1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one vial contains:
BCG (Bacillus Calmette Guérin) bacteria seed RIVM derived from seed 1173-P2
……2×10^8 to 3×10^9 viable units

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for intravesical use.

White powder and colourless, clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of non-invasive urothelial bladder carcinoma:

- curative treatment of carcinoma in situ
- prophylactic treatment of recurrence of:
  - urothelial carcinoma limited to mucosa:
    - Ta G1-G2 if multifocal and/or recurrent tumour
    - Ta G3
  - urothelial carcinoma in lamina propia but not the muscular of the bladder (T1)
  - carcinoma in situ

4.2 Posology and method of administration

Dosage
The content of one vial is required for one bladder instillation. Instructions for reconstitution are given under 6.6.

Duration
Carcinoma in situ
A standard treatment schedule consists of one intravesical instillation of BCG-medac per week for six consecutive weeks as induction therapy. BCG treatment must not start until 2 – 3 weeks after transurethral resection (TUR). After a treatment-free interval of 4 weeks intravesical administration should continue using maintenance therapy for at least one year. Maintenance treatment schemes are described below.

Induction therapy (Prophylactic treatment of recurrence)
BCG therapy should begin about 2 – 3 weeks after (TUR) or bladder biopsy, and without traumatic catheterisation, and be repeated at weekly intervals for 6 weeks. In intermediate and high-risk tumours this should be followed by maintenance therapy.

Maintenance therapy
One schedule consists of a 12 months therapy with treatments at monthly intervals. Another maintenance scheme consists of 3 instillations at weekly intervals at month 3, 6, 12, 18, 24, 30, and 36. In this scheme a total of 27 instillations are administered 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.

Administration
BCG-medac should be administered in the conditions required for intravesical endoscopy.
The patient should not drink over a period of 4 hours before the instillation until 2 hours after the instillation. The bladder must be emptied before BCG-instillation. BCG-medac is introduced into the bladder by means of a catheter and at low pressure. The instilled BCG-medac suspension must remain in the bladder for a period of 2 hours if possible. During this period the suspension should have sufficient contact with the entire mucosal surface of the bladder. Therefore the patient should be mobilised as much as possible. After 2 hours the patient should void the instilled suspension by preference in a sitting position.
In case of no specific medical contra-indication, a hyperhydratation is recommended to patient for 48 hours following each instillation.
BCG-medac should not be used in children as safety and efficacy have not been established.
There are no special instructions for the use in elderly.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

BCG-medac should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., positive HIV serology, leukaemia, lymphoma), cancer therapy (e.g., cytostatic drugs, radiation) or immunosuppressive therapy (e.g. corticosteroids).

BCG-medac should not be administered to persons with active tuberculosis. The risk of active tuberculosis must be ruled out by appropriate anamnesis and if indicated by diagnostic tests according to local guidelines.

Past history of radiotherapy of the bladder.

Treatment with BCG-medac is contraindicated in women during lactation (see section 4.6).

BCG-medac must not be instilled before 2 to 3 weeks after a TUR, a bladder biopsy or a traumatic catheterisation.

Perforation of the bladder (see section 4.4).

Acute urinary tract infection (see section 4.4).

4.4 Special warnings and precautions for use

BCG-medac may not be used for subcutaneous, intradermal, intramuscular or intravenous administration or vaccination.

Treatment of symptoms, signs or syndrome
See section 4.8.

Number of BCG instillations
Side effects of BCG-treatment are frequent but generally mild and transient. Adverse reactions usually increase with the number of BCG-instillations.

Severe systemic BCG infection/reaction
Systemic BCG infections/reactions have been rarely reported and are described as fever > 39.5 °C during at least 12 hours, fever > 38.5 °C during at least 48 hours, miliary pneumonia, granulomatous hepatitis, liver function test abnormalities, organic dysfunction (other than genito-urinary tract) with granulomatous inflammation at biopsy, Reiter's syndrome.
The possibility of severe systemic BCG infections has to be considered before starting the therapy.
Traumatic instillation could promote BCG septicaemic events with possible septic shock and potential fatalities.
Urinary tract infection should be excluded before each bladder instillation of BCG (bladder mucous membrane inflammation may increase the risk of haematologic dissemination of BCG). If a urinary tract infection is diagnosed during BCG-therapy, the therapy should be interrupted until the urinalysis is normalised and treatment with antibiotics is completed.
Infection of implants and grafts has been reported in patients with e.g. aneurysm or prosthesis.

Persistence of BCG
There have been single case reports in which BCG bacteria persisted in the urinary tract for more than 16 months.

Fever or gross haematuria
Treatment should be postponed until resolution of concurrent fever or gross haematuria.

Low bladder capacity
The risk of bladder contracture may increase in patients with low bladder capacity.

HLA-B27
Patients with positive HLA-B27 could have an increase of the occurrence of reactional arthritis or Reiter's syndrome.

Handling precautions
BCG-medac should not be handled either in the same room or by the same personnel preparing cytotoxic drugs for intravenous administration. BCG-medac should not be handled by a person who presents well-known immunodeficiency. A contact of BCG-medac with skin and mucosa should be avoided. Contamination can lead to hypersensitivity reaction or infection of the concerned area.

Patients with immunodeficiency
Patients with well-known immunodeficiency must avoid contact with patients under treatment with BCG.

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.

Pregnancy
BCG-medac is not recommended during pregnancy (see section 4.6).

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

General hygiene
It is recommended to wash hands and genital area after micturition. This applies especially to the first micturitions following BCG instillation. If skin lesions are contaminated, we recommend the use of an appropriate disinfectant.

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.

4.5 Interaction with other medicinal products and other forms of interactions

BCG-bacteria are sensitive to antituberculous drugs (e.g. ethambutol, streptomycin, p-aminosalicylic acid (PAS), isoniazid (INH) and rifampicin), antibiotics, antiseptics and lubricants. A resistance against pyrazinamide and cycloserine has been described.

During intravesical BCG instillation therapy, simultaneous administration of antituberculous agents and antibiotics like fluoroquinolones, doxycycline or gentamicin should be avoided due to sensitivity of BCG to those drugs.

4.6 Pregnancy and lactation

Pregnancy (see section 4.4):
There are no adequate data from the use of BCG-medac in pregnant women. Reproductive animal studies are not performed. BCG-medac is not recommended during pregnancy.

Lactation:
There are no adequate data from the excretion of these bacteria in breast milk. This treatment is contra-indicated in nursing women (see section 4.3).

4.7 Effects on ability to drive and use machines

Local or systemic symptoms during therapy with BCG-medac could affect the ability to drive or operate machines.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency and undesirable effect**
Infections and infestations	Very common (> 1/10): Cystitis and inflammatory reactions (granulomata) of the bladder Uncommon (> 1/1,000, < 1/100): Urinary tract infection, orchitis, severe systemic BCG reaction/infection, BCG sepsis, miliary pneumonitis, skin abscess, Reiter's syndrome (conjunctivitis, asymmetrical oligoarthritis and cystitis) Rare (> 1/10,000, < 1/1,000):

System organ class	Frequency and undesirable effect
	Vascular infection (e.g. infected aneurysm), renal abscess Very rare (< 1/10,000): BCG infection of implants and surrounding tissue (e.g. aortic graft infection, cardiac defibrillator, hip or knee arthroplasty), cervical lymphadenitis, regional lymph node infection, osteomyelitis, bone marrow infection, psoas abscess, infection of the glans penis, orchitis or epididymitis resistant to antituberculous therapy
Blood and lymphatic system disorders	Uncommon (> 1/1,000, < 1/100): Cytopenia, anemia
Immune system disorders	Very common (> 1/10): Transient systemic BCG reaction (fever < 38.5 °C, flu-like symptoms including malaise, fever, chills, general discomfort) Very rare (< 1/10,000): Hypersensitivity reaction (e.g. oedema of eyelids, cough)
Eye disorders	Very rare (< 1/10,000): Chorioretinitis, conjunctivitis, uveitis
Vascular disorders	Very rare (< 1/10,000): Vascular fistula
Respiratory, thoracic and mediastinal disorders	Uncommon (> 1/1,000, < 1/100): Pulmonary granuloma
Gastrointestinal disorders	Very common (> 1/10): Nausea Very rare (< 1/10,000): Vomiting, intestinal fistula, peritonitis
Hepatobiliary disorders	Uncommon (> 1/1,000, < 1/100): Hepatitis
Skin and subcutaneous tissue disorders	Uncommon (> 1/1,000, < 1/100): Skin rash
Musculoskeletal and connective tissue disorders	Uncommon (> 1/1,000, < 1/100): Arthritis, arthralgia
Renal and urinary disorders	Very common (> 1/10): Frequent urination with discomfort and pain Uncommon (> 1/1,000, < 1/100): Macroscopic haematuria, bladder retraction, urinary obstruction, bladder contracture
Reproductive system and breast disorders	Very common (> 1/10): Asymptomatic granulomatous prostatitis Uncommon (> 1/1,000, < 1/100): Epididymitis, symptomatic granulomatous prostatitis Not known (cannot be estimated from the available data): genital disorders (e.g. vaginal pain, dyspareunia)
General disorders and administration site conditions	Common (> 1/100, < 1/10): Fever > 38.5 °C Uncommon (> 1/1,000, < 1/100): Hypotension

Side effects of BCG-treatment are frequent but generally mild and transient. Adverse reactions usually increase with the number of BCG-instillations.

In uncommon cases, arthritis/arthralgias, skin rash, may occur. In most cases of arthritis, arthralgias and skin rash, these can be attributed to hypersensitivity reactions of the patient to BCG. It may be necessary in some cases to discontinue the administration of BCG-medac.

Local adverse reactions:
Discomfort and pain when urinating and frequent urination occur in up to 90 % of the patients. The cystitis and inflammatory reaction (granulomata) may be an essential part of the antitumour activity. Further local side effects which are uncommonly observed: macroscopic haematuria, urinary tract infection, bladder retraction, urinary obstruction, bladder contracture, symptomatic granulomatous prostatitis, orchitis and epididymitis. Renal abscess is rarely observed. Furthermore genital disorders (e.g. vaginal pain, dyspareunia) may occur with an unknown frequency.

Transient systemic BCG reaction:
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.

Severe systemic adverse reactions/infections:
Systemic adverse reactions/infections are defined as: Fever > 39.5 °C during at least 12 hours, fever > 38.5 °C during at least 48 hours, miliary pneumonia due to BCG, granulomatous hepatitis, liver function test abnormalities, organic dysfunction (other than genito-urinary tract) with granulomatous inflammation at biopsy, Reiter's syndrome. Severe systemic BCG reaction/infection can lead to BCG sepsis which is a life-threatening situation.

Treatment recommendations see table below.

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 resolvement is observed, administer isoniazid (INH)* for 3 months. In case of antituberculosis 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. Administer isoniazid (INH)* and rifampicin*, for 3 to 6 months according to severity. In case of antituberculosis 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. Administer antihistaminic or non-steroidal anti-inflammatory drugs. If no response, administer isoniazid* for 3 months. In case of antituberculosis treatment, therapy with BCG-medac should definitively be discontinued.

Treatment of symptoms, signs and syndrome	
Symptoms, signs or syndrome	**Treatment**
7) Systemic BCG reaction/infection** without septic shock signs ** see definition systemic BCG reaction/infection	Definitely discontinue therapy with BCG-medac. Consider a consultation with a specialist for infectious diseases. Administer a triple drug anti-tuberculosis therapy* for 6 months.
8) Systemic BCG reaction/infection with septic shock signs	Definitely discontinue treatment with BCG-medac. Administer immediately a triple anti-tuberculosis 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 drugs currently used, except for pyrazinamide. If a triple antituberculosis therapy is necessary, the combination usually recommended is isoniazid (INH), rifampicin and ethambutol.

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. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Overdosage is unlikely to occur as one vial of BCG-medac corresponds to one dose.

There are no data indicating that an overdosage may lead to any other symptoms than the described undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulating agent
ATC Code: L03AX03

BCG-medac is a lyophilised suspension of live Bacillus Calmette-Guérin bacteria derived from Mycobacterium bovis, strain RIVM.

BCG-medac stimulates the immune system and has anti-tumour activity.

Study data suggest that BCG acts as a non-specific immunopotentiator, not by a single mechanism but by a variety of actions involving cells of the immune system. BCG has a stimulating effect on the spleen, enhances macrophage function in the spleen and activates natural killer cells. BCG instillation

stimulates the increase of granulocytes, monocytes/macrophages and T-lymphocytes, indicating local activation of the immune system. Cytokines IL1, IL2, IL6 and TNFα are also increased.

5.2 Pharmacokinetic properties

Most of the bacilli are excreted in the urine in the first hours after the instillation. Whether mycobacteria might be able to pass the intact urothelial wall is still unknown. There have been single case reports in which BCG bacteria persisted in the urinary tract for more than 16 months (see section 4.4).

5.3 Preclinical safety data

BCG strain RIVM was tested for toxicity, immunostimulative properties and antitumour activity in a variety of animals. High doses of BCG caused weight retardation in mice and also liver disturbance was observed. Intravenous injection in rabbits appeared to be pyrogenic. Repeated instillations in guinea pigs induced inflammatory reactions in the bladder wall. As unwanted side effects granulomatous lesions in the liver and lung were present in high doses. Intravesical application in dogs showed minimal mechanical lesions of the urothelium whereas no signs of active inflammation were observed in the suburothelial stroma.
No mutagenicity, carcinogenicity and reproduction studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: polygeline, glucose anhydrous and polysorbate 80.
Solvent: sodium chloride and water for injections.

6.2 Incompatibilities

BCG-medac is incompatible with hypotonic and hypertonic solutions.

6.3 Shelf life

2 years or 3 years when the amount of viable units at release is greater than 5×10^8 cfu/vial, in any case not longer than 4 years from the date of harvest.

After reconstitution the product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a rubber stopper + 50 ml of solvent in a bag (PVC) with a connecting piece and a catheter adapter (conical or Luer-Lock adapter) with or without catheter – pack size of 1, 3, 5 or 6.

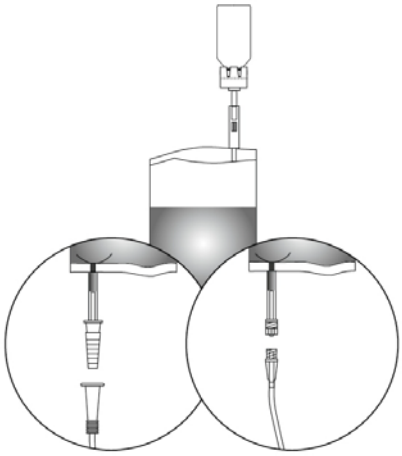
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

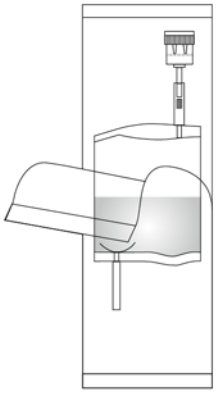
Instructions for use/handling
Before use the product has to be resuspended under aseptic conditions with sterile 0.9 % sodium chloride solution (see below). Remix the suspension before use by rotating gently. Avoid skin contact with BCG-medac. The use of gloves is recommended.

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

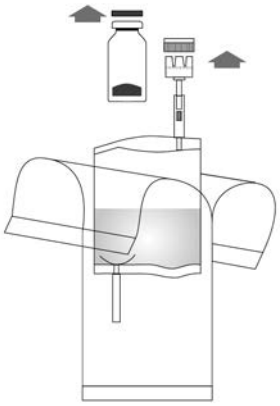
The following handling instructions are used for the system with conical or Luer-Lock adapter.



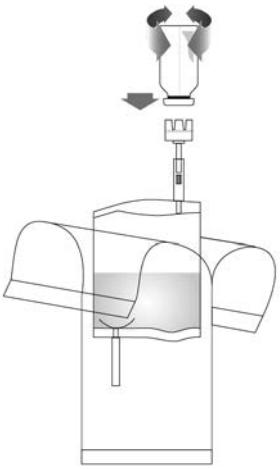
1. Tear open the protective bag but do not remove it completely! This will protect the tip of the instillation system from contamination up to the last minute.



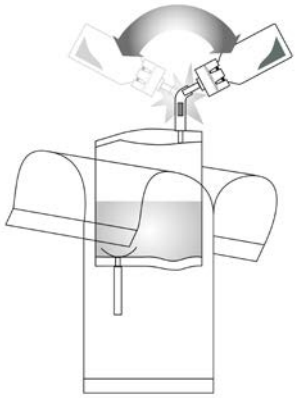
2. Remove the caps of the vial and instillation system. Lay out a disposal bag.



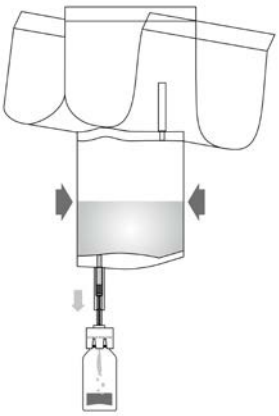
3. Press the BCG-medac vial upright and firmly onto the adapter of the instillation system. Turn the vial 3 – 4 times in both directions.



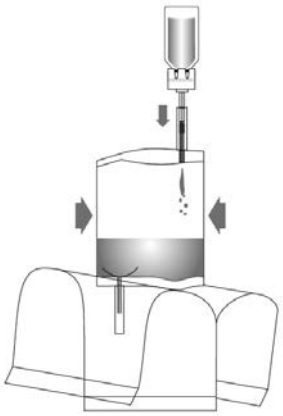
4. Break open the mechanism in the tube of the adapter by repeated bidirectional bending. This establishes the connection. Please hold the tube – and not the vial – during this process!



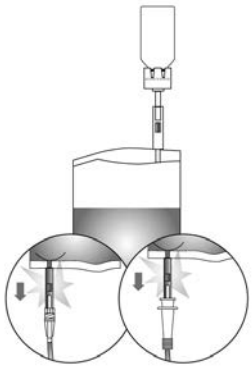
5. Pump the liquid into the vial. Please ensure that the vial is not completely filled!



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 directional 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.



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

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstraße 3
D-20354 Hamburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PA 623/4/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th April 2002
Date of last renewal: 2nd October 2006

10. DATE OF REVISION OF THE TEXT

05/2014