hours</td>
<td>Symptomatic treatment with paracetamol.</td>
</tr>
<tr>
<td>6. Cutaneous eruption, arthralgias or arthritis or Reiter’s syndrome</td>
<td>Discontinue therapy with BCG-medac. Administer antihistaminic or non-steroidal anti-inflammatory drugs. If no response, administer isoniazid* for 3 months. In case of antituberculous treatment, therapy with BCG-medac should definitively be discontinued.</td>
</tr>
<tr>
<td>7. Systemic BCG reaction/infection** without septic shock signs**</td>
<td>Definitely discontinue treatment with BCG-medac. Consider a consultation with a specialist for infectious diseases. Administer a triple drug antituberculous therapy* for 6 months. **see definition systemic BCG reaction</td>
</tr>
<tr>
<td>8. Systemic BCG reaction/infection with septic shock signs</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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. 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 should be considered to minimize the risk of traumatic catheterisation. 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).
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. Press the BCG-medac vial upright and firmly onto the adapter of the instillation system. Turn the vial 3 – 4 times in both directions.

4. Break open the mechanism in the tube of the adapter by repeated bidirectional bending. This establishes the connection. Please hold the tube – and not the vial – during this process!
5. Pump the liquid into the vial. Please ensure that the vial is not completely filled!

6. Invert the combined system; pump in air with the vial at the top. Draw the reconstituted BCG into the instillation system. Do not remove the vial.
7. Keep the instillation system upright. Now remove the protective bag completely. Connect the catheter adapter to the catheter. Now break open the closure mechanism in the tube by bidirectional bending and instil the drug. At the end of instillation free the catheter by pressing air through. Keep the solvent bag squeezed and place it together with the catheter into the disposal bag.