

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BCG-medac, powder and solvent for intravesical suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one vial contains:

BCG (Bacillus Calmette-Guérin) bacteria derived from *Mycobacterium bovis*, seed RIVM derived from seed 1173-P2

2 x 10⁸ to 3 x 10⁹ viable units

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for intravesical suspension

Powder:

White or almost white powder or porous cake with shades of yellow and grey

Solvent:

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

BCG-medac must be administered by healthcare professionals experienced in this therapy.

BCG-medac is intended for intravesical use following reconstitution.

For instructions on preparation of the BCG-medac suspension before administration, see section 6.6.

Posology

Adults and the elderly

The content of one vial, resuspended as indicated, is required for one instillation into the urinary bladder.

Induction therapy

BCG-therapy should begin about 2 – 3 weeks after transurethral resection (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 treatment schemes are described below.

Maintenance therapy

Based on clinical studies, maintenance therapy following induction is highly recommended. The recommended 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.

Although maintenance therapy reduces recurrence and may reduce progression, the adverse reactions 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. The need for maintenance treatment every 6 months beyond the first year of treatment should further be evaluated on the basis of tumour classification and clinical response.

Paediatric population

The safety and efficacy of BCG-medac in children have not been established. No data are available.

Method of administration

The patient should not drink over a period of 4 hours before the instillation until 2 hours after the instillation.

A urethral catheter is inserted into the bladder under aseptic conditions. A sufficient quantity of lubricant should be used to reduce the chance of traumatising the urinary mucosa and therefore the risk of severe complications and also to reduce discomfort for the patient associated with the procedure. The bladder must be emptied before BCG-instillation. Complete draining of the bladder after catheterisation reduces residual lubricant which may have reached the bladder before BCG-medac is instilled.

BCG-medac is introduced into the bladder by means of a catheter and at low pressure. The instilled BCG-medac suspension should remain in the bladder for a period of 2 hours. 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 or, in case of a bed-ridden patient, should be turned over from back to abdomen and vice versa every 15 minutes. After 2 hours the patient should void the instilled suspension in a sitting position.

In case of no specific medical contraindication, hyperhydration of the patient is recommended for the 48 hours following each instillation.

Patients treated with BCG-medac should be given the package leaflet and the patient alert card.

4.3 Contraindications

Hypersensitivity to the active substance 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 which might result in an increased risk of severe systemic infections (see section 4.4).

Acute urinary tract infection (see section 4.4). Asymptomatic, isolated leukocyturia and asymptomatic bacteriuria are not contraindications for intravesical therapy with BCG-medac, and antibiotic prophylaxis is not necessary.

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.

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.

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.

General hygiene for the patient

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.

Tuberculin tests

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.

Detection of Bacillus Calmette-Guérin

Physicians should be aware that a negative germ biopsy and negative test results do not rule out a systemic BCG-infection. In several cases germ detection was not successful even though the patient experienced a systemic BCG-infection. The available methods (microscopy, PCR and/or cultures and/or a detection of tuberculosis-compatible histology) are not reliable.

Severe systemic BCG-infections/reactions

Traumatic instillation could promote BCG-septicaemic events with possible septic shock and a life-

threatening situation. For treatment options see section 4.8

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.

The possibility of severe systemic BCG-infections with the necessity of anti-tuberculosis therapy has to be considered before starting the BCG-therapy, especially in elderly patients (see Elderly patients) and patients with hepatic impairment.

Severe systemic BCG-infections/reactions have been reported in less than 5 %. For signs and symptoms please refer to section 4.8.

In case of a suspicion of a systemic infection a physician specialised in infectious diseases should be consulted. BCG-infection can be potentially fatal. For further information please refer to section 4.8.

In contrast to systemic infections, Reiter's syndrome presents as a mainly immuno-mediated reaction, which is not necessarily caused by disseminated BCG but could also be triggered by BCG only localised in the urinary tract system.

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.

Flare-up of latent BCG-infection (including delayed diagnosis)

There have been single case reports in which BCG-bacteria persisted in the body for several years. Those latent BCG-infections might flare-up years after the initial infection, arising especially from granulomatous pneumonitis, abscesses, infected aneurysms, infection of an implant, graft or the surrounding tissue.

The patient has to be made aware of the possibility of late flare-up of latent BCG-infections and educated regarding the actions if symptoms like fever and weight loss of unknown origin occur.

In case of suspicion of a flare-up of latent BCG-infection a physician specialised in infectious diseases should be consulted.

Elderly patients

BCG-administration in elderly patients is not contraindicated. However, the risk of a systemic BCG-infection/reaction should be considered before the first administration is performed. Elderly patients may suffer from renal or hepatic impairment which could have an influence on the treatment with anti-tuberculosis medicinal products in case of severe systemic BCG-infection/reaction. Particular caution should also be exercised in elderly patients with reduced general condition.

Pregnancy

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

Patients with contact to immunosuppressed persons

Patients treated with BCG-medac should employ adequate hygienic measures if in contact with immunosuppressed patients. *M. bovis* is less pathogenic than *M. tuberculosis* and man-to-man transmission has not been reported yet, but it cannot be excluded especially in immunosuppressed

patients.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Breast-feeding

There is insufficient information on the excretion of BCG/metabolites in human milk. BCG-medac is contraindicated during breast-feeding (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

Undesirable effects are listed below by system organ class and frequency. Frequencies below are defined as: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or not known (cannot be estimated from the available data).

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

System organ class	Frequency and undesirable effects
Infections and	<u>Very common</u>

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infestations	<p>Cystitis and inflammatory reactions (granuloma) of the bladder, asymptomatic granulomatous prostatitis</p> <p><u>Uncommon</u></p> <p>Urinary tract infection, orchitis, epididymitis, symptomatic granulomatous prostatitis, severe systemic BCG-reaction/infection, BCG-sepsis, miliary pneumonitis, skin abscess, Reiter's syndrome (conjunctivitis, asymmetrical oligoarthritis and cystitis)</p> <p><u>Rare</u></p> <p>Vascular infection (e.g. infected aneurysm), renal abscess</p> <p><u>Very rare</u></p> <p>BCG-infection of implants and surrounding tissue (e.g. aortic graft infection, cardiac defibrillator, hip or knee arthroplasty), regional lymph node infection, osteomyelitis, bone marrow infection, peritonitis, psoas abscess, infection of the glans penis, orchitis or epididymitis resistant to anti-tuberculous therapy</p>
Blood and lymphatic system disorders	<p><u>Uncommon</u></p> <p>Cytopenia, anaemia</p> <p><u>Very rare</u></p> <p>Cervical lymphadenitis</p> <p><u>Not known</u></p> <p>Haemophagocytic syndrome</p>
Immune system disorders	<p><u>Very common</u></p> <p>Transient systemic BCG-reaction (fever < 38.5 °C, flu-like symptoms including malaise, fever, chills, general discomfort, myalgia)</p> <p><u>Very rare</u></p> <p>Hypersensitivity reaction (e.g. oedema of eyelids, cough)</p>
Eye disorders	<p><u>Very rare</u></p> <p>Chorioretinitis, conjunctivitis, uveitis</p>
Vascular disorders	<p><u>Uncommon</u></p> <p>Hypotension</p> <p><u>Very rare</u></p> <p>Vascular fistula</p> <p><u>Not known</u></p> <p>Vasculitis (including vasculitis of the central nervous system)</p>
Respiratory, thoracic and mediastinal disorders	<p><u>Uncommon</u></p> <p>Pulmonary granuloma</p>
Gastrointestinal disorders	<p><u>Very common</u></p> <p>Nausea</p> <p><u>Common</u></p> <p>Diarrhoea, abdominal pain</p> <p><u>Very rare</u></p> <p>Vomiting, intestinal fistula</p>
Hepatobiliary disorders	<p><u>Uncommon</u></p> <p>Hepatitis</p>
Skin and subcutaneous tissue disorders	<p><u>Uncommon</u></p> <p>Skin rash</p>
Musculoskeletal and connective tissue disorders	<p><u>Common</u></p> <p>Myalgia</p> <p><u>Uncommon</u></p> <p>Arthritis, arthralgia</p>
Renal and urinary	<p><u>Very common</u></p>

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disorders	Frequent urination with discomfort and pain <u>Common</u> Urinary incontinence <u>Uncommon</u> Macroscopic haematuria, bladder retention, urinary tract obstruction, contracted bladder <u>Not known</u> Renal failure, pyelonephritis, nephritis (including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis)
Reproductive system and breast disorders	<u>Not known</u> Genital disorders (e.g. vaginal pain, dyspareunia), oligospermia, azospermia
General disorders and administration site conditions	<u>Very common</u> Fatigue <u>Common</u> Fever > 38.5 °C <u>Very rare</u> Peripheral Oedema
Investigations	<u>Uncommon</u> Hepatic enzyme increased <u>Not known</u> Prostatic specific antigen (PSA) increased

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

In common cases myalgia and 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 adverse reactions 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 medicinal 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

Distinguishing a BCG-infection from a BCG immune reaction poses a challenge, as the symptoms are very similar at the beginning. In contrast to this a transient systemic BCG-reaction is a very common adverse reaction that must be differentiated.

The clinical signs and symptoms of a BCG-infection/reaction at the beginning are fever > 39.5 °C

during at least 12 hours, fever > 38.5 °C during at least 48 hours and worsening of general condition. Typical signs of an infection are the development of miliary pneumonia, granulomatous hepatitis, liver function test abnormalities (especially an elevation in alkaline phosphatase), organic dysfunction (other than genito-urinary tract) with granulomatous inflammation at biopsy over time. In case of a suspicion of a systemic infection a physician specialised in infectious diseases should be consulted. BCG-infection can be potentially fatal.

Although the symptoms of a systemic BCG-infection do not differ from tuberculosis, the patient does not need to be isolated, because *M. bovis* is less pathogenic for humans than *M. tuberculosis*.

In case of a flare-up of a latent infection the patients usually present with symptoms of fever and weight loss of unknown origin. Several case reports show that the diagnosis is challenging as the symptoms vary and a causal relationship with BCG-infection is not suspected by physicians. A correct and early diagnosis and as a consequence, an appropriate treatment is important for the outcome, especially in elderly or debilitated patients, to avoid fatal consequences. **Please note that a patient alert card is available with focus on the topic which has to be handed over to the patient (see also section 4.4).**

In case of suspicion of a flare-up of latent BCG-infection a physician specialised in infectious diseases should be consulted.

The additional use of corticosteroids might be recommended in case of sepsis, granulomatous reactions (e.g. lung or liver) and other immune-mediated reactions.

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	<i>Symptomatic treatment</i>
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. 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 anti-tuberculosis treatment, therapy with BCG-medac should definitively be discontinued.

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7) Systemic BCG-reaction/infection** without septic shock signs	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 and low dose corticosteroid therapy.
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.

** definition see above

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 the national reporting system listed in [Appendix V](#).

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: Immunostimulants, Other immunostimulants, 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.

Mechanism of action

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 TNF α 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 adverse reactions 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 5×10^8 cfu/vial, in any case not longer than 4 years from the date of harvest.

The physical and chemical in-use stability has been demonstrated for 24 hours when stored protected from light at room temperature (20 °C – 25 °C) or refrigerator temperature (2 °C – 8 °C).

From a microbiological point of view, the medicinal product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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 (advanced polypropylene, APP) with a vial connector and a catheter connector, with or without catheter and Luer-Lock to conical connector.

Pack sizes:

- 1, 3, 5 or 6 vial(s), solvent bag(s), Luer-Lock to conical connector(s), with or without catheter(s).
- 1 or 3 vial(s), solvent bag(s), with or without catheter(s).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Important information on the use of BCG-medac

BCG-medac may only be used by experienced healthcare professionals.

Ensure suitable storage (see section 6.4) and the integrity of the packaging.

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

BCG-medac must not be administered subcutaneously, intradermally, intramuscularly, intravenously or for vaccination against tuberculosis.

The Luer-Lock catheter connector of the solvent bag may only be used for intravesical instillation!

Basic principles and protective measures for the use of BCG-medac

In general, direct contact with BCG-medac should be avoided. BCG-medac is a medicinal product that can cause infection in humans and pose a risk to healthcare professionals. A hazard may occur if the medicinal product is able to enter the body via injured skin, if aerosols are inhaled, droplets get into the eyes or come into contact with mucous membranes, or if ingested. Do not eat, drink or smoke in the work areas and do not store any food, drinks or tobacco products here. BCG-medac must not be handled in a room in which cytotoxic medicinal products are being prepared for intravenous use, nor handled by personnel who are preparing cytotoxic medicinal products for intravenous use.

The medicinal product must not be handled by persons with a known immunodeficiency.

It is recommended that closed, splashproof protective gown, disposable gloves, an FFP2 respirator mask and safety goggles with side shields are worn as personal protective equipment during handling. BCG-medac may only be transported in closed containers (for storage conditions after reconstitution, see section 6.3).

After finishing work, wipe down the work surfaces with suitable disinfectant solution. After working and in the case of contact with skin, disinfect your hands using hand disinfectant, allow them to dry, wash them and use skin care products.

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.

Preparation of the reconstituted intravesical suspension

Before use, the medicinal product must be resuspended under aseptic conditions using sterile 0.9% (9 mg/mL) sodium chloride solution (see instructions for use, step 7). The catheter should be placed with special care to avoid injuries to the urethral and urinary bladder epithelium, which can lead to systemic BCG infection. Use of a lubricant is recommended to minimise the risk of traumatic catheterisation and to make the procedure more comfortable. Women might need less lubricant than men. It has not been observed that a possible antiseptic effect of the lubricant may influence the efficacy of the product. Drain the bladder after catheterisation to reduce the amount of lubricant potentially introduced before you administer BCG-medac. The suspension is mixed by gently swirling before use. Macroscopically visible particles have no influence on the efficacy and safety of the medicinal product.

The contents of the vial are intended for single use/single dose only. Any remaining suspension must be disposed of.

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

Behaviour in the event of emergencies and spillage of BCG-medac

Wear protective clothing and avoid stirring up dust.

Cover the spilled BCG-medac suspension with cellulose and moisten it with a disinfectant that is proven to be effective against mycobacteria. After wiping up the spilled BCG-medac suspension,

clean the surface again with disinfectant solution and allow it to dry. Spillage on the skin should be treated using a suitable disinfectant.

First aid

Always consult a doctor in case of contamination.

In case of contact with the skin: remove contaminated clothing. Disinfect and clean the skin and check for contamination of wounds.

In case of contact with the eyes: rinse the affected eye with sufficient eyewash solution or, alternatively, with water. Remove contact lenses if applicable.

In case of ingestion: rinse mouth with plenty of water.

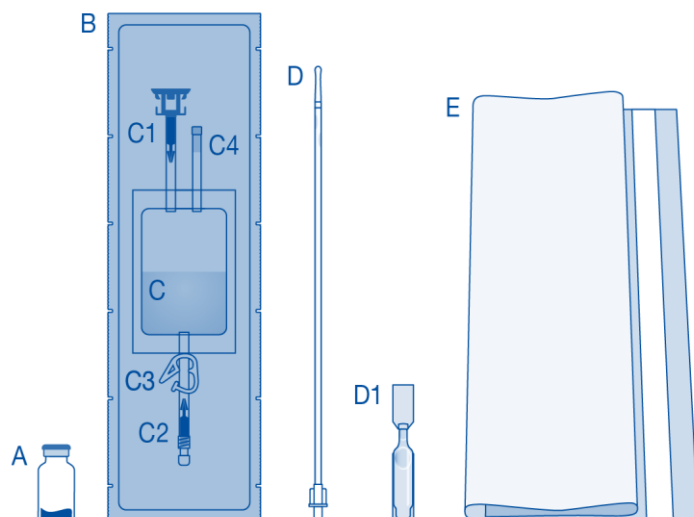
In case of inhalation: ensure a sufficient supply of fresh air.

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

Instructions for users of BCG-medac

Constituents and application of the instillation set |<with catheter, without Luer-Lock to conical connector>

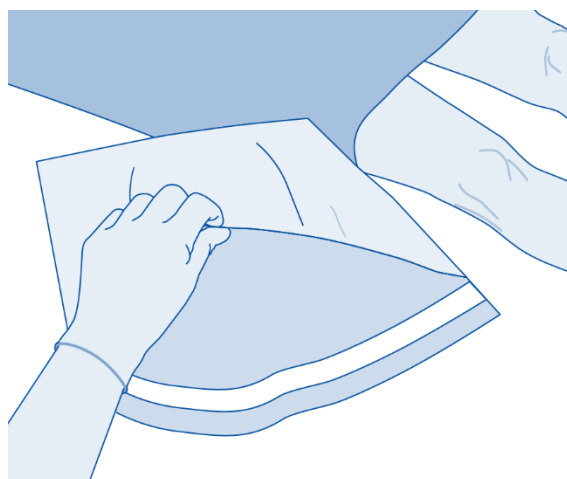
Main constituents of the instillation set



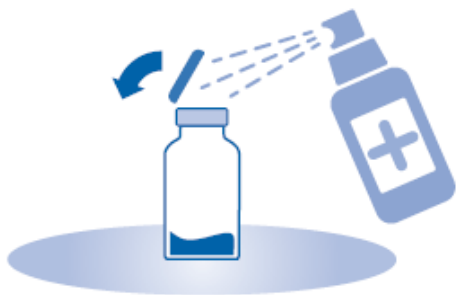
Main constituent	Description
A	Vial with powder
B	Protective cover
C	Solvent bag with 0.9% (9 mg/mL) sodium chloride solution
C1	Vial connector with protective cap and break-open seal
C2	Luer-Lock catheter connector with protective cap and break-open seal
C3	Pressure clamp
C4	Filling port without application function
D	Luer-Lock catheter
D1	Lubricant
E	Disposal bag

Connecting the vial to the solvent bag

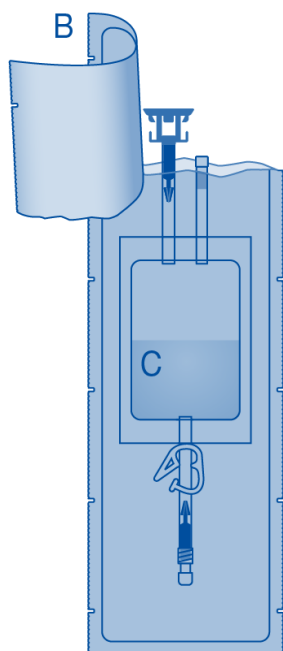
1. Lay out the disposal bag (E) ready for direct disposal of the set after instillation to prevent contamination.



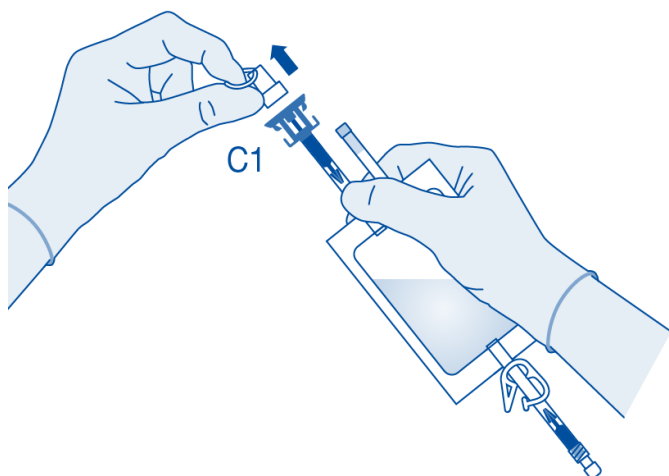
2. Remove the flip-off cap from the vial (A) and disinfect the stopper according to local regulations.



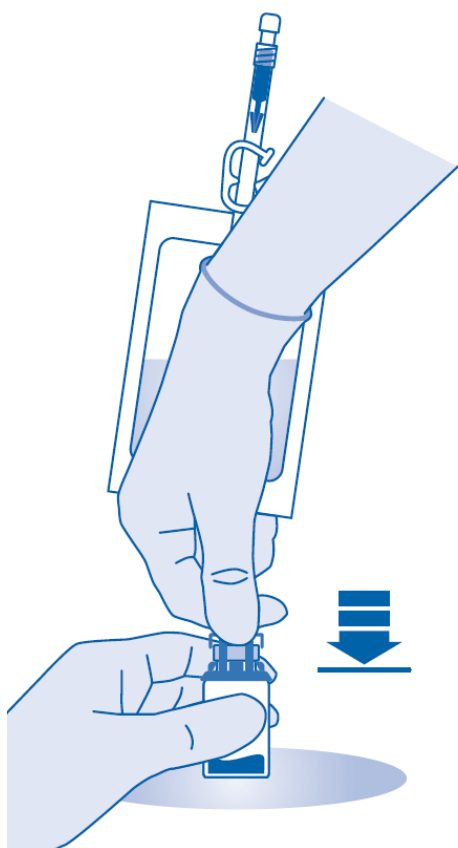
3. Tear open the protective cover (B) of the solvent bag (C) and remove the protective cover completely.



4. Remove the protective cap from the vial connector (C1).

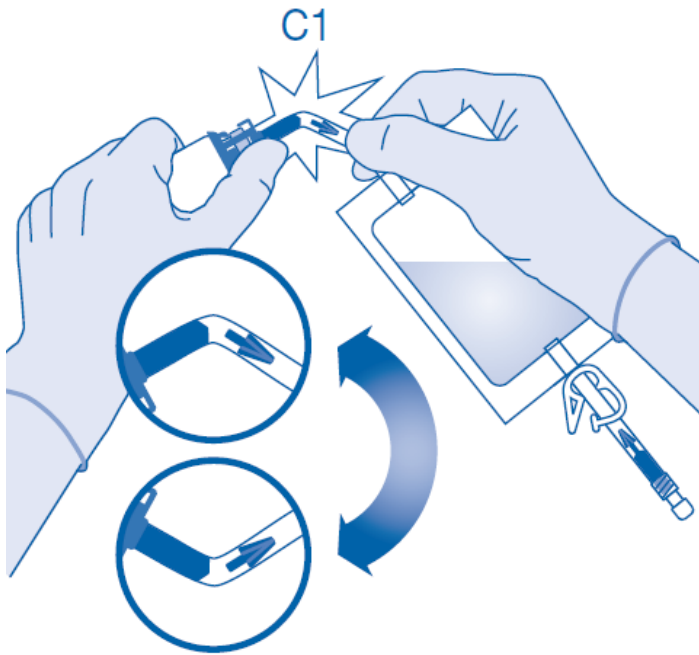


5. Push the connector onto the vial up to the stop.



Mixing the powder with the solvent

6. Bend the break-open seal inside the tube of the vial connector (C1) up and down multiple times to break the seal.



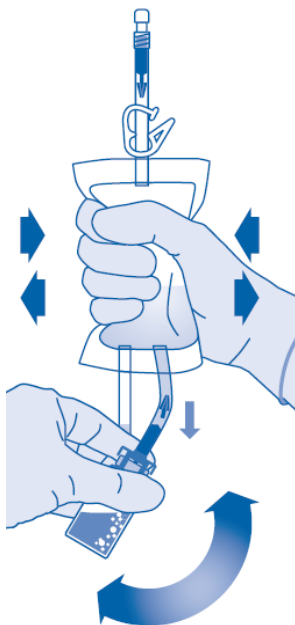
7. Hold the **solvent bag** so that the **vial is below it**.

Squeeze the solvent bag multiple times to transfer enough solvent into the vial.

Make sure that the vial is **not** filled completely to allow for the subsequent transfer of the suspension into the solvent bag. Some solvent may remain inside the bag.

Swirl the vial **slowly** to minimise heavy foaming while mixing the medicinal product with the solvent. If there is a lot of foam, leave the vial to rest briefly (a few minutes).

The contents of the vial have to form a homogeneous suspension. This may take a few minutes.



8. Turn the **solvent bag** upside down and hold it so that the **vial is above it**.

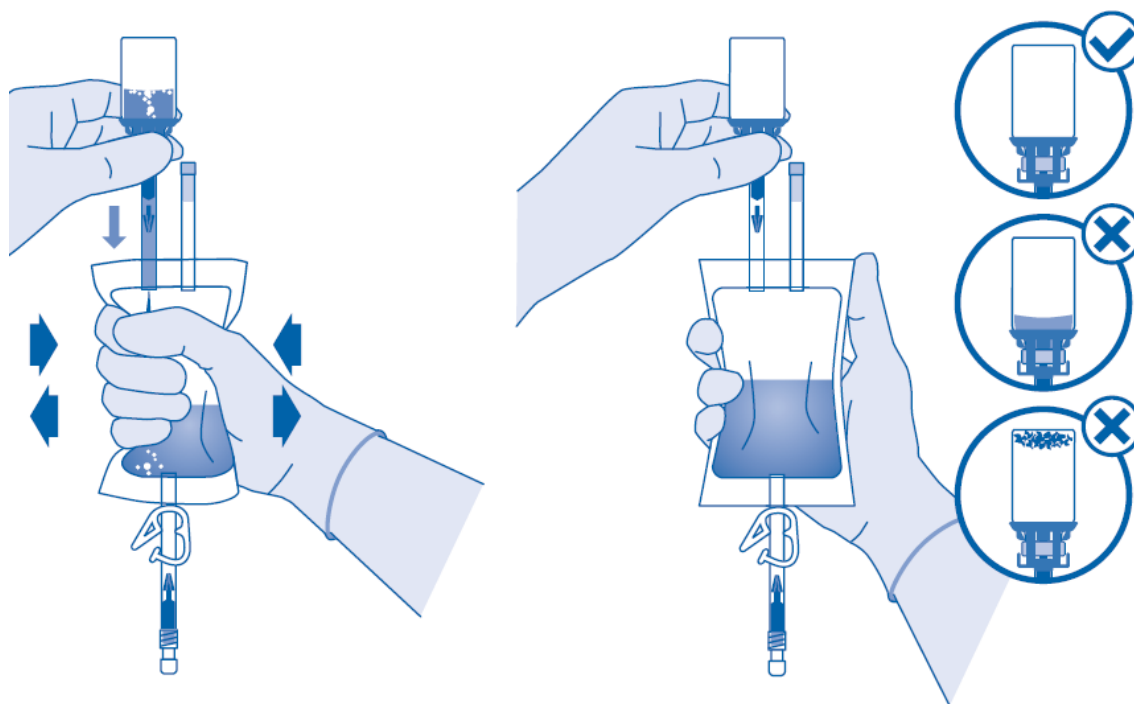
Hold the vial.

Squeeze the solvent bag multiple times until the vial is completely empty.

If any powder remains inside the vial, repeat steps 7 and 8.

From a microbiological point of view the medicinal product should be used immediately. If the medicinal product is not used immediately, please see section 6.3 “Shelf life”.

The suspension should not be instilled at refrigerator temperature in order to prevent the patient from feeling the need to urinate resulting in a shortened exposure time.



Catheterisation

9. Catheterise the patient according to local regulations and the instructions for use using the enclosed Luer-Lock catheter (D) and lubricant (D1) or another suitable catheter and/or lubricant.

Empty the urinary bladder using the catheter.

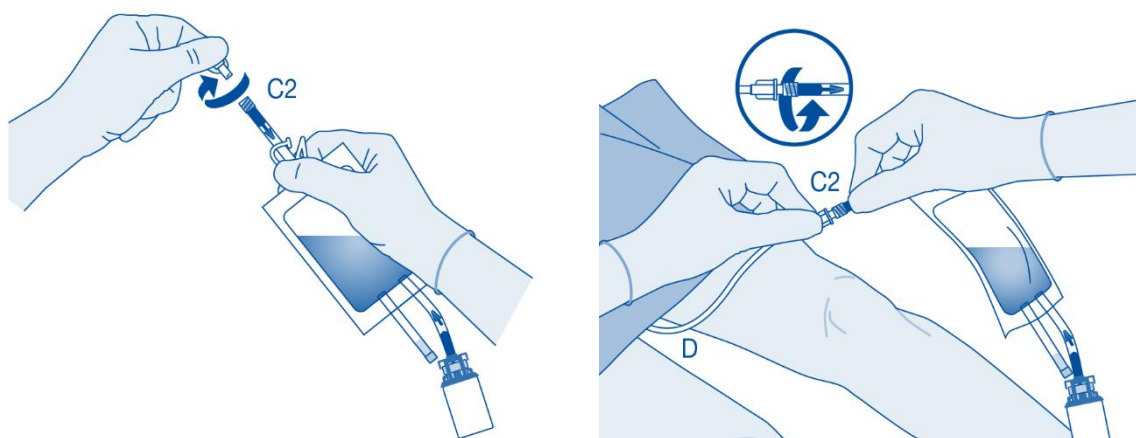
Connecting the catheter to the solvent bag

10. To mix any sediments, rotate and swirl the bag before connecting it.

Do not administer the suspension at refrigerator temperature.

Remove the protective cap from the catheter connector (C2).

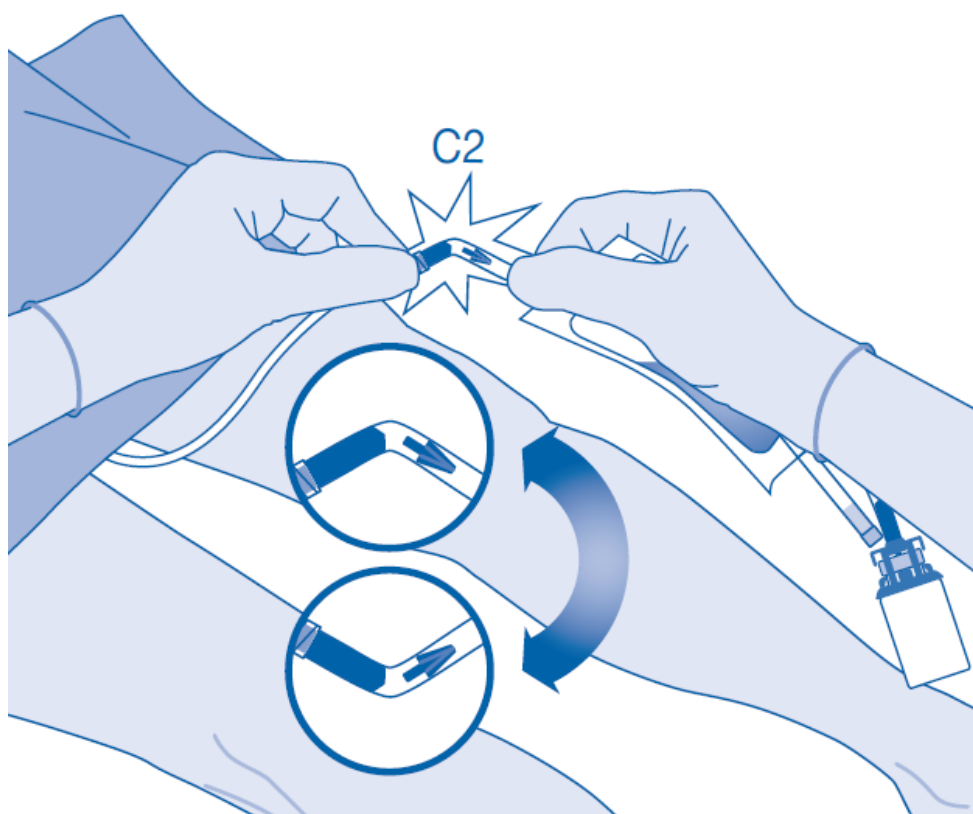
Connect the patient's Luer-Lock catheter (D) with the catheter connector (C2) of the solvent bag.



Instillation

11. Bend the break-open seal inside the tube of the catheter connector (C2) up and down multiple times to break the seal.

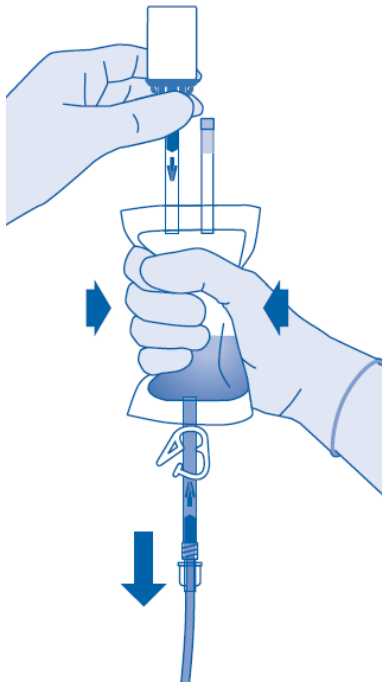
Hold the patient's catheter steady while doing so.



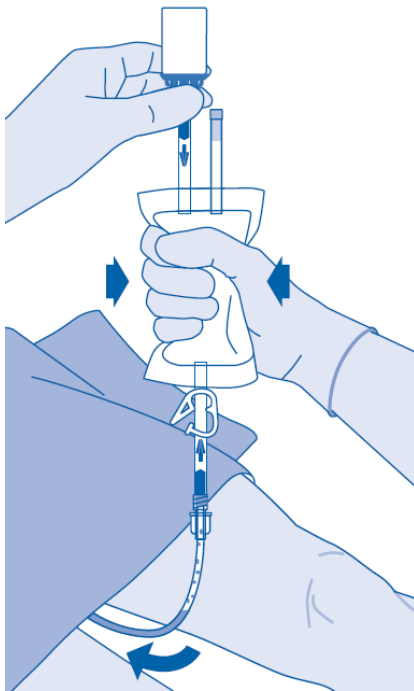
12. Hold the solvent bag with the **vial upside down above the bag**.

Squeeze the solvent bag **gently** with the other hand so that the medicinal product is **slowly** instilled into the patient's urinary bladder.

Continue to squeeze until the solvent bag and the vial are empty.

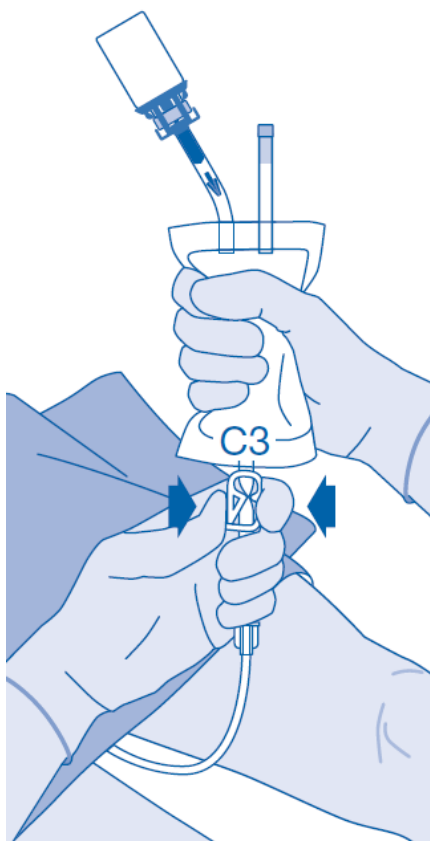


13. Squeeze the remaining air out of the solvent bag to empty the catheter as much as possible.

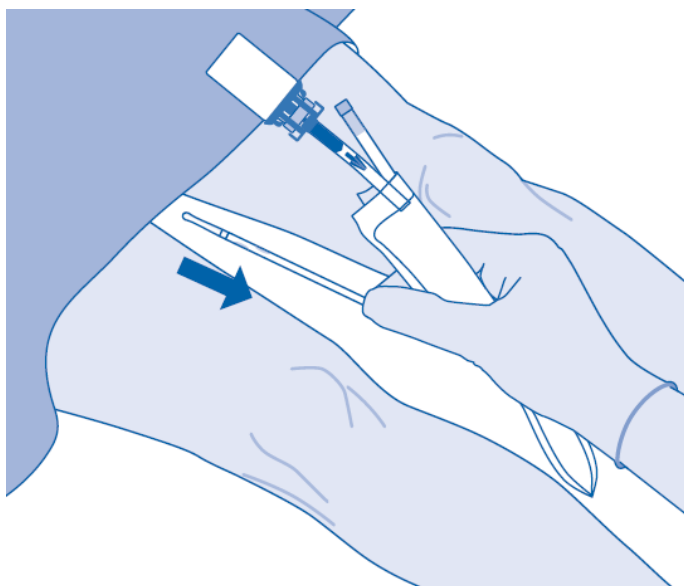


After instillation

14. Closing the pressure clamp (C3) prevents a reflux of fluid into the catheter and minimises the risk of contamination. Alternatively, you can keep the solvent bag compressed while performing steps 15 and 16.

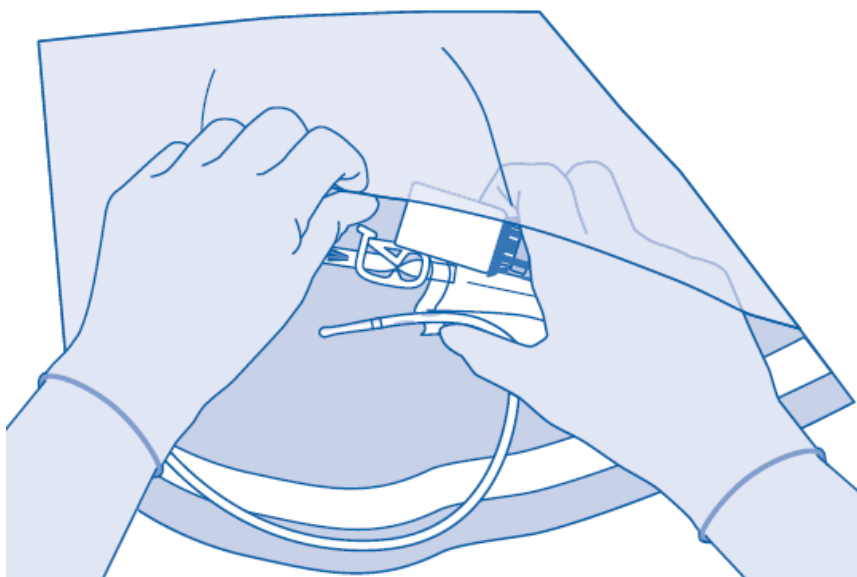


15. Remove the catheter **carefully** from the bladder without disconnecting the solvent bag from the catheter. Avoid contamination from splashing droplets.



16. Dispose of the product according to national regulations using the disposal bag.

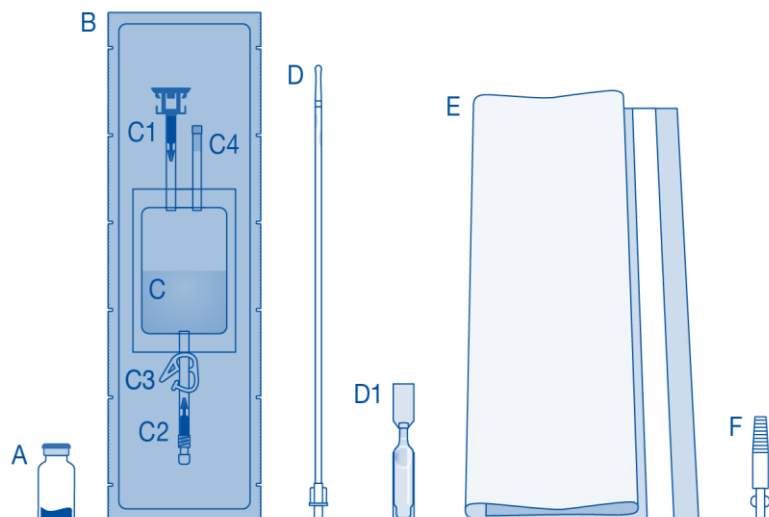
The contents of the vial are intended for single use/single dose only. Any remaining suspension must be disposed of.



Instructions for users of BCG-medac

Constituents and application of the instillation set <with catheter and Luer-Lock to conical connector>

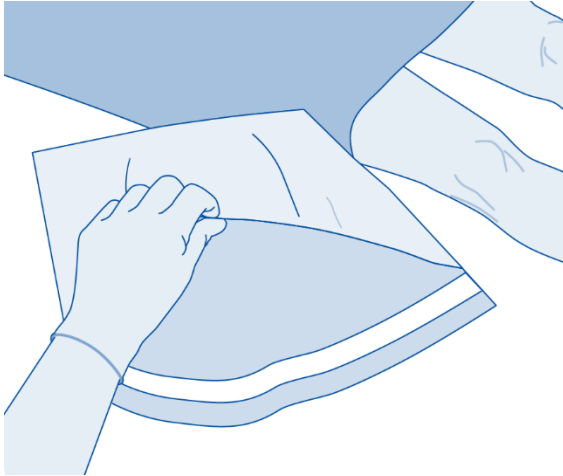
Main constituents of the instillation set



Main constituent	Description
A	Vial with powder
B	Protective cover
C	Solvent bag with 0.9% (9 mg/mL) sodium chloride solution
C1	Vial connector with protective cap and break-open seal
C2	Luer-Lock catheter connector with protective cap and break-open seal
C3	Pressure clamp
C4	Filling port without application function
D	Luer-Lock catheter
D1	Lubricant
E	Disposal bag
F	Luer-Lock to conical connector

Connecting the vial to the solvent bag

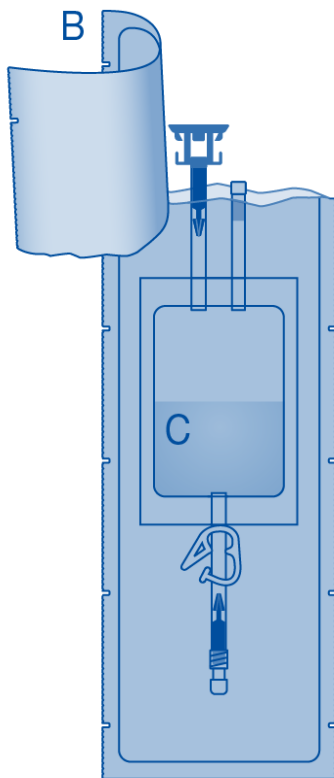
1. Lay out the disposal bag (E) ready for direct disposal of the set after instillation to prevent contamination.



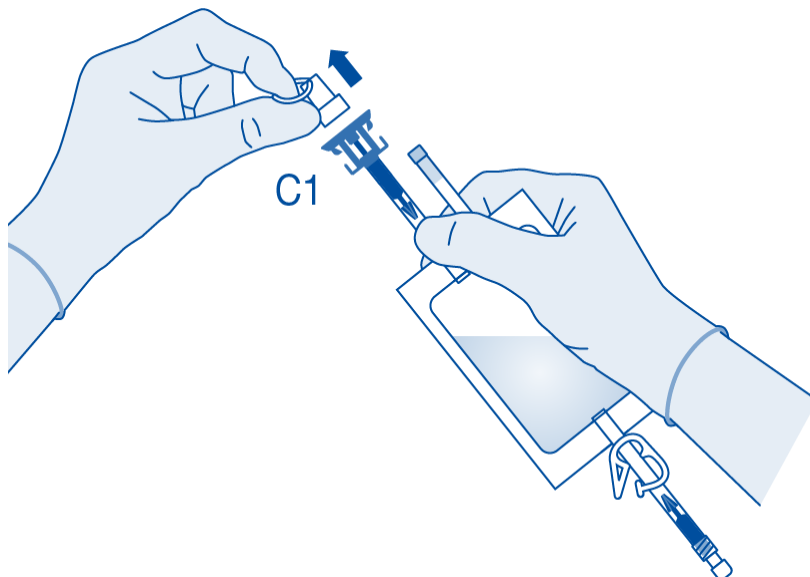
2. Remove the flip-off cap from the vial (A) and disinfect the stopper according to local regulations.



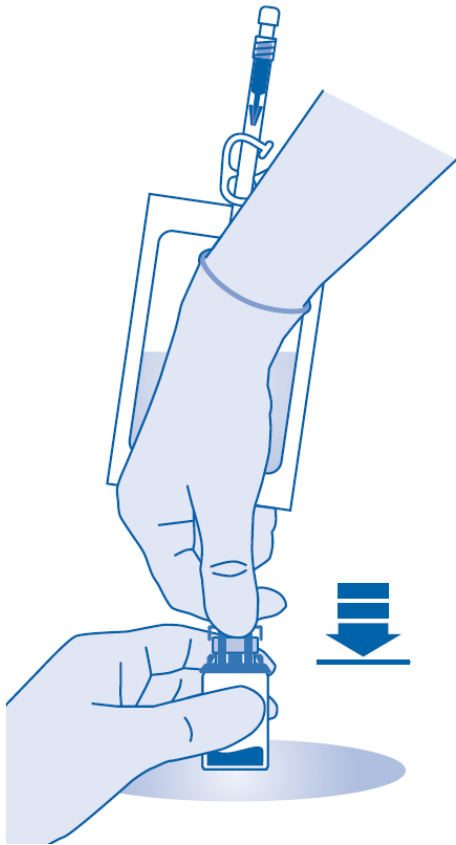
3. Tear open the protective cover (B) of the solvent bag (C) and remove the protective cover completely.



4. Remove the protective cap from the vial connector (C1).

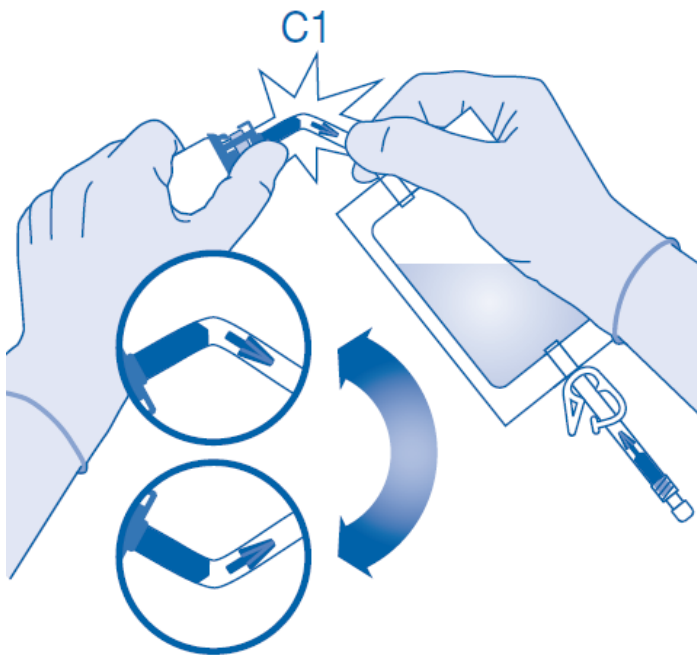


5. Push the connector onto the vial up to the stop.



Mixing the powder with the solvent

6. Bend the break-open seal inside the tube of the vial connector (C1) up and down multiple times to break the seal.



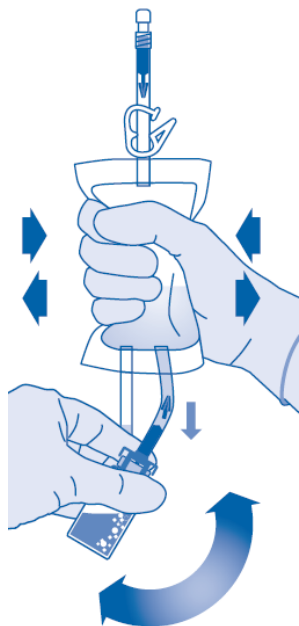
7. Hold the **solvent bag** so that the **vial is below it**.

Squeeze the solvent bag multiple times to transfer enough solvent into the vial.

Make sure that the vial is **not** filled completely to allow for the subsequent transfer of the suspension into the solvent bag. Some solvent may remain inside the bag.

Swirl the vial **slowly** to minimise heavy foaming while mixing the medicinal product with the solvent. If there is a lot of foam, leave the vial to rest briefly (a few minutes).

The contents of the vial have to form a homogeneous suspension. This may take a few minutes.



8. Turn the **solvent bag** upside down and hold it so that the **vial is above it**.

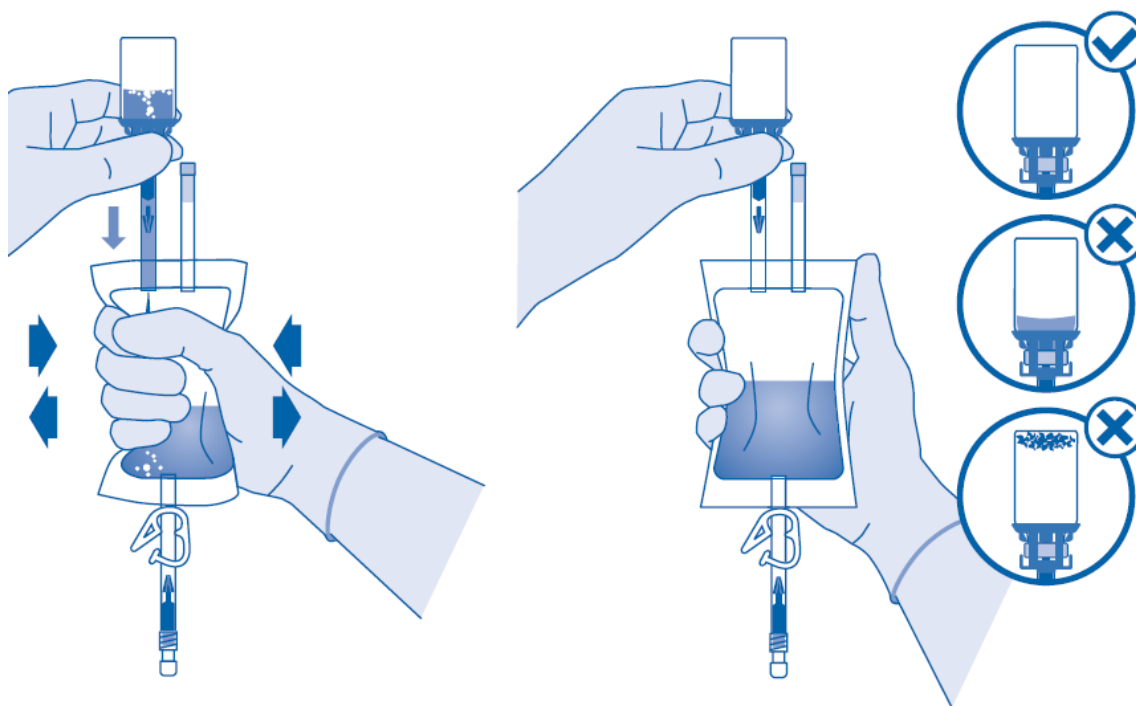
Hold the vial.

Squeeze the solvent bag multiple times until the vial is completely empty.

If any powder remains inside the vial, repeat steps 7 and 8.

From a microbiological point of view the medicinal product should be used immediately.
If the medicinal product is not used immediately, please see section 6.3 “Shelf life”.

The suspension should not be instilled at refrigerator temperature in order to prevent the patient from feeling the need to urinate resulting in a shortened exposure time.



Catheterisation

9. Catheterise the patient according to local regulations and the instructions for use using the enclosed Luer-Lock catheter (D) and lubricant (D1) or another suitable catheter and/or lubricant.

Empty the urinary bladder using the catheter.

Note for use with self-selected catheter with conical connector:

The enclosed Luer-Lock to conical connector (F) must be used to connect the bag to the self-selected catheter (not shown).

To do this, the following additional steps must be carried out:

- Remove the protective cap from the catheter connector (C2, see step 10).
- Rotate and swirl the bag before connecting to remix any sediments.
- Connect the Luer-Lock to conical connector (F) to the catheter connector (C2) of the bag.
- Carefully connect the bag with the connector (F) to the patient's catheter.
- Then proceed with step 11.

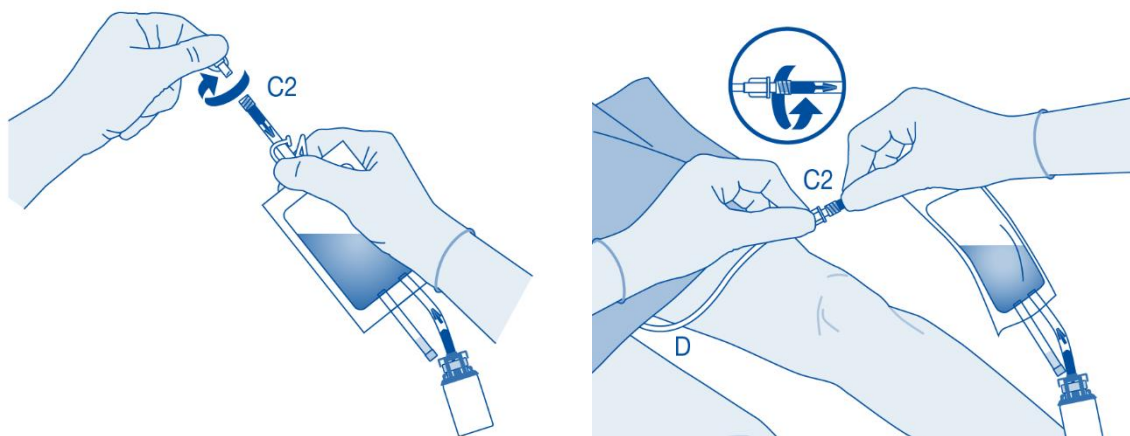
Connecting the catheter to the solvent bag

10. To mix any sediments, rotate and swirl the bag before connecting it.

Do not administer the suspension at refrigerator temperature.

Remove the protective cap from the catheter connector (C2).

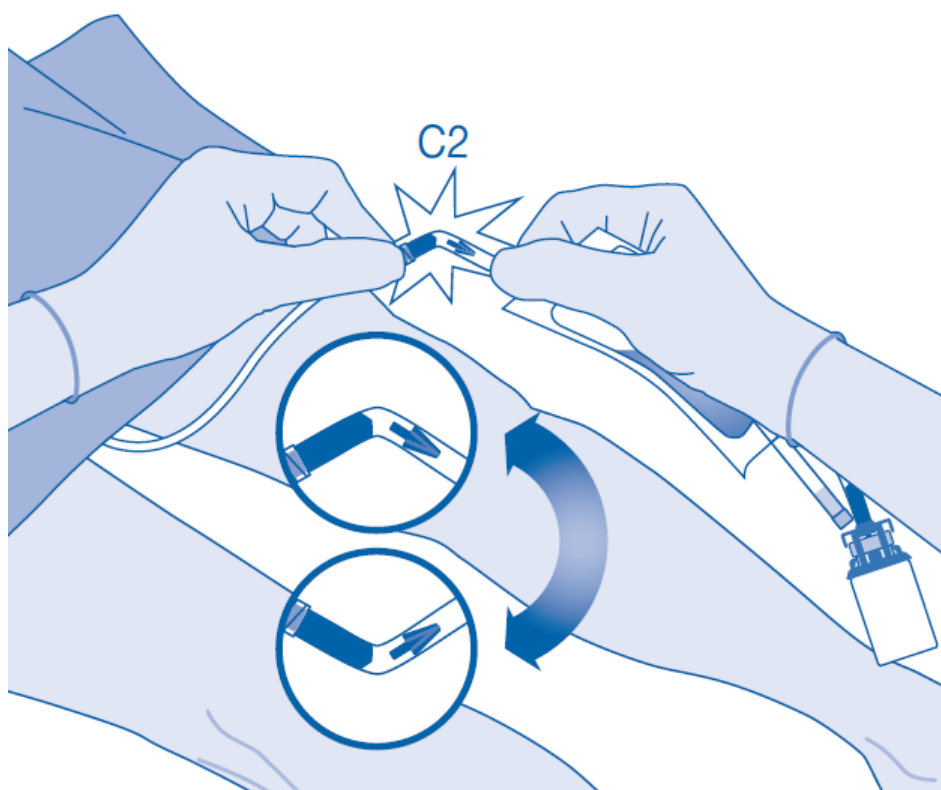
Connect the patient's Luer-Lock catheter (D) with the catheter connector (C2) of the solvent bag.



Instillation

11. Bend the break-open seal inside the tube of the catheter connector (C2) up and down multiple times to break the seal.

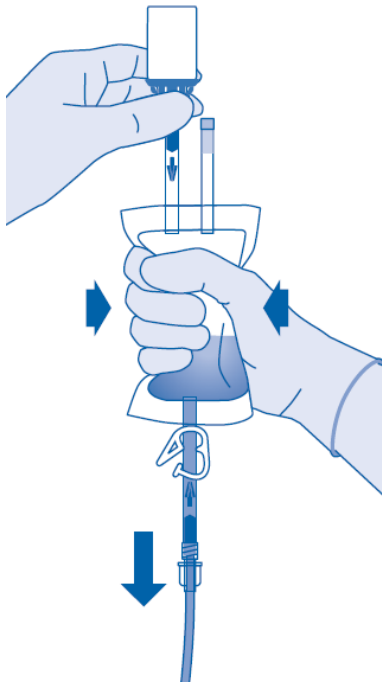
Hold the patient's catheter steady while doing so.



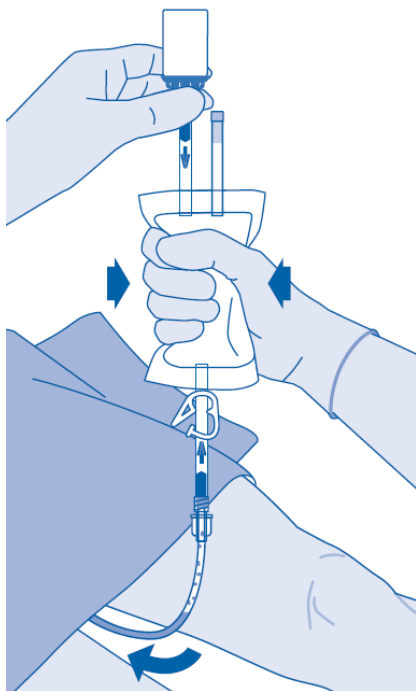
12. Hold the **solvent bag** with the **vial upside down above the bag**.

Squeeze the solvent bag **gently** with the other hand so that the medicinal product is **slowly** instilled into the patient's urinary bladder.

Continue to squeeze until the solvent bag and the vial are empty.

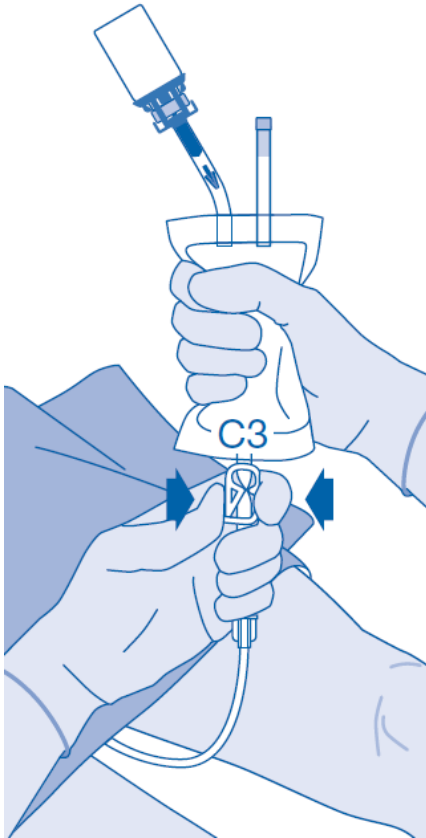


13. Squeeze the remaining air out of the solvent bag to empty the catheter as much as possible.

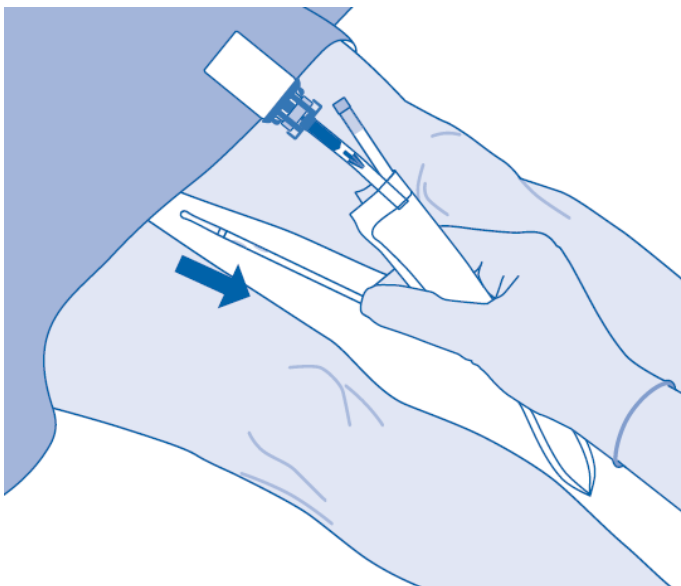


After instillation

14. Closing the pressure clamp (C3) prevents a reflux of fluid into the catheter and minimises the risk of contamination. Alternatively, you can keep the solvent bag compressed while performing steps 15 and 16.

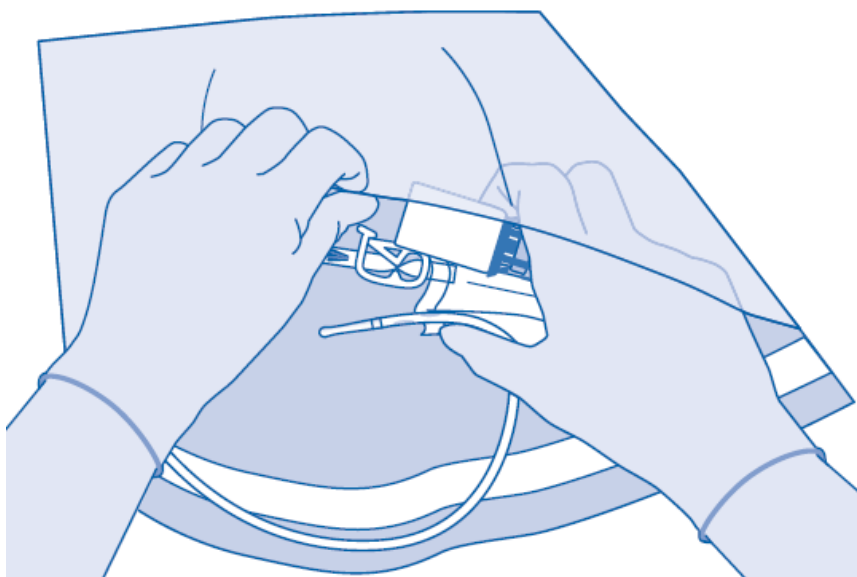


15. Remove the catheter **carefully** from the bladder without disconnecting the solvent bag from the catheter. Avoid contamination from splashing droplets.



16. Dispose of the product according to national regulations using the disposal bag.

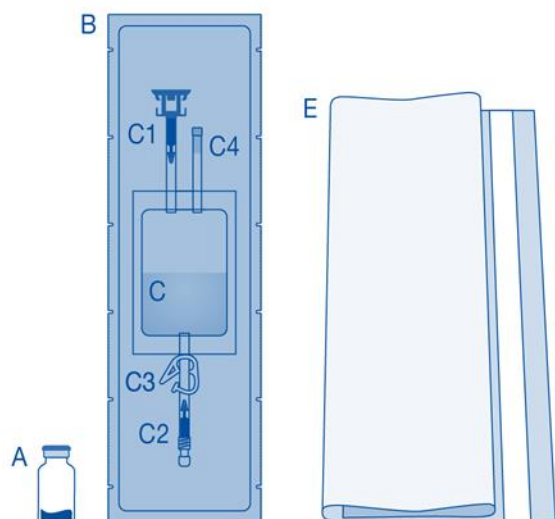
The contents of the vial are intended for single use/single dose only. Any remaining suspension must be disposed of.



Instructions for users of BCG-medac

Constituents and application of the instillation set <without catheter, without Luer-Lock to conical connector>

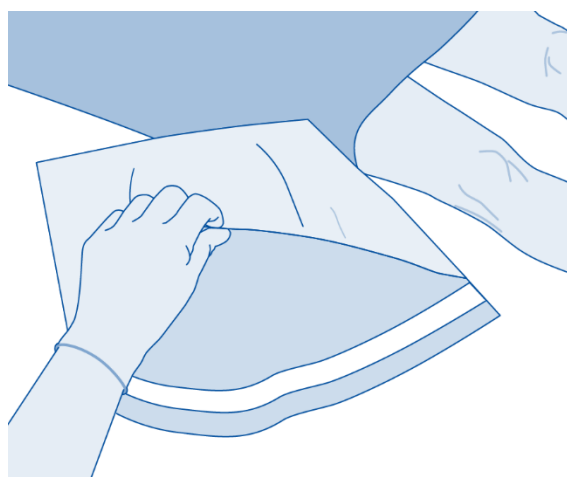
Main constituents of the instillation set



Main constituent	Description
A	Vial with powder
B	Protective cover
C	Solvent bag with 0.9% (9 mg/mL) sodium chloride solution
C1	Vial connector with protective cap and break-open seal
C2	Luer-Lock catheter connector with protective cap and break-open seal
C3	Pressure clamp
C4	Filling port without application function
E	Disposal bag

Connecting the vial to the solvent bag

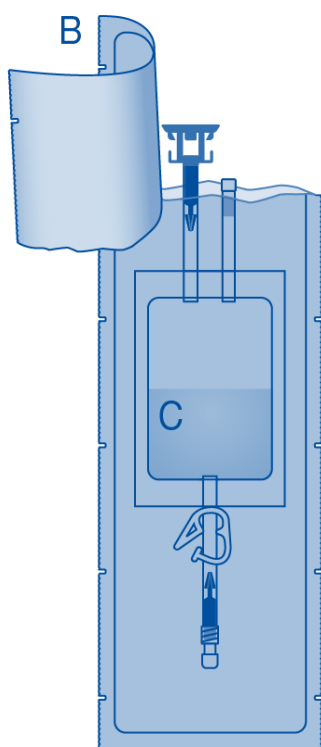
1. Lay out the disposal bag (E) ready for direct disposal of the set after instillation to prevent contamination.



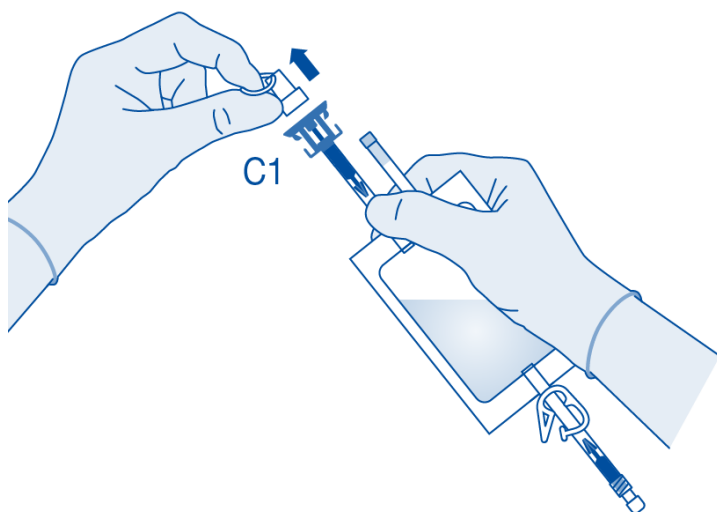
2. Remove the flip-off cap from the vial (A) and disinfect the stopper according to local regulations.



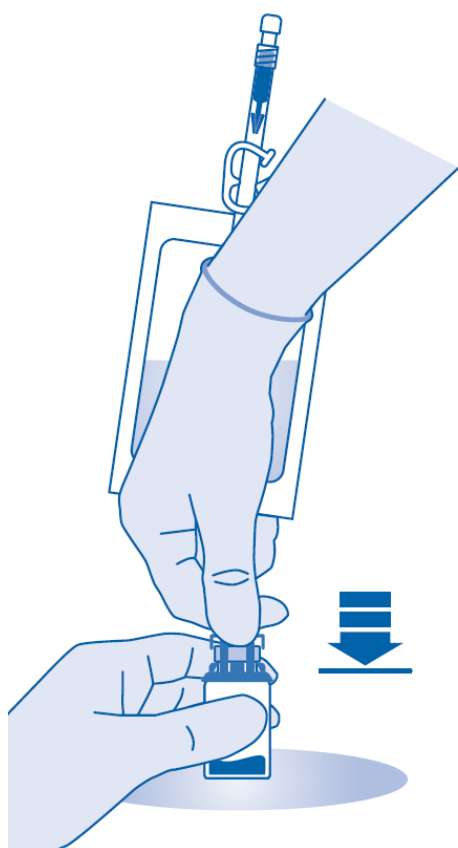
3. Tear open the protective cover (B) of the solvent bag (C) and remove the protective cover completely.



4. Remove the protective cap from the vial connector (C1).

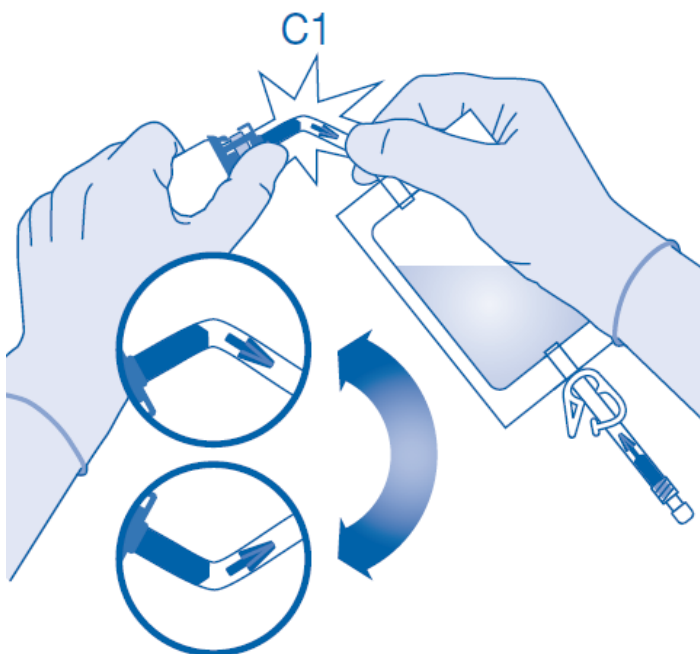


5. Push the connector onto the vial up to the stop.



Mixing the powder with the solvent

6. Bend the break-open seal inside the tube of the vial connector (C1) up and down multiple times to break the seal.



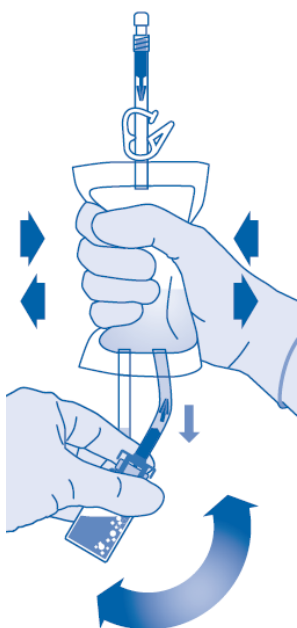
7. Hold the **solvent bag** so that the **vial is below it**.

Squeeze the solvent bag multiple times to transfer enough solvent into the vial.

Make sure that the vial is **not** filled completely to allow for the subsequent transfer of the suspension into the solvent bag. Some solvent may remain inside the bag.

Swirl the vial **slowly** to minimise heavy foaming while mixing the medicinal product with the solvent. If there is a lot of foam, leave the vial to rest briefly (a few minutes).

The contents of the vial have to form a homogeneous suspension. This may take a few minutes.



8. Turn the **solvent bag** upside down and hold it so that the **vial is above it**.

Hold the vial.

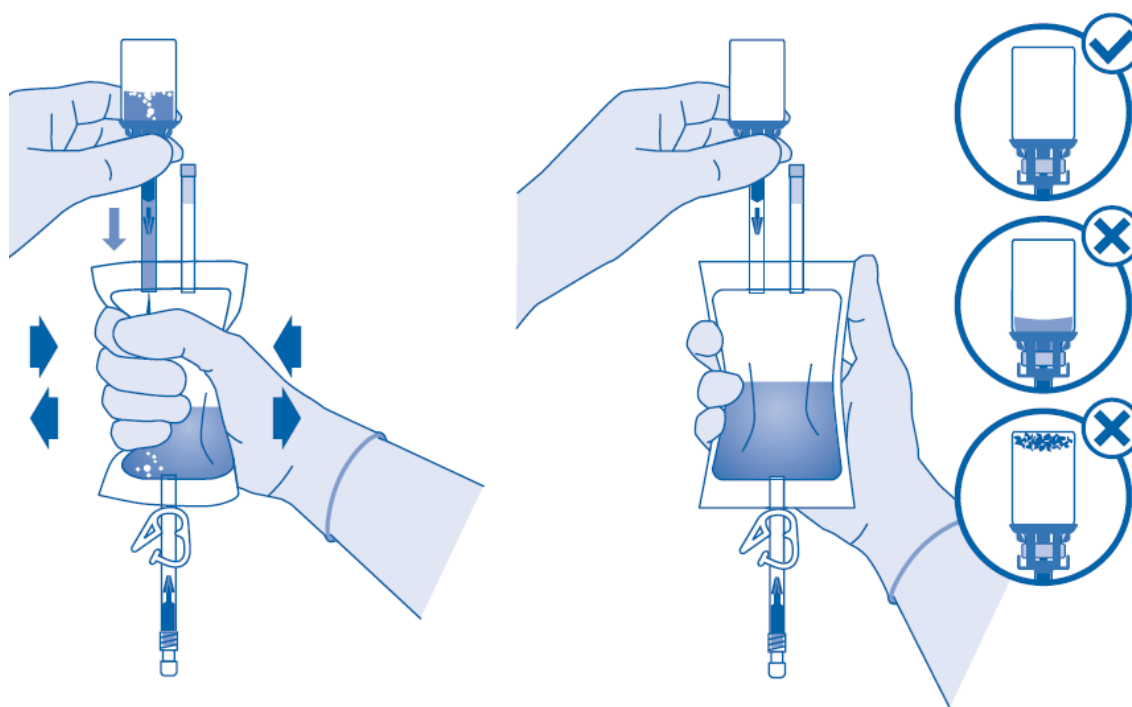
Squeeze the solvent bag multiple times until the vial is completely empty.

If any powder remains inside the vial, repeat steps 7 and 8.

From a microbiological point of view the medicinal product should be used immediately.

If the medicinal product is not used immediately, please see section 6.3 “Shelf life”.

The suspension should not be instilled at refrigerator temperature in order to prevent the patient from feeling the need to urinate resulting in a shortened exposure time.



Catheterisation

9. Catheterise the patient according to local regulations and the instructions for use using a suitable catheter and lubricant.

Empty the urinary bladder using the catheter.

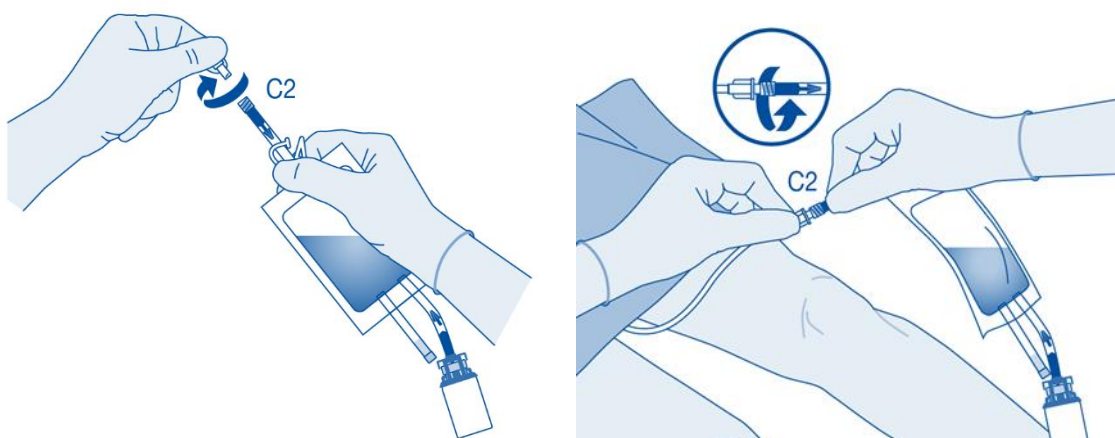
Connecting the catheter to the solvent bag

10. To mix any sediments, rotate and swirl the bag before connecting it.

Do not administer the suspension at refrigerator temperature.

Remove the protective cap from the catheter connector (C2).

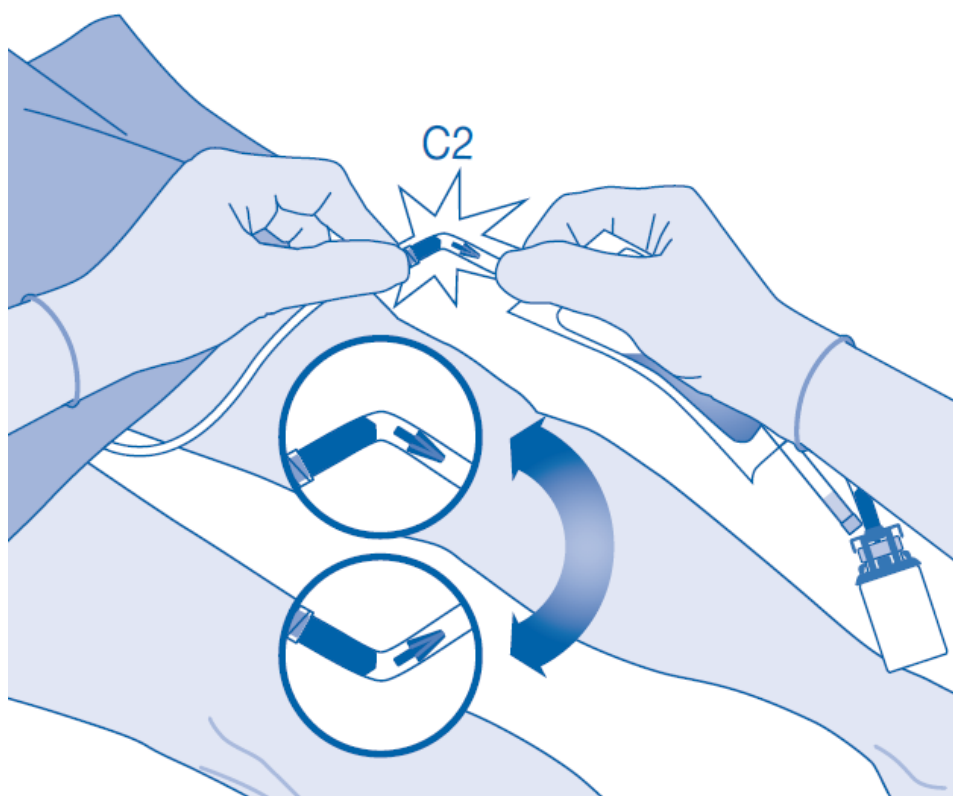
Connect the patient's catheter with the catheter connector (C2) of the solvent bag.



Instillation

11. Bend the break-open seal inside the tube of the catheter connector (C2) up and down multiple times to break the seal.

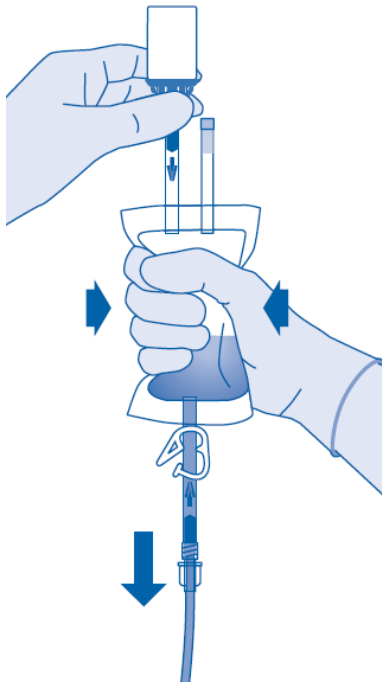
Hold the patient's catheter steady while doing so.



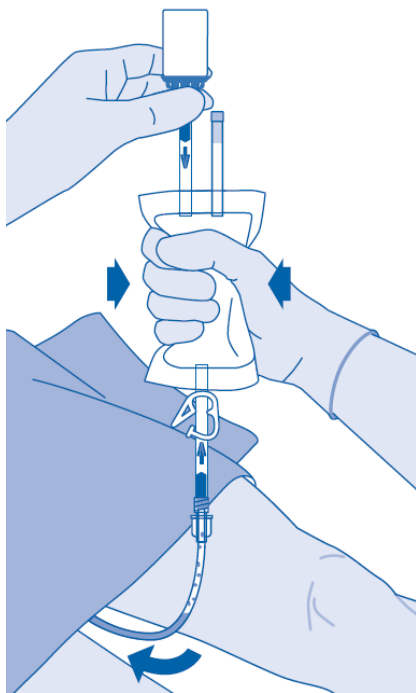
12. Hold the **solvent bag** with the **vial upside down above the bag**.

Squeeze the solvent bag **gently** with the other hand so that the medicinal product is **slowly** instilled into the patient's urinary bladder.

Continue to squeeze until the solvent bag and the vial are empty.

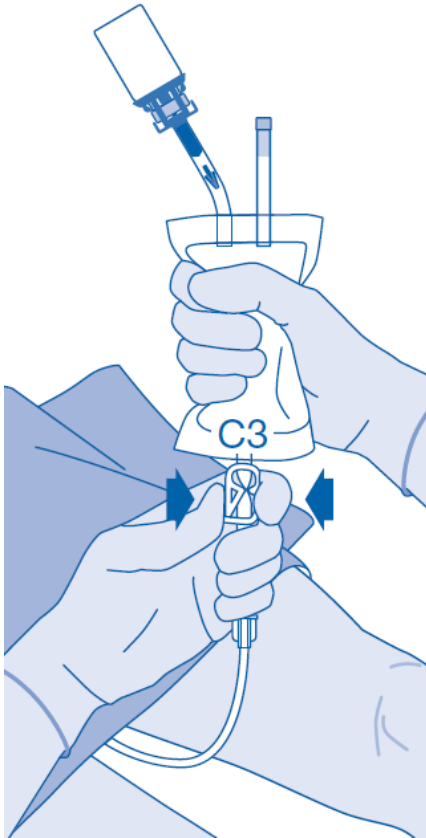


13. Squeeze the remaining air out of the solvent bag to empty the catheter as much as possible.

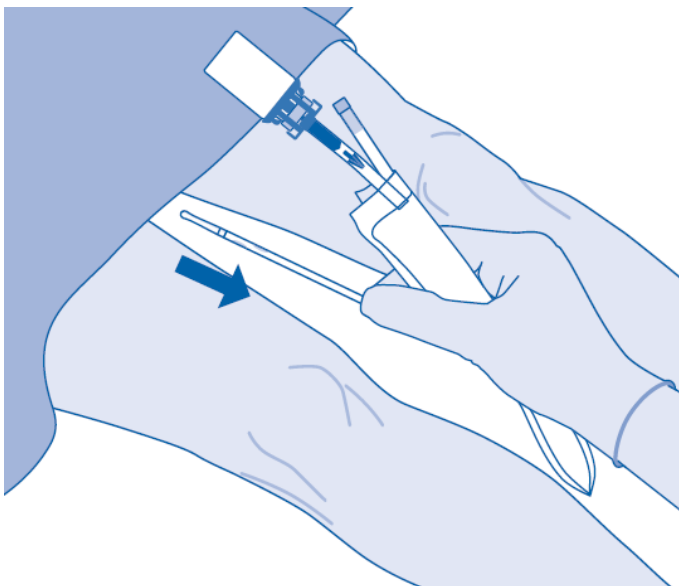


After instillation

14. Closing the pressure clamp (C3) prevents a reflux of fluid into the catheter and minimises the risk of contamination. Alternatively, you can keep the solvent bag compressed while performing steps 15 and 16.

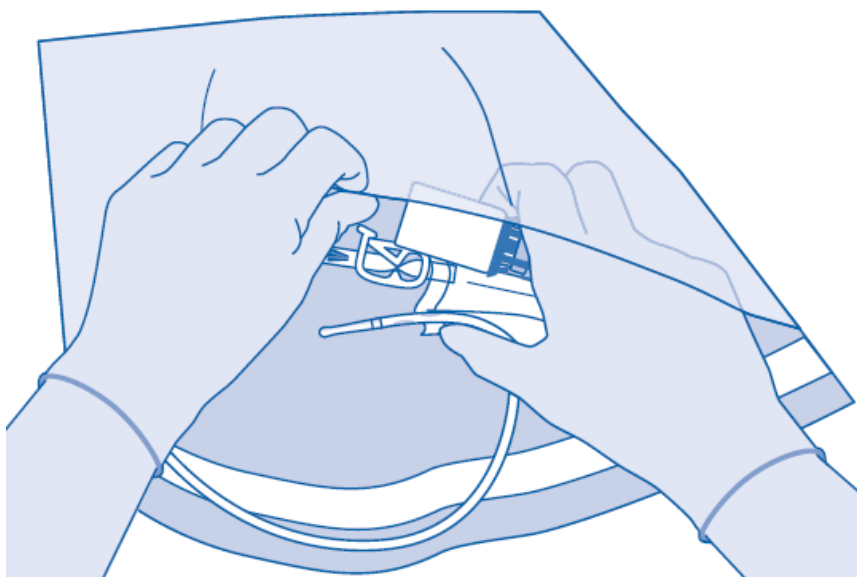


15. Remove the catheter **carefully** from the bladder without disconnecting the solvent bag from the catheter. Avoid contamination from splashing droplets.



16. Dispose of the product according to national regulations using the disposal bag.

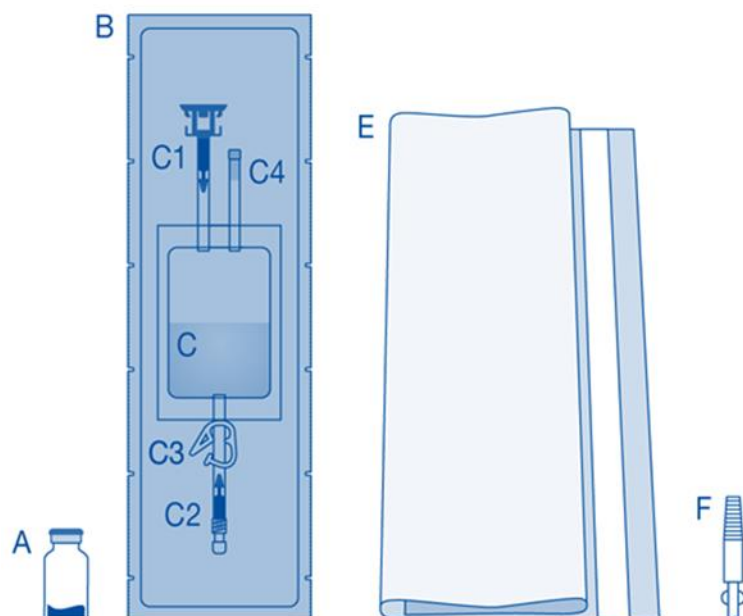
The contents of the vial are intended for single use/single dose only. Any remaining suspension must be disposed of.



Instructions for users of BCG-medac

Constituents and application of the instillation set <without catheter, with Luer-Lock to conical connector>

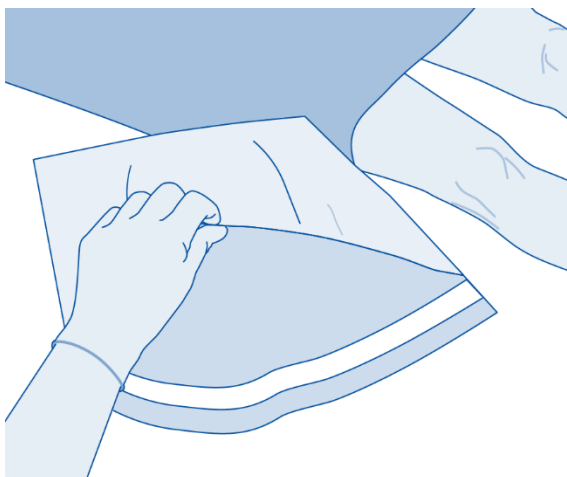
Main constituents of the instillation set



Main constituent	Description
A	Vial with powder
B	Protective cover
C	Solvent bag with 0.9% (9 mg/mL) sodium chloride solution
C1	Vial connector with protective cap and break-open seal
C2	Luer-Lock catheter connector with protective cap and break-open seal
C3	Pressure clamp
C4	Filling port without application function
E	Disposal bag
F	Luer-Lock to conical connector

Connecting the vial to the solvent bag

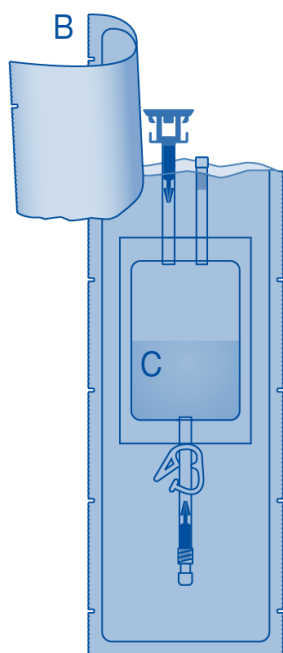
1. Lay out the disposal bag (E) ready for direct disposal of the set after instillation to prevent contamination.



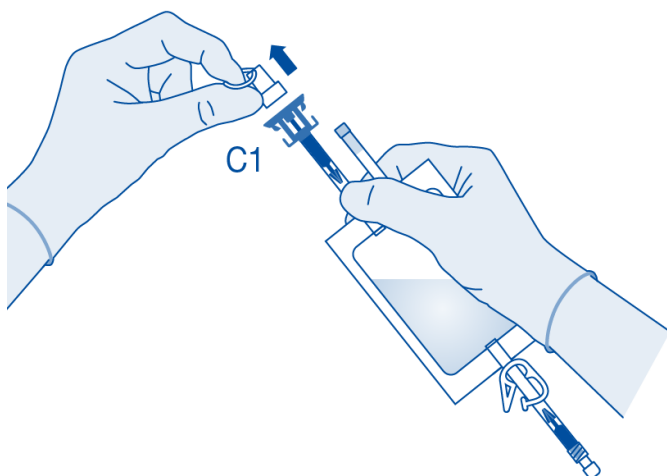
2. Remove the flip-off cap from the vial (A) and disinfect the stopper according to local regulations.



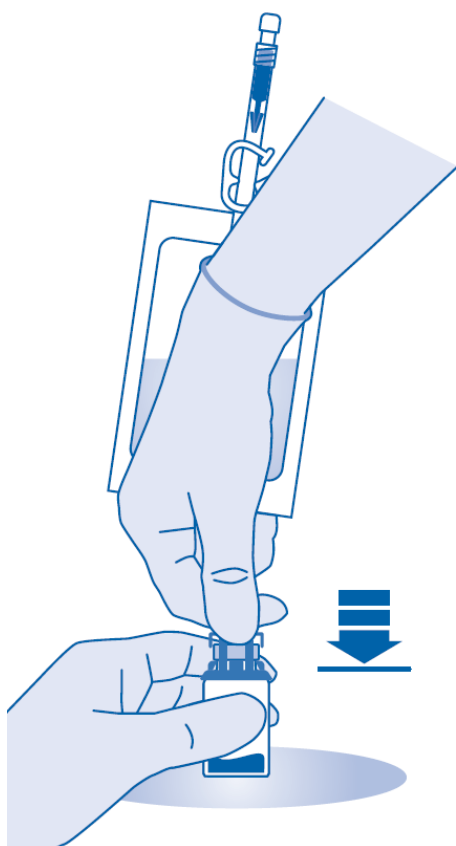
3. Tear open the protective cover (B) of the solvent bag (C) and remove the protective cover completely.



4. Remove the protective cap from the vial connector (C1).

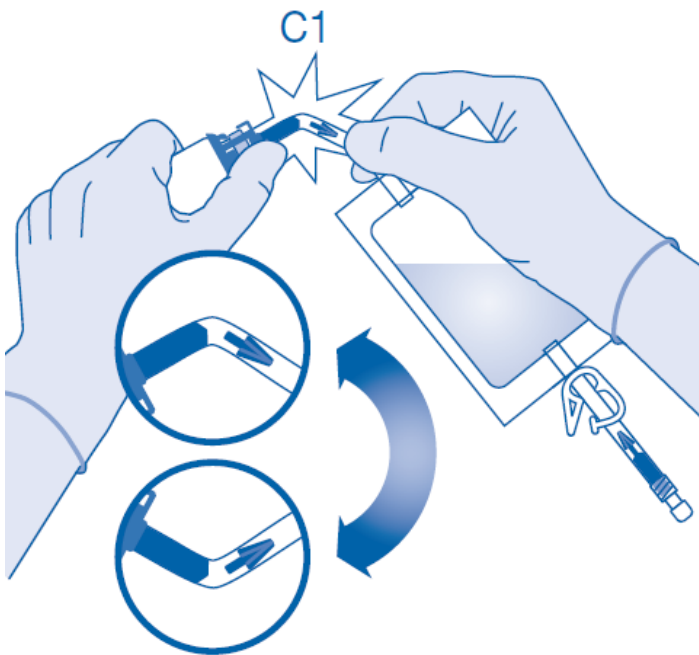


5. Push the connector onto the vial up to the stop.



Mixing the powder with the solvent

6. Bend the break-open seal inside the tube of the vial connector (C1) up and down multiple times to break the seal.



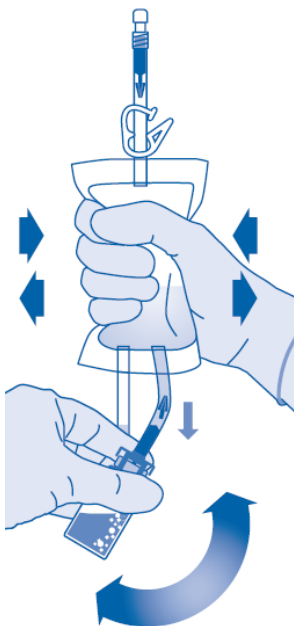
7. Hold the **solvent bag** so that the **vial is below it**.

Squeeze the solvent bag multiple times to transfer enough solvent into the vial.

Make sure that the vial is **not** filled completely to allow for the subsequent transfer of the suspension into the solvent bag. Some solvent may remain inside the bag.

Swirl the vial **slowly** to minimise heavy foaming while mixing the medicinal product with the solvent. If there is a lot of foam, leave the vial to rest briefly (a few minutes).

The contents of the vial have to form a homogeneous suspension. This may take a few minutes.



8. Turn the **solvent bag** upside down and hold it so that the **vial is above it**.

Hold the vial.

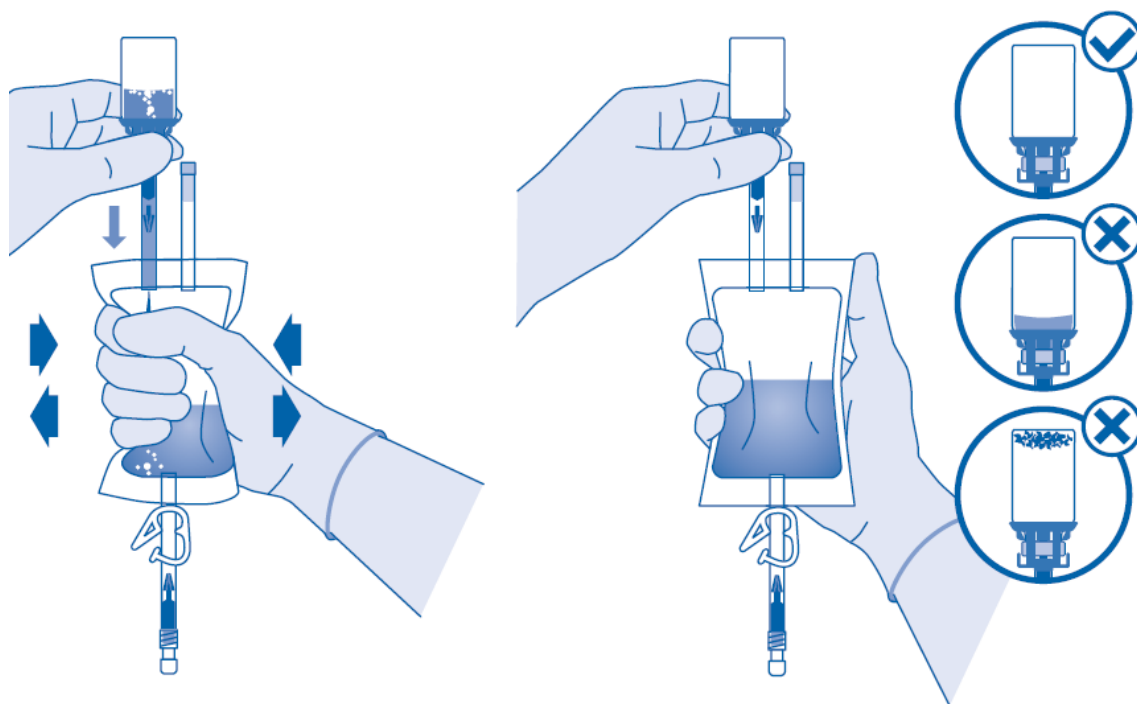
Squeeze the solvent bag multiple times until the vial is completely empty.

If any powder remains inside the vial, repeat steps 7 and 8.

From a microbiological point of view the medicinal product should be used immediately.

If the medicinal product is not used immediately, please see section 6.3 “Shelf life”.

The suspension should not be instilled at refrigerator temperature in order to prevent the patient from feeling the need to urinate resulting in a shortened exposure time.



Catheterisation

9. Catheterise the patient according to local regulations and the instructions for use using a suitable catheter and lubricant.

Empty the urinary bladder using the catheter.

This pack does not contain a catheter. Use the enclosed connector (F) to connect the bag to the patient's catheter with a conical connector (not shown).

To do this, the following additional steps must be carried out:

- Remove the protective cap from the catheter connector (C2, see step 10).
- Connect the connector (F) to the catheter connector (C2) of the bag.
- Carefully connect the bag with the connector (F) to the patient's catheter.
- Then proceed with step 11.

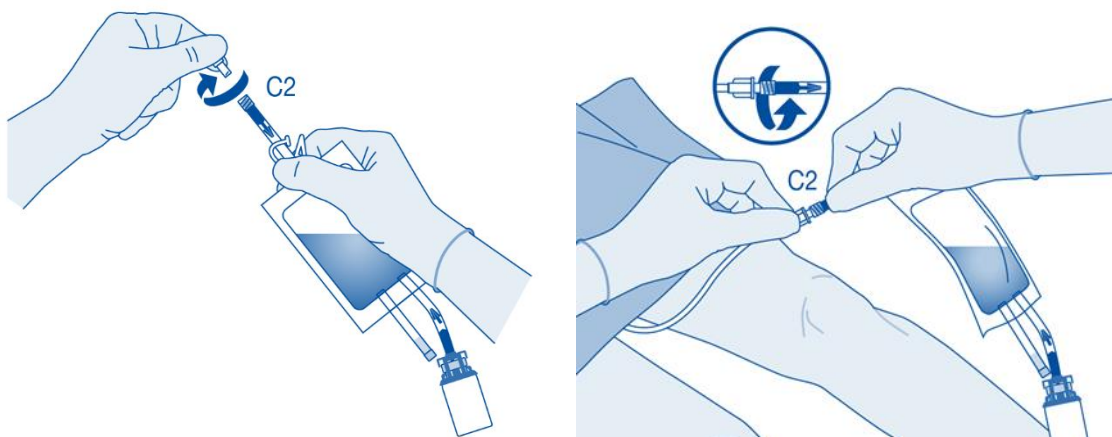
Connecting the catheter to the solvent bag

10. To mix any sediments, rotate and swirl the bag before connecting it.

Do not administer the suspension at refrigerator temperature.

Remove the protective cap from the catheter connector (C2).

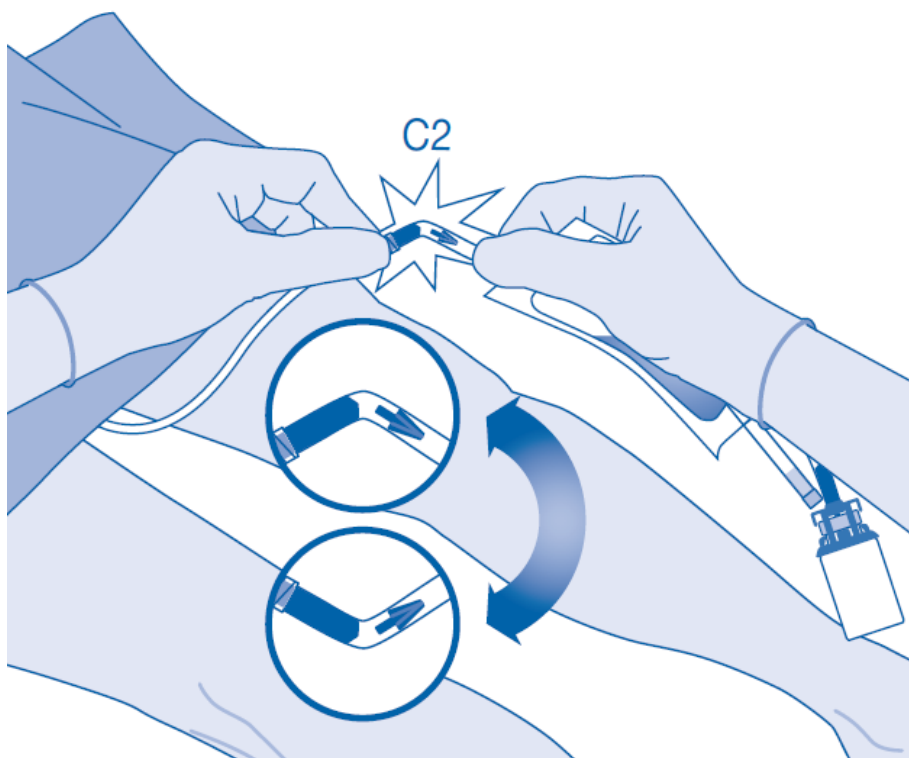
Connect the patient's catheter with the catheter connector (C2) of the solvent bag.



Instillation

11. Bend the break-open seal inside the tube of the catheter connector (C2) up and down multiple times to break the seal.

Hold the patient's catheter steady while doing so.



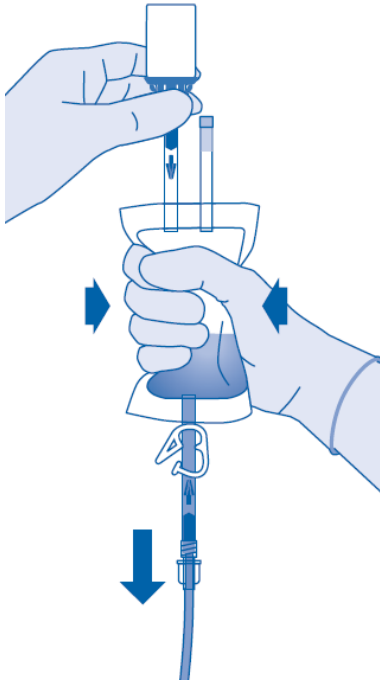
12. Hold the **solvent bag** with the **vial upside down above the bag**.

spc (common) BCG-medac, powder and solvent for intravesical suspension

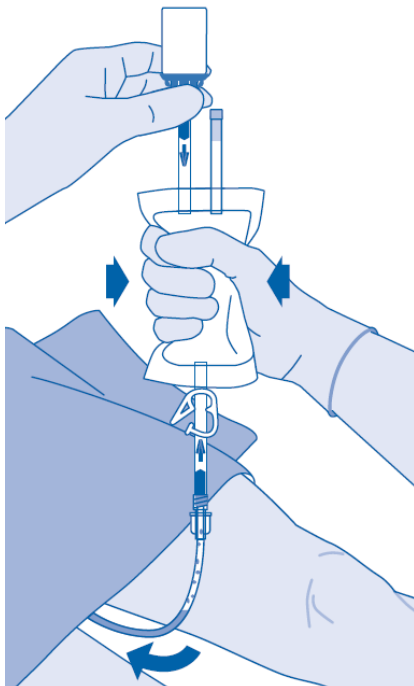
Date of common version: 12/2024

Squeeze the solvent bag **gently** with the other hand so that the medicinal product is **slowly** instilled into the patient's urinary bladder.

Continue to squeeze until the solvent bag and the vial are empty.

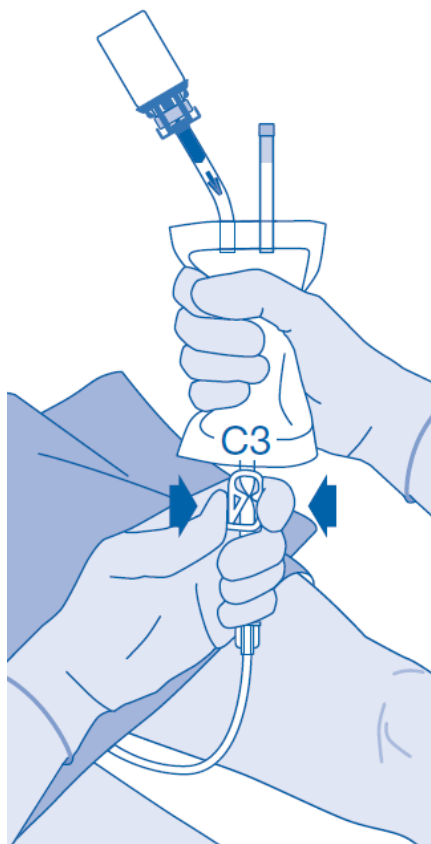


13. Squeeze the remaining air out of the solvent bag to empty the catheter as much as possible.

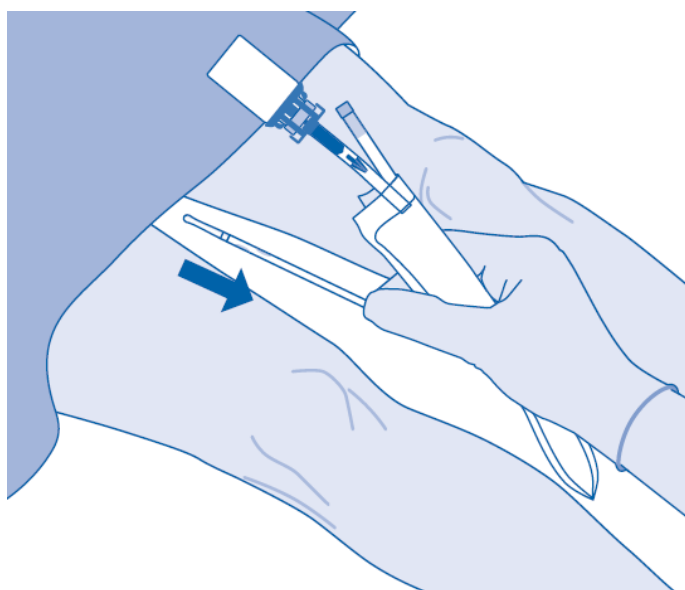


After instillation

14. Closing the pressure clamp (C3) prevents a reflux of fluid into the catheter and minimises the risk of contamination. Alternatively, you can keep the solvent bag compressed while performing steps 15 and 16.



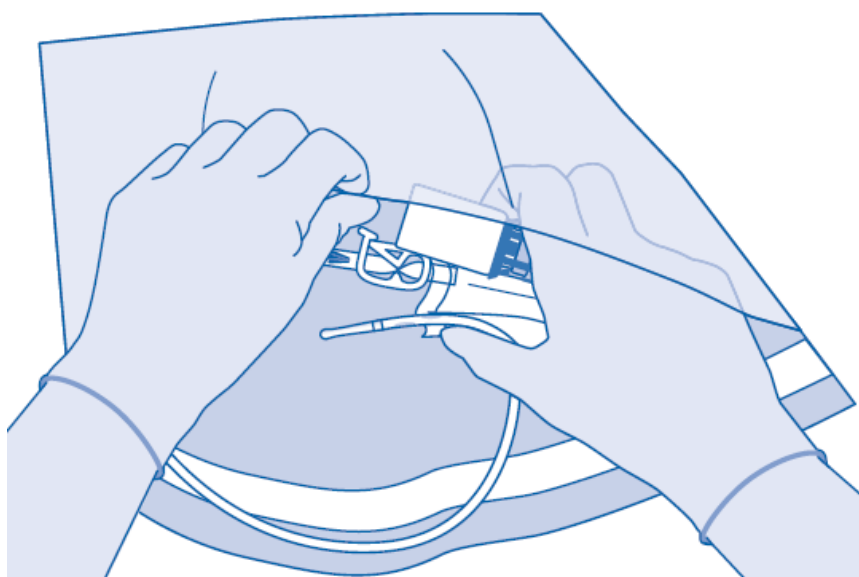
15. Remove the catheter **carefully** from the bladder without disconnecting the solvent bag from the catheter. Avoid contamination from splashing droplets.



16. Dispose of the product according to national regulations using the disposal bag.

The contents of the vial are intended for single use/single dose only. Any remaining suspension
spc (common) BCG-medac, powder and solvent for intravesical suspension
Date of common version: 12/2024

must be disposed of.



7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

12/2024