Patient leaflet: Information for user

Onko BCG 50

Onko BCG 100

Powder and solvent for solution for intravesical administration

BCG ad immunocurationem

BCG for immunotherapy

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm

them, even if their symptoms are the same as yours.

- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

This leaflet contains:

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

1 ampoule or vial of this medicine contains living but attenuated (i.e. non-virulent) BCG bacilli (Bacillus Calmette—Guérin), Moreau sub-strain suspended in 5% sodium glutamate solution and freeze-dried (vacuum sublimation).

1 ampoule or vial of Onko BCG 50 contains at least 150 mln living

BCG bacilli. 1 ampoule or vial of Onko BCG 100 contains at least

300 mln living BCG bacilli.

This medicine does not contain any preservatives.

This medicine is used in treatment of superficial, non-invasive urothelial carcinoma Ta, Tis, Tl.

This medicine should not be used in treatment of invasive bladder cancer, as there is only minimum chance for cure.

The lower dose of this medicine (50 mg) may be used in case of persistent adverse effects (e.g. dysuria, increased body temperature) or excessive reaction to TST (tuberculin sensitivity test).

BCG bacilli are utilized in therapy of some cancer types as a non-specific immunostimulant.

The intravesical BCG administration is intended to destroy the primary tumour as well as delay or prevent its recurrence. The specific mechanism of action of BCG has not been fully explained. It is thought that its activity involves inducing the inflammatory process within the urinary bladder wall, which protects the system from cancer development and stimulates the patient's immune system.

2. What you need to know before you are given 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 ingredients in

this medicine (see 6 „Further information");

- if you have a congenital or acquired immune defect; _ if you are taking

immunosuppresants (e.g. corticosteroids, cytostatics, radiation therapy);

- if you have an active tuberculosis or other disease which requires treatment with tuberculostatics;

- if you have an urinary tract infection, until your urine culture is negative;

Other medicines and Onko BCG 50, Onko BCG 100

Please inform your doctor if you take any other medicines, including the ones available without a prescrption.

This medicine should not be used in patients using cytostatics and systemic steroids. Using local steroids is not a contraindication to treatment with Onko BCG 50, Onko BCG 100.

During therapy with Onko BCG 50, Onko BCG 100, the use of antibiotics should be limited, as these may show biocidal activity against BCG bacilli. The use of

acetylsalicylic acid derivatives (Aspirine) and some antithrombotic agents should also be avoided.

Pregnancy and breast-feeding

This medicine 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 Onko BCG 50, Onko BCG 100 is given

A single dose of Onko BCG 50, which is equivalent to a single dose used for the intravesical instillation is composed of the content of 1 vial or I ampoule (50 mg) reconstituted in I mL of isotonic solution of sodium chloride.

A single dose of Onko BCG 100, which is equivalent to a single dose used for the intravesical instillation is composed of the content of 1 vial or 1 ampoule (100 mg) reconstituted in I mL of isotonic solution of sodium chloride.

This medicine is intended to be prepared and administered only by the qualified healthcare staff in the following manner:

Using a sterile 5 ml. syringe, add 1 mL of solvent (isotonic solution of sodium chloride) into the vial containing the powder.

Swirl the vial/ ampoule gently and then draw all the solution back to the syringe in order to obtain a homogenous suspension and repeat that step three times. Do not shake the vial and avoid foaming the suspension.

Draw all the suspension from the vial/ ampoule to the 50mL syringe and dilute to the final volume with 49 mL of isotonic solution of sodium chloride.

Empty the bladder using 12-14 F catheter. Then, using the catheter, instill the entire BCG solution volume (50 mL) into the bladder. This step should be performed very slowly and be followed by intravesical instillation of 5 mL of sterile physiological saline solution in order to remove entire BCG suspension volume from the catheter.

The patient should refrain from drinking for 3-4 hours before and 2 hours after the medicine administration. Once the medicine is administered, the Foley catheter should be removed.

The administered BCG suspension should remain within the urinary bladder for 2 hours. During this period the patient needs to change their body position every 15 minutes (supine, prone, lateral position) and eventually empties their 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 intravesical instillation should be performed once a week and repeated for six consecutive weeks. The maintenance treatment aftewards should involve intravesical instillation of the medicine every 3 months, once a week for 3 consecutive weeks. If cancer recurrence is confirmed, the treatment scheme should be changed back to the six-week-protocol.

The tuberculin skin test (PT, PPI)) should be performed on every patient prior to treatment in order to assess the reactivity of the patient's immune system. If skin reaction is very intensive or the size of induration exceeds lcm (6mm diameter is considered a positive result) the immunotherapy should not be administered. After 6 weeks of treatment the tuberculin skin test should be repeated in order to assess the effect of treatment on the patient's overall immune system reactivity, which increases significantly in some patients.

Micturition after intravesical instillation

The patient should be instructed to urinate within 2 hours following intravesical instillation. If the patient finds it difficult to empty the bladder completely (urinary retention), the healthcare professional should help by inserting the Folley catheter into the bladder. The toilet should be decontaminated after the micturition using the standard disinfectants.

Important information

You should drink more fluids within 24 hours following the first post-therapeutic micturition, unless contraindicated by your doctor. During this time you should drink at least 12 cups (200 ml.) of fluids and urinate on a regular basis.

You should refrain from sexual activity within 48 hours following the intravesical instillation and use condoms within at least 1 week afterwards.

This medicine must not be administered into the blood vessels (intravenously, i.v.), under the skin (subcutaneously, s.c.) and into the muscles (intramuscularly, i.m.).

Lubricants used in order to facilitate urinary catheterization must not contain tuberculostatic agents.

The BCG suspension for intravesical instillation should be reconstituted and prepared directly before use.

If you are given 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 longer than indicated, the bladder should be flushed with the sterile, physiological saline solution several times. The bladder should be completely emptied (using the

Folley catheter in patients with urinary retention) and tuberculostatics should be administered in case of septic symptoms.

All these activities must be performed by the qualified healthcare professionals only.

If you miss a dose of Onko BCG 50, Onko BCG 100

Please notify your doctor about the missed dose.

4. Possible adverse effects

Like all medicines, this medicine can cause side effects. Treatment of non-invasive bladder cancer with intravesical instillations of Onko BCG 50, Onko BCG 100 is generaly well-tolerated by most patients, however both local and systemic adverse effects may occur.

Focal tuberculosis-like pulmonary lesions have been observed.

The most common adverse effect involves acute cystitis (cystitis acula), developing usually after second or third instillation. Frequent urination (polyuria), haematuria and dysuria reported on the day of treatment usually resolve within few hours.

More severe adverse effects of therapy have also been noted such as TB-like interstitial cystitis, prostatitis or epididymitis associated with caseous necrosis.

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

In patients with severe septic symptoms or arthritis the four-month-protocol may be used, accepted for bladder tuberculosis, involving administration of:

- three medicines QD for 2 months: rifampicin (600 mg), isoniazide (5mg per kg b.w) and ethambutole (25 mg per kg b.w. , potentially replaced with pyrazinamide 1500 mg)
- two medicines three times a week for 2 consecutive months: rifampicin (600 mg), isoniazide (10 mg per kg b.w.)

If a patient develops symptoms of arthritis, treatment with corticosteroids may be necessary in some cases.

In patients with the systemic infection symptoms itemized above treatment with Onko BCG 50, Onko BCG 100 must be stopped.

Apart from local adverse effects, systemic side effects may also occur, such as malaise, transient increased temperature (3 8-39^{0}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 described symptoms require treatment cessation and administration of tuberculostatic agents.

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

All the serious adverse effects associated with the intravesical instillation of the medicine usually resolve after 4 months of chemotherapy using the tuberculostatic agents.

Tell your doctor immediately or go to Accident and Emergency at the nearest hospital if you notice any of the following:

- **allergic reaction**, which may be symptomatized by breathing difficulty (dyspnea), cough, rash or facial swelling (edema)
- **tuberculosis**, which may be symptomatized by cough, high fever (over 39,5 ^{0}C) lasting over 12 hours, or fever (over 38,5 ^{0}C) lasting over 2 days

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

- yellow skin or eye coloration
- greyish or white stool coloration
- fever (over 38.5 ^{o}C) with chills, headache, muscle or joint pain lasting over 2 days.
- painful urination (dysuria) or urinary frequency (polyuria)
- ocular inflammation
- haematuria

In order to minimize these side effects you should:

- stop smoking (if you smoke)
- rest whenever you feel tired
- avoid drinking alcohol during treatment
- comply with all indications of your doctor and take the recommended medications on a regular basis

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

The medicine should be stored at 2 °C-8 °C temperature (in a refrigerator).

In order to protect the medicine from light, please store the vials/ ampoules in their external packaging.

Use directly 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 packaging and vial label.

After the intravesical instillation, the equipment and materials should be disposed of as Regulated Medical Waste.

Serial no. (LOT)

Expiry date (EXP)

6. Package content and further information

What Onko BCG 50, Onko BCG 100 contains

Onko BCG 50
1 powder ampoule/ vial contains:
BCG bacilli (Bacillus Calmette—Guérin), Moreau Brasillian sub-strain 50 mg

Onko BCG 100

1 powder ampoule/ vial contains:
BCG bacilli (Bacillus Calmette—Guérin), Moreau Brasillian sub-strain — 100 mg Excipients: sodium glutamate

1 solvent ampoule 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.

Pack content:

1 ampoule with powder a 50 mg + 1 ampoule with solvent a 1mL
1 vial with powder a 50 mg + 1 ampoule with solvent a 1mL
5 ampoules with powder a 50 mg + 5 ampoules with solvent a 1mL
5 vials with powder a 50 mg + 5 ampoules with solvent a 1mL
1 ampoule with powder a 100 mg + 1 ampoule with solvent a 1mL

1 vial with powder a 100 mg + 1 ampoule with solvent a 1mL
5 ampoules with powder a 100 mg + 5 ampoules with solvent a 1mL
5 vials with powder a 100 mg + 5 ampoules with solvent a 1mL

Marketing Authorisation Holder and Manufacturer

BIOMED-LUBLIN Wytwórnia Surowic i Szczepionek S.A.

Uniwersytecka 10, 20-029 Lublin, Poland

Phone (081)533 82

21

email:biomed@biom

ed.lublin.pl

This leaflet was last revised on January 18, 2012.