Summary of Product Characteristics

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 the 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 propria but not the muscular of the bladder (T1)
  - carcinoma *in situ*

4.2 Posology and method of administration

Posology
The content of one vial is required for one bladder instillation.

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-month-therapy with treatments at monthly intervals. Another maintenance scheme consists of 3 instillations 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, up to 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.

Although maintenance therapy reduces recurrence and may reduce progression, the side effects and discomfort of the treatment may outweigh the benefits for some patients. Thus, benefit-risk assessment and consideration of patient preferences is important before beginning or continuing maintenance treatment.

Method of 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 contraindication, hyperhydratation of the patient is recommended for the 48 hours following each instillation.

The safety and efficacy of BCG-medac in children have not been established. BCG-medac should thus not be used in this population.

There are no special instructions for use in the elderly.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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 medicinal products, 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 must 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 haematological 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 reactive 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 medicinal products for intravenous administration. BCG-medac should not be handled by a

person who presents with well-known immunodeficiency. 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, however, no man-to-man transmission has been reported yet.

Tuberculin cutaneous tests

The intravesical treatment with BCG-medac could induce sensitivity to tuberculin and complicate subsequent interpretation of tuberculin cutaneous tests for mycobacterial infection diagnosis. Therefore, reactivity to tuberculin should be measured 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, the use of an appropriate disinfectant is recommended.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

During intravesical BCG instillation therapy, simultaneous administration of anti-tuberculous agents and antibiotics like fluoroquinolones, doxycycline or gentamicin should be avoided due to sensitivity of BCG to those medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of BCG in pregnant women. Reproductive animal studies were not performed. BCG-medac is not recommended during pregnancy.

Breastfeeding
There is insufficient information on the excretion of BCG/metabolites in human milk. BCG-medac is contraindicated during breastfeeding (see section 4.3).

Fertility

Intravesical BCG therapy was found to adversely affect spermatogenesis and might cause oligospermia or azoospermia. Animal studies suggest that these effects might be transient and reversible. However, men should seek advice about the possibility of sperm preservation before starting therapy.

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 to < 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 to < 1/1,000): 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 anti-tuberculous therapy
Blood and lymphatic system disorders	Uncommon (≥ 1/1,000 to < 1/100): Cytopenia, anemia Not known (cannot be estimated from the available data): Haemophagocytic syndrome
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 to < 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 to < 1/100): Hepatitis
Skin and subcutaneous tissue disorders	Uncommon (≥ 1/1,000 to < 1/100): Skin rash
Musculoskeletal and connective tissue disorders	Uncommon (≥ 1/1,000 to < 1/100): Arthritis, arthralgia
Renal and urinary disorders	Very common (≥ 1/10): Frequent urination with discomfort and pain Uncommon (≥ 1/1,000 to < 1/100): Macroscopic haematuria, bladder retention, urinary tract obstruction, contracted bladder Not known (cannot be estimated from the available data): Renal failure, pyelonephritis, nephritis (including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis)
Reproductive system and breast disorders	Very common (≥ 1/10): Asymptomatic granulomatous prostatitis Uncommon (≥ 1/1,000 to < 1/100): Epididymitis, symptomatic granulomatous prostatitis Not known (cannot be estimated from the available data): genital disorders (e.g. vaginal pain, dyspareunia), oligospermia, azoospermia
General disorders and administration site conditions	Common (≥ 1/100 to < 1/10): Fever > 38.5 °C Uncommon (≥ 1/1,000 to < 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 and 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 patients. The cystitis and inflammatory reaction (granulomata) may be an essential part of the anti-tumour 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) Symptoms 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 anti-tuberculosis 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 anti-tuberculosis 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 anti-tuberculosis treatment, therapy with BCG-medac should definitively be discontinued.
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 anti-tuberculous medicinal products currently used, except for pyrazinamide. If a triple anti-tuberculosis 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 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.

4.9 Overdose

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 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 with low infectious potential 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, immunostimulatory properties and anti-tumour activity in a variety of animals. High doses of BCG caused weight retardation in mice, and liver disturbance was also 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 observed after 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 x 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 after reconstitution of the medicinal 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).

Pack sizes (conical adapter): 1, 3, 5 or 6 with or without catheter.
Pack sizes (LuerLock adapter): 1 or 3 with or without catheter.

Not all pack sizes may be marketed.

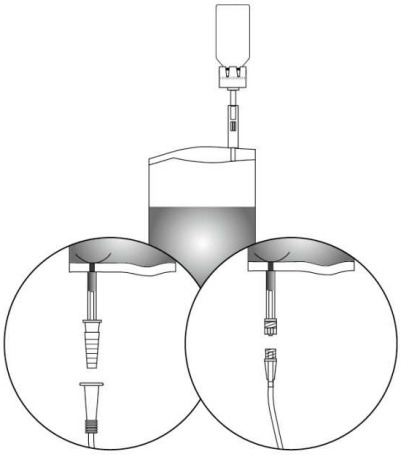
6.6 Special precautions for disposal and other handling

Instructions for use/handling

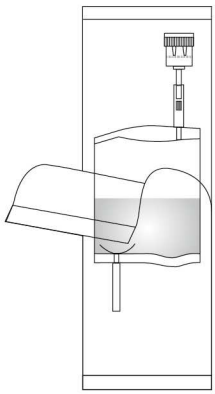
Administration of the catheter should be done carefully to avoid injuries of the epithelium which may lead to development of systemic BCG infection. Use of a lubricant should be considered to minimise the risk of traumatic catheterisation. Females might need less lubricant than males. A draining of the 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.

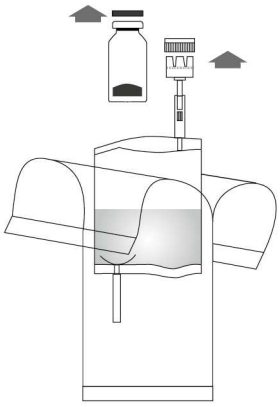
The following handling instructions are used for the system with conical or Luer-Lock adapter.



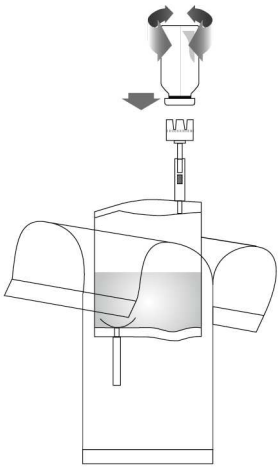
1. Tear open the protective bag but do not remove it completely! This will protect the tip of the instillation system from contamination up to the last minute.



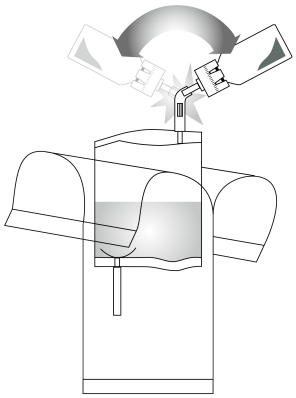
2. Remove the caps of the vial and instillation system. Lay out a disposal bag.



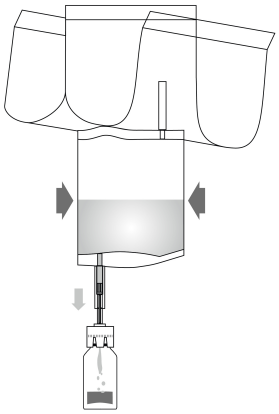
3. Press the BCG-medac vial upright and firmly onto the adapter of the instillation system. Turn the vial 3 – 4 times in both directions.



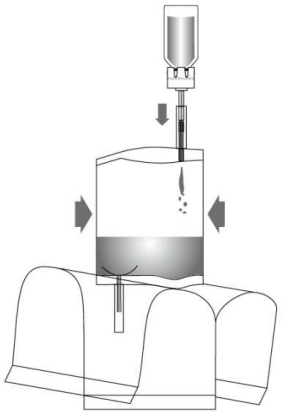
4. Break open the mechanism in the tube of the adapter by repeated bidirectional bending. This establishes the connection. Please hold the tube – and not the vial – during this process!



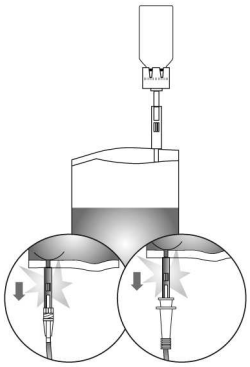
5. Pump the liquid into the vial. Please ensure that the vial is not completely filled!



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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PA 0623/004/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 April 2002
Date of last renewal: 02 October 2006

10. DATE OF REVISION OF THE TEXT

09/2015

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription