Package leaflet: Information for the user

Onko BCG 50
Onko BCG 100

Powder and solvent for suspension for intravesical use

BCG *ad immunocurationem*
BCG for immunotherapy

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, 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 get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Onko BCG 50, Onko BCG 100 is and what it is used for

1 ampoule or vial of the drug contains live attenuated (i.e. non-virulent) BCG (Bacillus Calmette-Guérin) bacilli, Brazilian BCG Moreau substrain suspended in 5% monosodium glutamate solution and freeze-dried in a high vacuum.

1 ampoule or 1 vial of Onko BCG 50 contains not less than 150 million live BCG bacilli.
1 ampoule or 1 vial of Onko BCG 100 contains not less than 300 million live BCG bacilli.

The medicine does not contain any preservatives.

The medicine is used in treatment of superficial, epithelial, non-invasive bladder tumors (carcinoma urotheliale T_a, T_{is}, T_1).
The medicine should not be used in invasive bladder cancer, as chances for recovery are scarce.
The medicine in a dose of 50 mg can be administrated in the case of recurring adverse reactions (dysuria, increased body temperature) or increased tuberculin skin reaction.

BCG bacilli have been used as a non-specific immunostimulating factor in the treatment of some types of cancer.

The intravesical BCG administration is intended to destroy the primary tumour, delay or prevent its recurrence. The specific mechanism of BCG action has not been fully explained. The drug is thought to work by stimulating an inflammatory process within the bladder wall that protects the body against cancer progression, and by stimulating the patient's immune system.

2. What you need to know before you use Onko BCG 50, Onko BCG 100

Do not use Onko BCG 50, Onko BCG 100

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6),
- if you have a congenital or acquired defect of the immune system,
- if you are taking immunosuppresants (e.g. corticosteroids, cytostatics, radiation therapy),
- if you have a urinary tract infection until you have a sterile urine culture,
- with significant bleeding from the bladder,
- with active tuberculosis or any other disease treated with tuberculostatics,
- before 2-3 weeks after transurethral resection (TUR),
- with bladder perforation.

Warnings and precautions

Talk to your doctor before using Onko BCG 50, Onko BCG 100.

Other medicines and Onko BCG 50, Onko BCG 100

Tell your doctor if you are taking, have recently taken or might take any other medicines.
The drug should not be used in patients treated concurrently with cytostatics and systemic steroids.
Topical steroids are not a contraindication to drug therapy.
During BCG treatment, the administration of antibiotics that may have a bactericidal effect on mycobacteria should be limited, as well as the administration of acetylsalicylic acid derivatives (Aspirin) and some anticoagulants.

Pregnancy and breast-feeding

The drug should not be used in pregnant or breast-feeding women.

Driving and using machines

The effect of Onko BCG 50, Onko BCG 100 on the ability to drive and use machines has not been studied.

3. How to use Onko BCG 50, Onko BCG 100

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

One dose of Onko BCG 50, corresponding to 1 dose used for 1 intravesical infusion, is the content of 1 ampoule or 1 vial (50 mg) reconstituted in 1 ml of isotonic solution of sodium chloride.

One dose of Onko BCG 100, corresponding to 1 dose used for 1 intravesical infusion, is the content of 1 ampoule or 1 vial (100 mg) reconstituted in 1 ml of isotonic solution of sodium chloride.

The medicine is prepared to use and administered only by qualified healthcare professional as follows:

Add 1 ml of the solvent (sterile isotonic solution of sodium chloride) to an ampoule or vial containing the powder, using a 2 ml or 5 ml sterile syringe. Carefully aspirate three times and re-discharge the contents of the ampoule or vial in order to obtain a homogenous suspension (avoid shaking and foaming the suspension). Then, collect the suspension from the ampoule or vial into a sterile 50 ml syringe and add 49 ml of the solvent (sterile isotonic solution of sodium chloride) to the container.

Remove urine from the bladder using a catheter inserted via the urethra. Then, slowly introduce the entire portion of BCG suspension (50 ml) via the catheter using a 50 ml sterile syringe, this operation should be done slowly. In order to empty the catheter completely from the BCG suspension, administer 5 ml of sterile isotonic solution of sodium chloride after the suspension has been introduced.

The patient should not drink liquids for 3-4 hours prior to and 2 hours after administration of the product. After administration of the drug through the catheter, it should be removed.

The instilled BCG suspension must remain in the bladder for 2 hours; during which the patient changes body position (abdomen, back and sideways) every 15 minutes, and empties the bladder after 2 hours.

The medicine should not be administered intravesically (bladder instillation) earlier than 14 days following the biopsy or transurethral resection (TUR).

The treatment should be performed once a week for six consecutive weeks, and then maintenance treatment is recommended every 3 months once a week for 3 consecutive weeks. If cancer recurrence is confirmed, the six-week treatment should be repeated.

Prior to treatment, the patient should undergo an intradermal tuberculin test (PT, PPI) to assess the degree of patient's immune reactivity. If the skin reaction is very intense or exceeds l cm in diameter (a reaction with a diameter of more than 6 mm is considered a positive reaction), planned immunotherapy with the medicine should be abandoned. After completion of the 6-week treatment, the intradermal tuberculin test should be repeated to assess the effect of the treatment on the patient's overall immune system reactivity. In some patients, this reactivity clearly increases.

Micturition

The patient should be instructed to urinate within 2 hours following intravesical instillation. If there are difficulties in emptying the bladder completely (urinary retention), the healthcare professional should insert the catheter into the bladder to empty the bladder of residual urine. After the micturition, the toilet is disinfected with standard disinfectants.

Important information

Unless your doctor tells you otherwise after taking the medicine, you should increase the amount of fluids you drink for 24 hours after the first urination. During this time, you should drink at least 12 glasses of fluids. Urinate on a regular basis.

Sexual abstinence is recommended within 48 hours of the infusion. Use condoms within at least 1 week afterwards.

This medicine must not be administered intravenously, subcutaneously or intramuscularly.

Catheter insertion lubricants should not contain tuberculostatic substances.

Prepare the BCG suspension for intravesical instillation immediately before the procedure.

Precautions should be taken when treating p-tuberculostatic and p-allergic complications.

If you use more Onko BCG 50, Onko BCG 100 than you should

If you are given too large dose of the medicine or it remains in your bladder for too long, the bladder should be flushed several times with the sterile, physiological sodium chloride solution. Use a catheter to remove urine from the bladder (in patients with urinary retention) and tuberculostatics in the event of septic symptoms.
These activities are performed by the qualified healthcare professionals only.

If you forget to use Onko BCG 50, Onko BCG 100

Tell your doctor if you have missed doses.

4. Possible side effects

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

Treatment of non-invasive bladder cancer with intravesical administration of Onko BCG 50, Onko BCG 100 is well-tolerated by most patients; however, both local and general side effects may occur.

Foci of tuberculosis-like granulation tissue in the lungs have been observed.

The most common adverse effect involves cystitis (cystitis acuta), developing usually after the second or third administration. Polyuria, haematuria and dysuria reported on the day of administration usually disappear within a few hours.

More serious side effects of the therapy are also known such as TB-like interstitial cystitis, prostatitis or epididymitis associated with caseous necrosis.

In patients with tuberculous prostatitis or persistent subfebrile status, a six-week treatment should be used involving QD bitherapy based on rifampicin (600 mg) and isoniazide (5 mg per kg body weight).

In patients with severe septic symptoms and arthritis, the four-month-protocol can be used, accepted for bladder tuberculosis,

involving administration of:

- three medicines daily for 2 months: rifampicin (600 mg), isoniazide (5 mg per kg body weight) and ethambutole (25 mg per kg body weight potentially replaced with pyrazinamide 1500 mg),

and

- two medicines three times a week for 2 consecutive months: rifampicin (600 mg), isoniazide (10 mg per kg body weight).

With symptoms of arthritis, it is sometimes necessary to use corticosteroids.

In patients with the above-mentioned symptoms of generalised infection, treatment with the medicine should be absolutely discontinued.

Apart from local adverse effects, systemic side effects may also occur, such as malaise, transient increased temperature (38°C-39°C), chills, nausea, muscle and joint pain, diarrhoea and genital pain.

Systemic adverse effects usually resolve within 1-3 days.

In extremely rare cases, the above-mentioned symptoms require treatment cessation and administration of tuberculostatic agents.

Focal tuberculosis-like hepatic granulomatous lesions have also been observed.

All the more serious adverse effects associated with the intravesical administration of the medicine usually resolve after 4 months of anti-tuberculosis chemotherapy.

Contact your doctor immediately or go to the nearest hospital if you experience the following symptoms:

- **allergic reaction**, which may include difficulty breathing, cough, rash or facial swelling,
- **tuberculosis infection**, which may include cough, high fever (above 39.5°C) lasting more than 12 hours, or fever (above 38.5°C) lasting more than 2 days.

Contact your doctor as soon as possible if you notice any of the following:

- yellow eyes or skin,
- greyish or whitish stools,
- fever (below 38.5°C) with chills, headache, myalgia or arthralgia lasting more than 2 days,
- dysuria or polyuria,
- ocular inflammation,
- hematuria.

To alleviate side effects, you should:

- stop smoking (if the patient is a tobacco smoker),
- rest when you feel tired,
- avoid drinking alcohol,
- follow all medical recommendations and take medications recommended by your doctor.

The frequency of side effects has been determined as follows: 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), including isolated reports, unknown frequency.

<u>Infections and infestations</u>

unknown frequency - tuberculous inflammation of the deeper layers of the bladder wall, tuberculous infection (cough, high fever lasting more than 12 hours (above 39.5ºC) or fever lasting more than 2 days (above 38.5ºC), prostatitis and/or epididymitis with formation of caseous necrosis foci
Immune system disorders
unknown frequency - allergic reaction (breathing difficulties, cough, rash, facial oedema)
Eye disorders
unknown frequency - ocular inflammation, yellow eyes
Respiratory, thoracic and mediastinal disorders
unknown frequency - foci of the tuberculous-like granulation tissues in the lungs
Gastrointestinal disorders
unknown frequency – diarrhoea, nausea, greyish or whitish stools
Hepatobiliary disorders
unknown frequency - foci of the tuberculous-like granulation tissue in the liver
Skin and subcutaneous tissue disorders
unknown frequency - yellow skin
Musculoskeletal and connective tissue disorders
unknown frequency - myalgia, arthralgia, arthritis
Renal and urinary disorders
unknown frequency - vesical tenesmus on the day of administration, pollakiuria, haematuria, polyuria, dysuria, cystitis
Reproductive system and breast disorders
unknown frequency - pain in the genital area
General disorders and administration site conditions
unknown frequency - chills, fever (below 38.5ºC) with chills, headache, myalgia or arthralgia lasting more than 2 days, short-term increase in body temperature (38ºC - 39ºC), malaise

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse, including any possible side effects not listed in this leaflet. You can also report side effects directly to the Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products: Al. Jerozolimskie 181C, 02-222 Warszawa, Phone: +48 22 49-21-301, fax: +48 22 49-21-309, web page: https://smz.ezdrowie.gov.pl.
Side effect can be also reported to Marketing Authorization Holder.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Onko BCG 50, Onko BCG 100

Store in a refrigerator (2ºC -8ºC).
Keep the ampoules or vials in the outer carton in order to protect from light.

Use immediately after reconstitution.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

The expiry date refers to the last day of that month.

After the end of the treatment, the equipment and materials should be disposed of in accordance with hazardous waste regulations.

Lot no. (Lot)
Expiry date (EXP)

6. Contents of the pack and other information

What Onko BCG 50, Onko BCG 100 contains

- The active substance is BCG (*Bacillus Calmette-Guérin*) bacilli, Moreau Brasillian substrain

- The excipient is monosodium glutamate

Onko BCG 50
1 ampoule or 1 vial with the powder contains:
BCG bacilli - 50 mg

Onko BCG 100
1 ampoule or 1 vial with the powder contains:
BCG bacilli - 100 mg

1 ampoule with the solvent contains isotonic solution of sodium chloride - 1 ml

What Onko BCG 50, Onko BCG 100 looks like and contents of the pack

Dry amorphous powder, white or light-cream colour.

Contents of the pack:

1 ampoule with 50 mg powder and 1 ampoule with 1 ml solvent
1 vial with 50 mg powder and 1 ampoule with 1 ml solvent
5 ampoules with 50 mg powder and 5 ampoules with 1 ml solvent
5 vials with 50 mg powder and 5 ampoules with 1 ml solvent
1 ampoule with 100 mg powder and 1 ampoule with 1 ml solvent
1 vial with 100 mg powder and 1 ampoule with 1 ml solvent
5 ampoules with 100 mg powder and 5 ampoules with 1 ml solvent
5 vials with 100 mg powder and 5 ampoules with 1 ml solvent

Marketing Authorisation Holder and Manufacturer

„BIOMED-LUBLIN" Wytwórnia Surowic i Szczepionek Spółka Akcyjna
Uniwersytecka Street No. 10, 20-029 Lublin, Poland
tel +48 81 533 82 21
fax +48 81 533 80 60
e-mail: biomed@biomedlublin.com

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