swissmedic

Date: 1 April 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

BCG-medac

International non-proprietary name:	live, attenuated bacillus Calmette-Guérin (BCG) (RIVM)
Pharmaceutical form:	powder and solvent for intravesical suspension
Dosage strength(s):	2 x 10^8 to 3 x 10^9 CFU
Route(s) of administration:	intravesical
Marketing authorisation holder:	pharma services Oehler GmbH
Marketing authorisation no.:	69954
Decision and decision date:	approved on 5 March 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for live, attenuated bacillus Calmette-Guérin (BCG) (RIVM) in the above-mentioned medicinal product.

Authorisation in accordance with Article 14 paragraph 1 a^{bis} TPA
The applicant requested a simplified authorisation procedure in accordance with Article 14 paragraph 1 a ^{bis} TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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 in the muscular of the bladder (T1)
- carcinoma in situ

2.2.2 Approved indication

Treatment of non-invasive urothelial bladder carcinoma:
• curative treatment of carcinoma in situ
• prophylactic treatment of recurrence of:
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- urothelial carcinoma in lamina propria but not in the muscular of the bladder (T1)
- carcinoma in situ

2.2.3 Requested dosage

Summary of the requested standard dosage:

BCG-medac is intended for intravesical use following reconstitution.

Adults and the elderly
The content of 1 vial, resuspended as indicated, is required for 1 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 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 over a period of 3 years.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	21 June 2024
Formal objection	17 July 2024
Response to formal objection	30 July 2024
Formal control completed	13 August 2024
List of Questions (LoQ)	5 December 2024
Response to LoQ	4 April 2025
Preliminary decision	2 July 2025
Response to preliminary decision	19 September 2025
Labelling corrections and/or other aspects	11 December 2025
Response to labelling corrections and/or other aspects	15 January 2026
Final decision	5 March 2026
Decision	approval

Based on Art. 14 para. 1 letter a^{bis} TPA, the authorisation of BCG-medac, powder and solvent for intravesical suspension, is based primarily on the medicinal product BCG-medac, powder and solvent for intravesical suspension, which contains the same active substance and has been authorised in Germany for more than 10 years. Apart from the quality-related aspects, for which Swissmedic has conducted an independent scientific review (based on primary data), this SwissPAR refers to the authorisation of the foreign medicinal product BCG-medac, powder and solvent for intravesical suspension.

3 Quality aspects

3.1 Drug substance

INN: Bacillus Calmette-Guérin
The drug substance of BCG-medac is a preparation of live bacteria. It is prepared from attenuated (weakened) live bovine tuberculosis bacillus *Mycobacterium bovis,* “Bacillus Calmette-Guérin (BCG)”, strain RIVM.
Manufacture: The production is based on a seed lot system. The working seed vial is thawed and the bacteria are cultured in fermenters of increasing size up to the production culture stage. Upon reaching stationary phase, the bacterial mass is harvested, concentrated, and washed with stabilising solution. The drug substance is neither isolated nor stored. Validation covering the drug substance manufacturing process has therefore been presented together with the drug product.
Specification: Due to a continuous manufacturing process, the drug substance is not isolated for testing. Adequate in-process controls are in place.
Stability: No drug substance shelf-life has been established. The drug substance is not isolated because the product is manufactured in a continuous process.

3.2 Drug product

Description and composition:
The finished drug product is a powder (lyophilisate) for suspension for intravesical administration. BCG-medac contains $2*10^8$ to $3*10^9$ colony-forming units of BCG in a glass vial, and a NaCl solution in a bag as solvent for suspension.

Pharmaceutical development has been satisfactorily described.

Manufacture:
The manufacturing process for the finished drug product comprises formulation of the final bulk, aseptic filling, and freeze-drying. Adequate in-process controls are in place. Process validation studies were executed at commercial scale using 3 consecutive validation batches, indicating a consistent manufacturing process.

Specification:
The specifications include, for example, tests for appearance, identity, count of viable units, virulent mycobacteria, microbiological purity, water content, ratio count of viable units of the final bulk in relation to the final lot, and bacterial endotoxins. The analytical procedures used comply with Ph. Eur and are in-house methods.

Container Closure System:
The container closure system of the lyophilisate containing live, attenuated BCG is a 20 mL colourless glass vial. The NaCl solution is filled in 50 mL plastic bags.

Stability: BCG-medac is stored at 2 – 8°C, protected from light. Two different shelf-lives have been defined, based on the viable units determined at release. For $< 5 \times 10^8$ colony forming units at release, the claimed shelf-life is 24 months, and for $\geq 5 \times 10^8$ colony forming units at release, the claimed shelf-life is 36 months. The claimed shelf-lives are justified based on stability studies performed according to ICH guidance. The reconstituted solution can be stored for 24h at 2 – 8°C, protected from light.

3.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

4 Nonclinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview or risk assessment for the authorisation of BCG-medac, powder and solvent for intravesical suspension. The approval of BCG-medac, powder and solvent for intravesical suspension, is based on the medicinal product BCG-medac, powder and solvent for intravesical suspension, which contains the same active substance and has been authorised in Germany for more than 10 years.

5 Clinical aspects

For the application for the authorisation of the medicinal product BCG-medac, powder and solvent for intravesical suspension, Swissmedic has conducted only a summary review of efficacy and safety. The authorisation of BCG-medac, powder and solvent for intravesical suspension, is based primarily on the medicinal product BCG-medac, powder and solvent for intravesical suspension, which contains the same active substance and has been authorised in Germany for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator medicinal product BCG-medac, powder and solvent for intravesical suspension.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for BCG-medac was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

BCG-medac

Powder and solvent for intravesical suspension

The efficacy and safety of BCG-medac have only been reviewed summarily by Swissmedic. The marketing authorisation of BCG-medac is based on BCG-medac with information as of December 2024, which contains the same active substance and is authorised in Germany.

Composition

Active substances

BCG (Bacillus Calmette-Guérin) bacteria derived from Mycobacterium bovis, seed RIVM derived from seed 1173-P2 (2×10^8 to 3×10^9 viable units), live attenuated

Excipients

Powder: polygeline, glucose anhydrous and polysorbate 80.

Solvent: sodium chloride (9 mg/ml, equivalent to 3.54 mg sodium/ml), water for injections.

Pharmaceutical form and active substance quantity per unit

Powder and solvent for intravesical suspension

Powder:

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

Solvent:

0.45 g/50 ml sodium chloride (colourless, clear solution)

After reconstitution, one vial contains:

2×10^8 to 3×10^9 colony forming units (CFU), live attenuated BCG (Bacillus Calmette-Guérin) bacteria derived from Mycobacterium bovis, seed RIVM derived from seed 1173P2.

Indications/Uses

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

Dosage/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 “Other information”.

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. If this is not successful, the patient should be catheterised by healthcare professionals to remove the remaining urine. After emptying the bladder, the toilet is cleaned with standard disinfectants

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

Patient alert card:
Patients must be informed about the risks of treatment and the precautions to ensure the safe administration of BCG-medac. Furthermore, the patient alert card should be given to the patient before treatment begins.

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.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in the section “Composition”.

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).

Gross haematuria
In the event of gross haematuria, treatment should be postponed until the symptoms subside.

BCG-medac should not be administered to persons with active tuberculosis or with diseases requiring the use of tuberculostatic agents such as streptomycin, para-aminosalicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol. 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 pregnancy and lactation (see section “Pregnancy, lactation”).

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 “Warnings and precautions”).

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

Febrile infections or fever of unknown origin.

Warnings and precautions
BCG-medac must not be used for subcutaneous, intradermal, intramuscular or intravenous administration or vaccination.

Treatment of symptoms, signs or syndrome See section “Undesirable effects”.

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 “Undesirable effects”.

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 “Undesirable effects”.

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 “Undesirable effects”.

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.

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.

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.

Interactions

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.

Pregnancy, 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 contraindicated 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 “Contraindications”).

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.

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.

Undesirable effects

Undesirable effects are listed below by system organ class and frequency. Frequencies below are defined as: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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 infestations	<u>Very common</u> Cystitis and inflammatory reactions (granuloma) of the bladder, asymptomatic granulomatous prostatitis <u>Uncommon</u> 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) <u>Rare</u> Vascular infection (e.g. infected aneurysm), renal abscess <u>Very rare</u> 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
Blood and lymphatic system disorders	Uncommon Cytopenia, anaemia Very rare Cervical lymphadenitis Not known Haemophagocytic syndrome
Immune system disorders	Very common Transient systemic BCG reaction (fever < 38.5 °C, flu-like symptoms including malaise, fever, chills, general discomfort, myalgia) Very rare Hypersensitivity reaction (e.g. oedema of eyelids, cough)
Eye disorders	Very rare Chorioretinitis, conjunctivitis, uveitis
Vascular disorders	Uncommon Hypotension Very rare Vascular fistula Not known Vasculitis (including vasculitis of the central nervous system)
Respiratory, thoracic and mediastinal disorders	Uncommon Pulmonary granuloma
Gastrointestinal disorders	Very common Nausea Common Diarrhoea, abdominal pain Very rare Vomiting, intestinal fistula
Hepatobiliary disorders	Uncommon Hepatitis
Skin and subcutaneous tissue disorders	Uncommon Skin rash
Musculoskeletal and	Common

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

Mild, transient adverse reactions are frequent and may increase in the course of the therapy.
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 “Warnings and precautions”).**

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	*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. 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.
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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/effects

ATC code

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 TNFα are also increased.

Pharmacodynamics
Not applicable.

Clinical efficacy
Not applicable.

Pharmacokinetics
Absorption
Not applicable.

Distribution
Not applicable.

Metabolism
Not applicable.

Elimination
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.

Kinetics in specific patient groups
Not applicable.

Preclinical 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.

Other information

Incompatibilities

BCG-medac is incompatible with hypotonic and hypertonic solutions.

Shelf life

Do not use this medicinal product after the expiry date which is stated on the packaging after “EXP”.

Shelf life after opening

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.

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 “Shelf life after opening”.
Keep out of the sight and reach of children.

Instructions for handling

Important information on the use of BCG-medac

BCG-medac may only be used by experienced healthcare professionals.
Ensure suitable storage (see section “*Special precautions for storage*”) 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!

Information for healthcare professionals

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 opening, see section "*Shelf life after opening*").
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.

Authorisation number

69954 (Swissmedic)

Packs

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 Luer-Lock catheter connector, with or without catheter.

Pack sizes:

1 vial, 1 solvent bag, 1 catheter with lubricant (A)

1 vial, 1 solvent bag (A)

3 vials, 3 solvent bags, 3 catheters with lubricant (A)

3 vials, 3 solvent bags (A)

Marketing authorisation holder

pharma services oehler gmbh, Wollerau

Manufacturer

medac GmbH, Wedel, Germany

Date of revision of the text

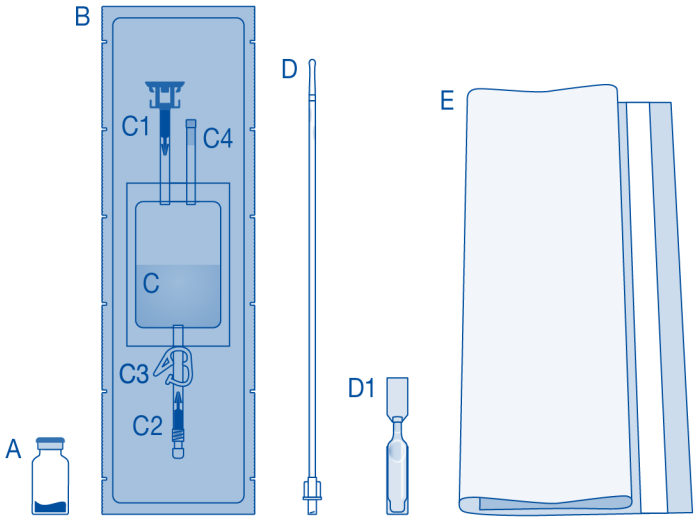
Foreign reference medicinal product: December 2024

With safety-relevant additions by Swissmedic: December 2025

Instructions for users of BCG-medac

Constituents and application of the instillation set

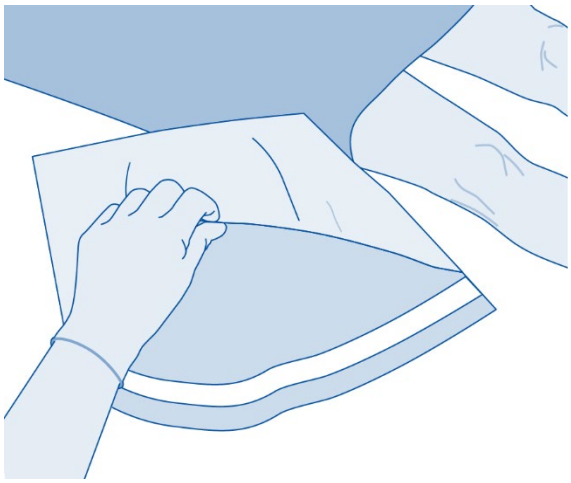
Main constituents of the instillation set



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 (included in pack sizes with catheter; for pack sizes without catheter, please use a suitable catheter)
D1	Lubricant (included in pack sizes with catheter; for pack sizes without catheter, please use a suitable lubricant)
E	Disposal bag

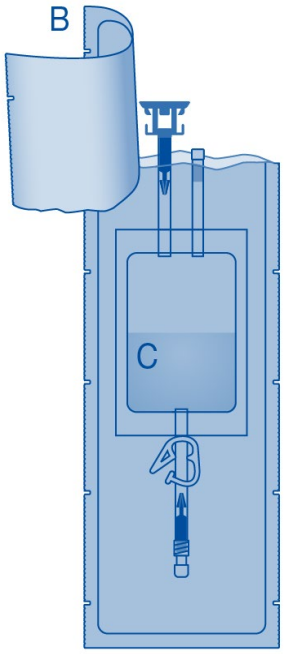
Connecting the vial to the solvent bag

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

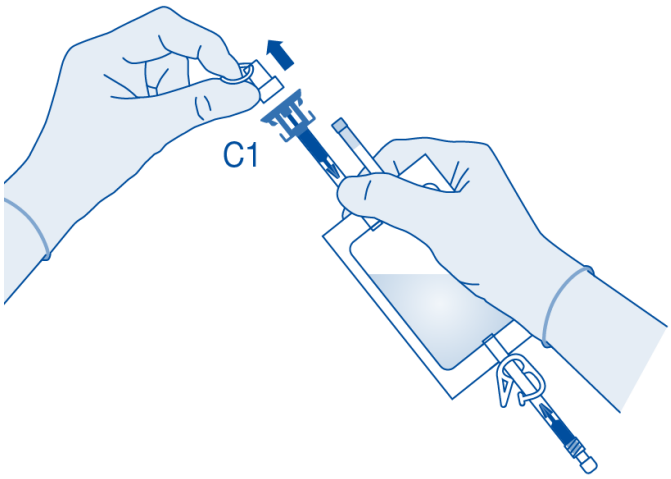


2. Remove the flip-off cap from the vial (A) and disinfect the stopper according to local regulations.

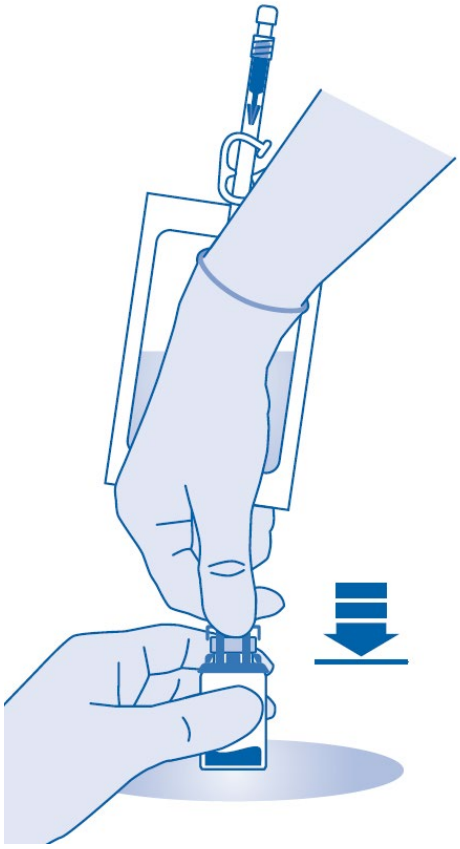
3. Tear open the protective cover (B) of the solvent bag (C) and remove the protective cover completely.



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

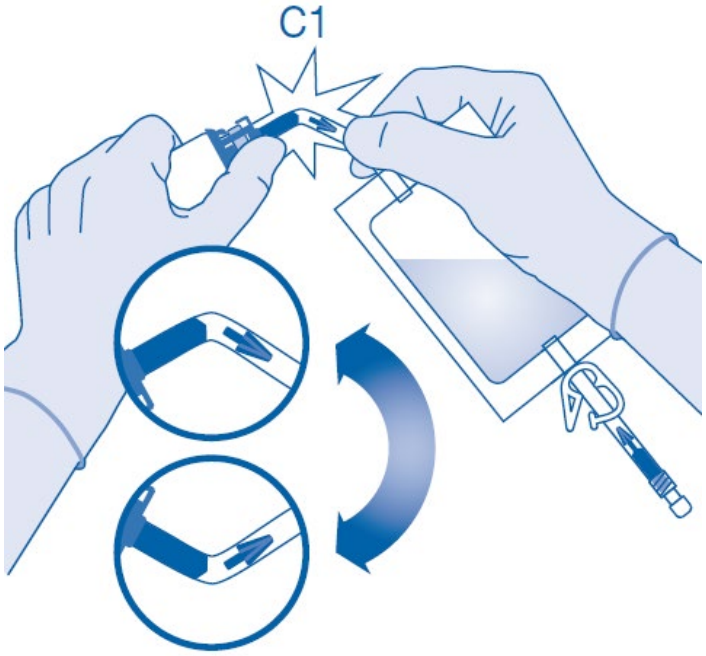


5. Push the connector onto the vial up to the stop.



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.



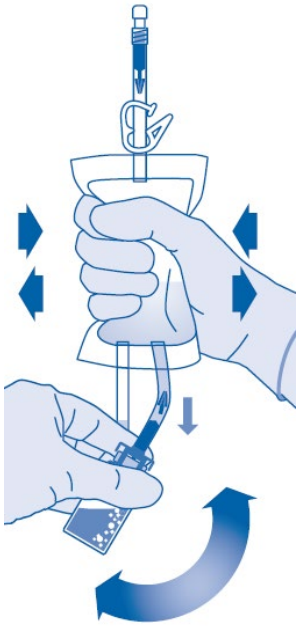
7. Hold the **solvent bag** so that the **vial is below it**.

   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.

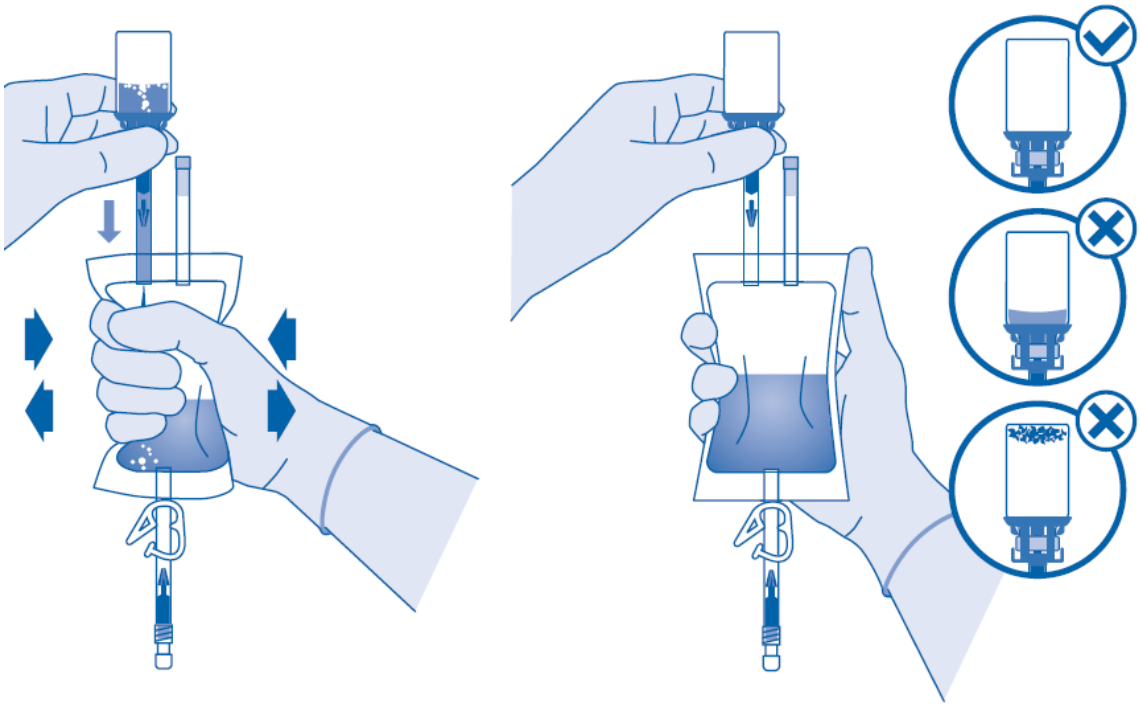
   Hold the vial.

   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 “Shelf life after opening”.

   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 catheter (D) and lubricant (D1) or another suitable catheter and/or lubricant.

   Empty the urinary bladder using the catheter.

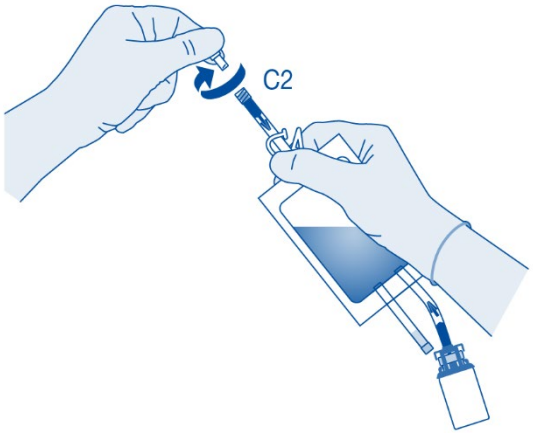
Connecting the catheter to the solvent bag

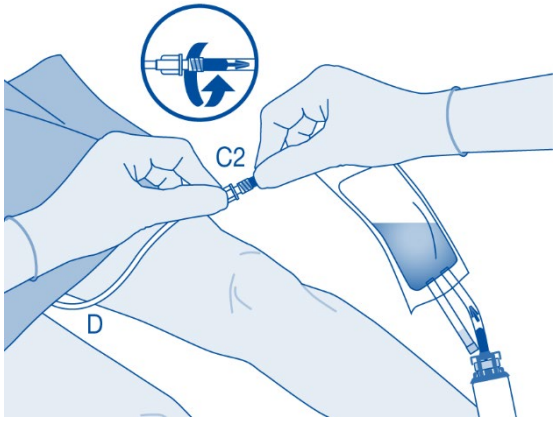
10. To mix any sediments, rotate and swirl the bag before connecting it.

    Do not administer the suspension at refrigerator temperature.

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

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

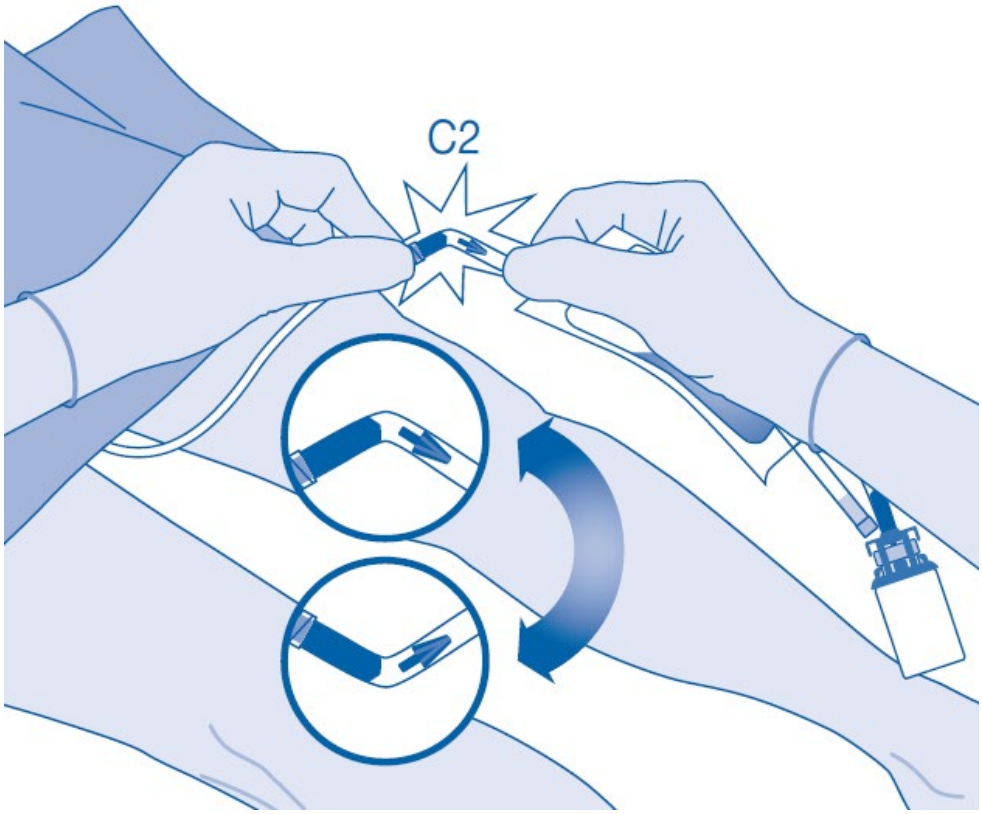




Instillation

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

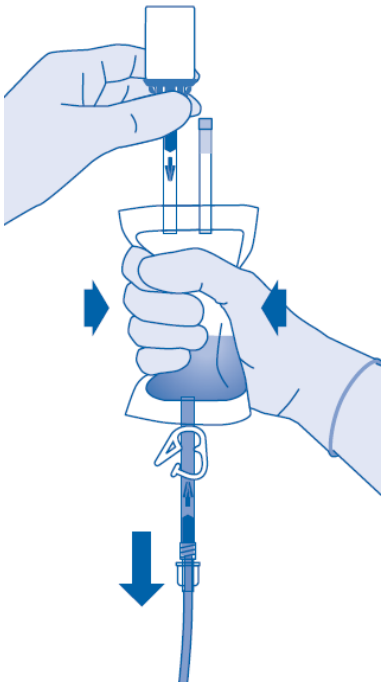
    Hold the patient's catheter steady while doing so.



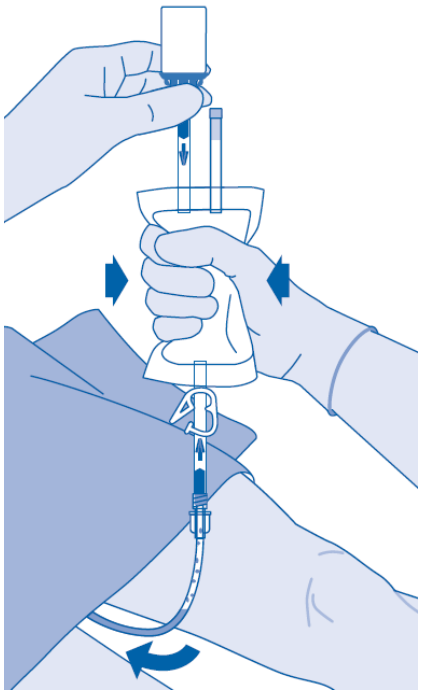
12. Hold the solvent bag with the **vial upside down above the bag**.

    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.

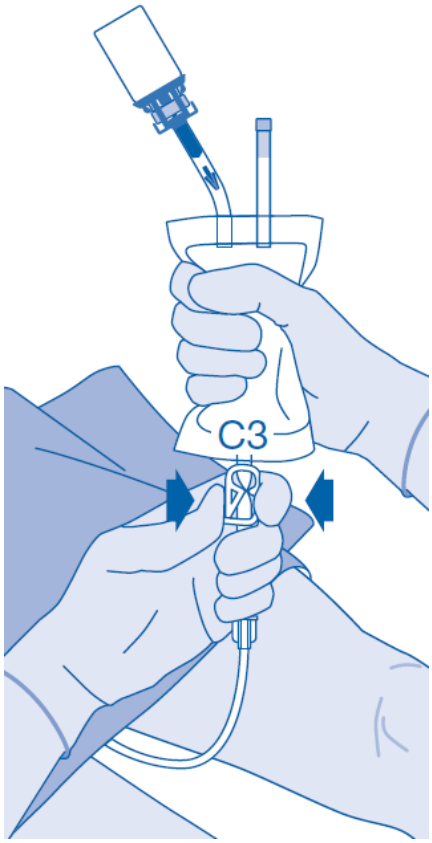


13. Squeeze the remaining air out of the solvent bag to empty the catheter as much as possible.

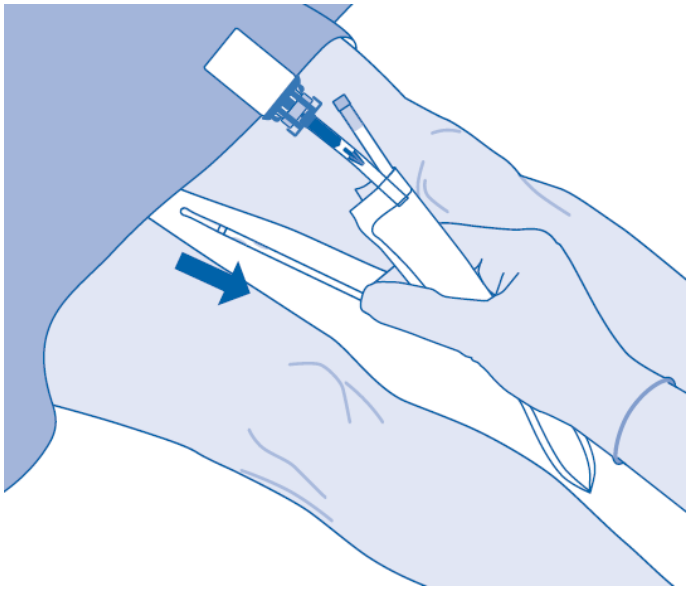


After instillation

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.