PATIENT INFORMATION LEAFLET

BCG vaccine, freeze-dried, 1 mg/mL, powder and solvent for suspension for injection

vaccine against tuberculosis

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep the leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you experience any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What BCG vaccine is and what it is used for

BCG vaccine is a freeze-dried vaccine consisting of live, attenuated *Mycobacterium bovis bacilli*, strain Bacillus Calmette-Guerin.
Vaccination with BCG vaccine elicits a cell-mediated immune response that confers a variable degree of protection against tuberculosis (protective effect of vaccination is 40-70%). Numerous BCG vaccine efficacy studies in children show that this vaccine does not prevent the infection with *M. tuberculosis*, but when applied immediately at birth it provides a significant protection of infants and little children against tuberculous meningitis and disseminated forms of tuberculosis. BCG vaccination does not prevent reactivation of latent pulmonary tuberculosis. The vaccine-induced protection decreases over time.
BCG vaccine is intended for active immunisation of all newborns and children at a high risk of tuberculosis to prevent severe clinical forms of tuberculosis (tuberculous meningitis and disseminated tuberculosis), and for active immunisation of adults at a high risk of developing tuberculosis.
BCG vaccine is given to newborns on being discharged from the maternity hospital. Children who have not received BCG vaccine until two months of age must be vaccinated in competent health institutions until they reach 12 months of age. BCG vaccine immunisation schedule is developed in compliance with the national immunisation programme.
Exceptionally, BCG vaccine can be administered to personnel in maternity hospitals and paediatric institutions, as well as to other healthcare workers with a high risk of exposure to tuberculosis, if they have not received the vaccine up to that moment in the primary vaccination. Also, BCG vaccine can be given to children at a high risk of tuberculosis who were not vaccinated in the primary vaccination, if members of their family have had tuberculosis or are coming from a country with a high prevalence of tuberculosis, or at the request of parents, if they are coming from a country in which BCG vaccination is not conducted.
BCG vaccine should be given only to persons who have not received BCG vaccine and who have not been infected with *Mycobacterium tuberculosis* or who have a negative tuberculin reaction. BCG vaccination has no value in the treatment of persons with tuberculosis (infection with *Mycobacterium tuberculosis*).

2. Before you receive BCG vaccine, freeze-dried

Do not use BCG vaccine:
Contraindications to active BCG vaccine immunisation are:

- serious allergic reactions (e.g. anaphylaxis) to certain components of the vaccine or manifested during administration of the previous vaccine dose;
- known severe immunodeficiency, such as haematological or solid tumours, chemotherapy, radiotherapy, or long immunosuppressive therapy (e. g. use of prednisone or an equivalent corticosteroid for ≥ 2 weeks in the dose ≥ 20 mg/day is considered a sufficient immunosuppressive dose that can lead to severe immunodeficiency); then congenital immunodeficiency (e.g. chronic granulomatous disease or interferon gamma receptor deficiency), as well as seriously immunocompromised persons with HIV infection (in those persons BCG vaccination increases the risk of a generalised BCG infection);
- pregnancy (although no harmful effects to the foetus have been associated with the vaccine, BCG vaccination should be postponed for the period after the delivery);
- active tuberculosis (BCG vaccine should not be given to patients who are receiving anti-tuberculosis medicines).

In case of a moderate to severe acute disease with or without fever, the administration of BCG vaccine should be postponed until the condition stabilises.
Prematurely born children or newborns with severe complications at birth (intracranial haemorrhage, *icterus gravis neonatorum*, *pemphigus gravis neonatorum*, etc.) are to be vaccinated as soon as their condition is normalised.

The vaccination should be postponed in persons with generalised infected skin conditions or burns. Eczema is not a contraindication, but the vaccine site must be lesion free.

Take special care with BCG vaccine:

- In case of a change in the physical appearance of the prepared BCG vaccine (colour change, presence of visible particles, not easily removable precipitate) the vaccine must not be applied.
- Prior to BCG administration, an assessment of the vaccinee's health status needs to be done to determine if certain contraindications to the application of BCG vaccine are present, or if there is a need to postpone immunisation until the status is clarified completely, i.e. until the status is stable.
- Prior to the vaccination, all relevant information on the vaccinee's medical status need to be collected so as to take appropriate precautions (if necessary).
- Prior to the immunisation, it is necessary to have a detailed medical history of the previous hypersensitive reactions for each patient. In patients allergic to certain medicines (or food), or those prone to hypersensitive reactions after contact with various agents, special precautions need to be taken during the BCG vaccine application.
- The health institution in which the vaccination takes place must provide suitable medical treatment in case of an anaphylactic shock. All vaccinees should be under the doctor's supervision for at least 30 minutes after the vaccine administration.
- Special caution is required during BCG vaccine administration in newborns and children with medical history suggestive of congenital immunodeficiency or any risk factors for HIV infection. Newborns who have potentially been exposed to HIV perinatally must not be given BCG vaccine until they have been confirmed not to be infected with HIV.
- Tuberculin positive persons do not require the vaccine. Administration of BCG vaccine to such persons may result in a severe local reaction.
- Per recommendations of infectious diseases experts, booster immunisation with BCG vaccine is no longer recommended.
- BCG vaccine must not be injected intravascularly and intramuscularly. When administering the vaccine, the needle should not enter a blood vessel or the surrounding muscle tissue. BCG vaccine must not be given by a too deep subcutaneous injection, due to the possibility of lymphadenitis and abscess development.
  BCG vaccine should be injected strictly intradermally!

Using other medicines

BCG vaccine may be given concurrently with other inactivated live vaccines, but at different injection sites using separate syringes.

Other vaccines to be given at the same time as BCG vaccine or during the next three months should not be given into the same (left) arm because of the risk of regional lymphadenitis.

BCG vaccine must not be mixed with other vaccines and/or other medicines in the same syringe.

Studies have shown that concurrent application of BCG vaccine and hepatitis B vaccine at birth does not have any influence on immunogenicity and safety of either vaccine. However, since the application of one live vaccine may interfere with the efficacy of another, BCG vaccine is not recommended to be administered in the period of 4 (four) weeks after the administration of any live vaccine.

Pregnancy and breast-feeding

Pregnancy

Preclinical trials of BCG vaccine reproductive toxicity have not been conducted and it is not known whether this vaccine (when administered to a pregnant woman) may show teratogenic effects and cause foetal harm. Therefore, BCG vaccination of pregnant women should be delayed until after delivery.

Breastfeeding

It is not known whether BCG vaccine is excreted in mother's milk. Because live vaccines may be excreted in human milk, special caution should be exercised when BCG vaccine is administered to a nursing woman.

Driving and using machines
BCG vaccine freeze-dried does not affect the psychophysical capacities.

3. How to use BCG vaccine, freeze-dried

Posology:
The dose of BCG vaccine for newborns and infants under 12 months of age is 0.05 mL of the reconstituted vaccine and contains 0.05 mg of *M. bovis BCG* (0.8-8.0 x 10^5 CFU).
The dose of BCG vaccine for children over 12 months of age and adults is 0.1 mL of the reconstituted vaccine and contains 0.1 mg of M. *bovis BCG* (1.6-16.0 x 10^5 CFU).

Method of administration:
BCG vaccine should be injected intradermally in the deltoid muscle area, at the junction of the external and internal side of the left upper arm. Use a sterile syringe of 1 mL subgraduated into hundredths of mL (1/100 mL) fitted with a needle for intradermal use.
The vaccine is to be reconstituted before use. Original solvent, delivered with the particular batch of the vaccine, should always be used. If alcohol is applied to swab the rubber stopper, it should be allowed to evaporate. The vaccine is to be reconstituted by transferring the solvent (1 mL) to the vial containing the freeze-dried vaccine using a sterile syringe fitted with a needle (the rubber stopper is not to be removed). To suspend the vaccine, the vial should be gently turned upside down a few times. Making of air bubbles should be avoided, due to precise dosing of the vaccine. The suspension should be homogenous and slightly opaque. Any unused reconstituted vaccine in a multi-dose presentation should be discarded after max. 4 hours.
BCG vaccine should be administered by specially trained medical personnel under the supervision of an experienced doctor. The vial should be gently swirled before drawing up each subsequent dose. Slightly more than one dose should be drawn up, and any air bubbles and extra vaccine should be removed. Antiseptics should be allowed to evaporate completely from the skin before the injection is made. The skin should be stretched between the thumb and index finger. The needle should be almost parallel with the skin surface and the bevel of the needle facing upwards. The needle should be inserted slowly, approximately 2 mm into the superficial layer of the dermis. The needle should be visible through the epidermis during insertion. The vaccine is to be injected slowly. A raised, blanched bleb sized 8 to 10 mm is a sign of correct BCG vaccine injection. The bleb at the injection site soon disappears and transient redness develops. Three weeks after, a specific reddish cell infiltrate appears which later colliquates and ulcerates. Over the next 2-5 months, it heals spontaneously leaving a scar 2-10 mm in diameter. The scar becomes stable, discoloured, and most often slightly retracted.

Note:
The recommended dosage for age should not be exceeded, as this increases the risk of more extensive local reactions and other undesired complications.
A new disposable syringe and intradermal needle should be used for each vaccinee.
Keep the vaccine at room temperature for a short while prior to the injection.

If you use more BCG vaccine than you should
It is unlikely a higher-than-recommended vaccine dose is used, considering it is administered in a health institution and under expert supervision.

If you forget to take BCG vaccine
If you fail to receive the vaccine at the proper time, please talk to your doctor.

Effects when treatment with BCG vaccine is stopped
Not applicable.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Per their frequency, adverse reactions are classified into:
very common (may affect more than 1 in 10 patients taking the medicine);
common (may affect up to 1 in 10 patients taking the medicine);
uncommon (may affect up to 1 in 100 patients taking the medicine);
rare (may affect up to 1 in 1,000 patients taking the medicine);
very rare (may affect up to 1 in 10,000 patients taking the medicine);
not known (frequency cannot be estimated from the available data);

The expected reaction to a successful BCG vaccination includes redness at the injection site, and after three weeks an infiltrate that ulcerates and heals spontaneously over 2 to 5 months, leaving a scar of 2-10 mm in diameter. It may also include enlargement of regional lymph nodes up to 1 cm.

A strong response to BCG vaccine may occur due to spreading of the infiltrate from the formed ulcer and forming of a larger post-vaccination scar. The reason for this could be subcutaneous vaccination (instead of intradermal) or a larger dose. The ulcer should be encouraged to dry and wearing clothes made of crude material should be avoided.

The estimation of adverse reactions frequency is based on WHO data.

<table>
<tr><th>frequency/organ system</th><th>very common</th><th>common</th><th>uncommon</th><th>rare</th><th>very rare</th></tr>
<tr><td rowspan="4">General disorders and injection site reactions</td><td rowspan="4"></td><td rowspan="4"></td><td>fever</td><td rowspan="3">disseminated BCG complications (osteitis or osteomyelitis)</td><td rowspan="3">disseminated BCG infection</td></tr>
<tr><td>enlargement of regional lymph nodes > 1 cm</td></tr>
<tr><td>induration</td></tr>
<tr><td>ulceration with a discharging ulcer at the injection site</td><td rowspan="2">suppurative lymphadenitis, abscess, keloid scar</td><td rowspan="2">lupoid skin disorders</td></tr>
<tr><td>early reactions (0 – 15 min)</td></tr>
<tr><td>immune system disorders</td><td>/</td><td>/</td><td>/</td><td>allergic reactions (rash, pruritus, urticaria) including anaphylaxis (anaphylactoid or anaphylactic reaction)</td><td>/</td></tr>
</table>

If any side effect becomes serious, or if you observe any side effect not stated in this leaflet, please inform the competent doctor about it.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine. You can report side effects to the Medicines and Medical Devices Agency of Serbia (ALIMS):
The Medicines and Medical Devices Agency of Serbia
National Pharmacovigilance Centre
458 Vojvode Stepe St, 11221 Belgrade
Republic of Serbia
website: www.alims.gov.rs
e-mail: nezeljene.reakcije@alims.gov.rs

5. How to store BCG vaccine, freeze-dried

Shelf-life
Keep out of sight and reach of children.

Do not use the vaccine after the expiration of the date stated on the outer packaging. The expiry date refers to the last day of that month.

Storing
Store the vaccine in the original packaging in a refrigerator at 2°C to 8°C, protected from light.
Store the reconstituted vaccine for maximum 4 hours in a refrigerator at 2°C to 8 °C, protected from light.

Do not freeze!

Unusable medicines are handed over to a pharmacy in which a notice is displayed stating that unusable medicines are collected from citizens in that pharmacy. Do not throw any medicines via wastewater or household waste. These measures will help to protect the environment.

6. Contents of the pack and further information

What BCG vaccine, freeze-dried contains
Active substance:
1 vial of the reconstituted vaccine contains 1 mg/1 mL (1.6-16.0 x 106 CFU/mL) of live, attenuated Bacillus Calmette-Guerin (*Mycobacterium bovis* BCG), which corresponds to 20 doses of 0.05 mL for newborns and infants under 12 months of age or 10 doses of 0.1 mL for adults and children over 12 months of age.

Excipients:
- Powder: gelatine, sucrose
- Solvent: sodium-chloride, water for injections

What BCG vaccine looks like and content of the pack
Appearance of powder: white lyophilisate in the shape of porous cake,
Appearance of solvent: clear, colourless solution,
Reconstituted vaccine: whitish suspension.

Interior packaging:
- Powder: vial of amber glass Type I (Ph. Eur.) sealed with red chlorobutyl rubber stopper and alu cap with blue plastic flip-off seal.
- solvent: 1 mL ampoule of clear borosilicate glass Type I (Ph. Eur.), with cutting line and coloured point above (OPC), without coloured ring.
External packaging: foldable cardboard box containing 5 vials with freeze-dried powder for suspension for injection and 5 ampoules of solvent, packed in PVC blister, and the Patient Information Leaflet.

Marketing Authorisation Holder and Manufacturer
INSTITUTE OF VIROLOGY, VACCINES AND SERA TORLAK
458 Vojvode Stepe St; Belgrade;
Tel: + 381 11 397 66 74; Fax: + 381 11 246 96 54;
E-mail: office@torlak.rs

This leaflet was last approved
June 2022

Dispensing regime:
The medicine can be dispensed in a health institution.

Marketing Authorisation number and date:
Number of authorisation: 515-01-03262-21-001
Date of authorisation: June 1, 2022
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THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY

Therapeutic indications
BCG vaccine is intended for active immunisation of all newborns and children at a high risk of tuberculosis to prevent severe clinical forms of tuberculosis (tuberculous meningitis and disseminated tuberculosis), and for active immunisation of adults at a high risk of developing tuberculosis.
BCG vaccine should be given only to persons who have not received BCG vaccine and who have not been infected with *Mycobacterium tuberculosis* or who have a negative tuberculin reaction. BCG vaccination has no value in the treatment of persons with tuberculosis (infection with *Mycobacterium tuberculosis*).

Dosage and method of administration
BCG vaccine is given to newborns on being discharged from the maternity hospital. Children who have not received BCG vaccine until two months of age must be vaccinated in competent health institutions until they reach 12 months of age. BCG vaccine immunisation schedule is developed in compliance with the national immunisation programme.
Exceptionally, BCG vaccine can be administered to personnel in maternity hospitals and paediatric institutions, as well as to other healthcare workers with a high risk of exposure to tuberculosis, if they have not received the vaccine up to that moment in the primary vaccination. Also, BCG vaccine can be given to children at a high risk of tuberculosis who were not vaccinated in the primary vaccination, if members of their family have had tuberculosis or are coming from a country with a high prevalence of tuberculosis, or at the request of parents, if they are coming from a country in which BCG vaccination is not conducted.
The dose of BCG vaccine for newborns and infants under 12 months of age is 0.05 mL of the reconstituted vaccine and contains 0.05 mg of *M. bovis BCG* (0.8-8.0 x 10^5 CFU).
The dose of BCG vaccine for children over 12 months of age and adults is 0.1 mL of the reconstituted vaccine and contains 0.1 mg of M. *bovis BCG* (1.6-16.0 x 10^5 CFU).

Method of application:
BCG vaccine should be injected intradermally in the deltoid muscle area, at the junction of the external and internal side of the left upper arm. Use a sterile syringe of 1 mL subgraduated into hundredths of mL (1/100 mL) fitted with a needle for intradermal use.
The vaccine is to be reconstituted before use. Original solvent, delivered with the particular batch of the vaccine, should always be used. If alcohol is applied to swab the rubber stopper, it should be allowed to evaporate. The vaccine is to be reconstituted by transferring the solvent (1 mL) to the vial containing the freeze-dried vaccine using a sterile syringe fitted with a needle (the rubber stopper is not to be removed). To suspend the vaccine, the vial should be gently turned upside down a few times. Making of air bubbles should be avoided, due to precise dosing of the vaccine. The suspension should be homogenous and slightly opaque. Any unused reconstituted vaccine in a multi-dose presentation should be discarded after max. 4 hours.
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Note:
A new disposable syringe and intradermal needle should be used for each vaccinee.
Keep the vaccine at room temperature for a short while prior to the injection.

Dispensing regime:
The medicine can be dispensed in a health institution.

List of excipients
Powder for suspension for injection:
Gelatine
Sucrose

Solvent for suspension for injection:
Sodium-chloride
Water for injections

Incompatibility
In the absence of compatibility testing, BCG vaccine should not be mixed with other vaccines and/or other medicines in the same syringe.

Shelf-life
Shelf-life of newly-opened medicine: 1 year
Shelf-life after reconstitution: max. 4 hours, in a refrigerator (2°C to 8 °C), protected from light.

Do not use the vaccine after the expiration of the date stated on the outer packaging.

Special precautions for storage
Keep out of sight and reach of children.
Store BCG vaccine in the original packaging in a refrigerator at 2°C to 8°C, protected from light.
For storing conditions after reconstitution, please see section “Shelf-life”.

Do not freeze!

Nature and content of the package
Interior packaging:
- Powder: vial of amber glass Type I (Ph. Eur.) sealed with red chlorobutyl rubber stopper and alu cap with blue plastic flip-off seal.
- solvent: 1 mL ampoule of clear borosilicate glass Type I (Ph. Eur.), with cutting line and coloured point above (OPC), without coloured ring.
External packaging: foldable cardboard box containing 5 vials with freeze-dried powder for suspension for injection and 5 ampoules of solvent, packed in PVC blister, and the Patient Information Leaflet.

Special precautions for disposal of a used medicinal product (and other instructions for handling the drug)
BCG vaccine, freeze-dried, contains live, attenuated *M. bovis* BCG germs, therefore, it is to be treated as an infectious agent during handling, preparing vaccine for use and disposing of unused materials.
Empty ampoules, unusable ampoules, as well as used syringes, needles and disinfectant material, should be disposed of safely in special polyethylene bags and purpose-built containers and disposed of properly with other medical waste.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.