SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onko BCG 100
Powder and solvent for suspension for intravesical use
BCG *ad immunocurationem*
BCG for immunotherapy

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Onko BCG 100
1 ampoule or 1 vial with the powder contains:
Live attenuated Bacillus Calmette-Guerin, Brazilian BCG Moreau substrain – 100 mg.
1 ampoule or 1 vial of Onko BCG 100 contains from 3.0×10^8 to 12.0×10^8 live BCG.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for intravesical use.
White or light cream powder, dry, amorphous.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The product is used in treatment of superficial, epithelial, non-invasive bladder tumours:
- T_{is} – carcinoma *in situ*
- T_a – epithelial carcinoma confined to the mucosa only
- T_1 - epithelial carcinoma confined to the dermis of the bladder

If side effects (dysuria, increased body temperature) occur after using Onko BCG 100, Onko BCG 50 may be used.

4.2. Posology and method of administration

Posology

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 sterile isotonic solution of sodium chloride.

Method of administration

Before opening the neck of the powder ampoule and the solvent ampoule before and after lapping, and the ampoule before and after removing the plastic cap, disinfect thoroughly with a cotton swab moistened with 70% ethanol and allow to dry.
After opening the ampoule or piercing the rubber stopper of the powder vial, introduce exactly 1 ml of isotonic sodium chloride solution with a syringe.

The solvent should be introduced in a gentle stream along the wall of the ampoule or vial. Then withdraw the entire contents of the syringe and return it gently to the ampoule or vial, avoiding foaming. Repeat until a homogeneous suspension is obtained. Transfer the suspension from the ampoule or vial to a sterile 50 ml syringe and add 49 ml of solvent (sterile isotonic sodium chloride solution). After reconstitution, a homogeneous, uniform suspension is obtained, with no visible conglomerates.

Remove urine from the bladder using a catheter inserted via the urethra. Then, introduce the entire portion of BCG suspension (50 ml) via the catheter using a 50 ml sterile syringe, this operation should be done slowly.
The patient should not drink liquids for 3-4 hours prior to and 2 hours after administration of the product. Remove catheter after product's administration.
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. For optimal efficacy, BCG Suspension should be administered as part of a maintenance regimen, so maintenance treatment is recommended once a week for three consecutive weeks at 3, 6, 12, 18, 24, 30 and 36 months. There are a number of different maintenance regimens, starting with 10 infusions over 18-27 weeks for a period of three years. However, it is not possible to say with certainty which regimen is the most effective.

If late recurrence is detected:
- *in situ* (Tis) 12 months after last exposure to BCG mycobacteria,
-Ta and T1HG (high risk) 6 months after last BCG exposure.
Complete treatment should be repeated.

Micturition:
2 hours after the drug administration, urination should be recommended, and if problems arise with complete bladder emptying (urine retention after micturition), the patient should be catheterized to remove residual urine. After urination, the toilet is disinfected with standard disinfectants.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Intravesical administration of the product should not be performed in patients:
– with congenital or acquired defect of the immune system,
– treated with immunosuppressants (e.g. corticosteroids, cytostatics or radiation therapy),
– during pregnancy, lactation or in case of suspected pregnancy,
– with urinary tract infection, until obtaining 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.
The product cannot be used for invasive bladder cancer.

4.4. Special warnings and precautions for use

Sexual abstinence is recommended within 48 hours following administration of the product into the bladder. Use condoms within at least 1 week after the instillation.

The product cannot be used intravenously, subcutaneously and intramuscularly.
After product administration, an amount of fluids taken in within 24 hours after first urination should be increased. During this time, at least 12 glasses of fluids should be taken in. Urinate on a regular basis.
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 granulomatous and allergic complications.

Exacerbation of latent BCG-infection (including delayed diagnosis)
It is possible for BCG mycobacteria to persist in the patient's body for several years after administration of the drug product. This latent BCG infection may worsen many years after the original infection, especially from granulomatous pneumonia, abscesses, infection within an aneurysm, implant, graft or surrounding tissue. The patient must be informed of the possibility of a subsequent exacerbation of latent BCG infections, and made familiar with the steps to be taken if symptoms such as fever and weight loss of unknown origin occur. If an exacerbation of latent BCG infection is suspected, an infectious disease specialist should be consulted.

4.5. Interaction with other medicinal products and other forms of interaction

Do not use the product 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.

4.6. Fertility, pregnancy and lactation

Pregnancy
The product should not be administered to pregnant women.

Breastfeeding
The product should not be administered to breastfeeding women.

4.7. Effects on ability to drive and use machines

Some adverse reactions may affect the ability to drive or operate machinery.

4.8. Undesirable effects

a. Summary of the safety profile

Like all medicines, Onko BCG 100 may cause side effects.
Treatment of non-invasive bladder cancer with the product for intravesical use is well-tolerated by most patients; however, both local and general adverse events may occur.
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 adverse events of the therapy are also known such as granulomatous cystitis, prostatitis or epididymitis associated with caseous necrosis.
In patients with granulomatous prostatitis or persistent subfebrile status, a six-week treatment should be used involving QD bitherapy based on 10 mg/kg rifampicin (600 mg) and 5 mg/kg isoniazide.

In patients with severe septic symptoms and arthritis, the four-month-protocol can be used, involving administration of:
- three medicines daily for 2 months:
10 mg/kg rifampicin (600 mg),5 mg/kg isoniazide
and 15 mg/kg ethambutole,
and
- two medicines three times a week for 2 consecutive months:
10 mg/kg rifampicin (600 mg), 10 mg/kg isoniazide.
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.

Foci of granulomatous changes in the lungs and the liver has been observed.

Adverse effects associated with possible BCG usually resolve after antimycobacterial treatment.

After administration of Onko BCG 100, the following side effects may appear:
– **allergic reaction**, which may include difficulty breathing, cough, rash or facial swelling,
– **BCG 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,
– yellow eyes or skin,
– greyish or whitish faeces,
– fever (below 38.5°C) with chills, headache, myalgia or arthralgia lasting more than 2 days,
– dysuria or polyuria,
– ocular inflammation,
– haematuria (see tabular summary of adverse reactions).

BCG infection after completion of immunotherapy
In isolated cases, BCG infection can manifest after the end of therapy (see section 4.4). Diagnosis can be difficult because doctors do not usually suspect a causal relationship between symptoms and previous BCG therapy. Early diagnosis and correctly selected therapy is important to the outcome of treatment, especially in elderly or immunocompromised patients, to avoid severe complications. There is a patient Warning card focusing on this topic, which the patient should receive after drug administration.

To alleviate side effect, it is recommended to:
– stop smoking (if the patient is a tobacco smoker),
– get some rest when feeling fatigue,
– avoid drinking alcohol,
– follow all doctor's recommendations and take medications recommended by the doctor.

b. Tabulated list of adverse reactions

The table below was prepared in accordance with the MedDRA System Organ Classes classification (System Organ Classes and recommended terminology).

The frequency has been determined according to the following criteria: 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), not known (cannot be estimated from the available data).

MedDRA System Organ Classes	Adverse reactions	Frequency
Infections and infestations	Granulomatous inflammation of the deeper layers of the bladder	Not known (cannot be estimated from the available data)
	BCG infection [cough, severe fever lasting longer than 12 hours (temperature above 39.5ºC) or fever lasting longer than two days (temperature above 38.5ºC)]	
	Prostatitis and/or epididymitis with formation of caseous necrosis foci	
Immune system disorders	Allergic reaction (breathing difficulties, cough, rash, facial oedema)	
Eye disorders	Inflammatory conditions of the eyeball	
	Yellow eyes	
Respiratory, thoracic and mediastinal disorders	Granulomatous changes in lungs	
Gastrointestinal disorders	Diarrhoea	
	Nausea	
	Greyish or whiteish stools	
Hepatobiliary disorders	Granulomatous changes in liver	
Skin and subcutaneous tissue disorders	Yellow skin	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	
	Arthritis	
Renal and urinary disorders	Vesical tenesmus on the day of administration	
	Pollakiuria	
	Haematuria	
	Polyuria	
	Marked pain when urinating	
	Cystitis	
Reproductive system and breast disorders	Pain in the genital area	
General disorders and administration site conditions	Chills	
	Fever (below 38.5ºC) with chills, headache, myalgia or arthralgia lasting longer than 2 days	
	Short-term increase in body temperature (38ºC - 39ºC)	
	Malaise	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products:

Al. Jerozolimskie 181C, 02-222 Warsaw, phone number: + 48 22 49-21-301, fax: + 48 22 49-21-309, web page: https://smz.ezdrowie.gov.pl.
Adverse reactions can also be reported to the Marketing Authorisation Holder.

4.9. Overdose

In case of administering an excessive dose or too long retention of the product in the bladder, rinse the bladder a few 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, ATC code: L03AX

5.2. Pharmacokinetic properties

BCG bacilli have been applied as a non-specific immunostimulating factor in the treatment of some types of carcinoma.
Intravesical administration of BCG is intended to eliminate primary tumour or to delay or prevent its consecutive recurrence. Specific mechanism of action of BCG has not been fully explained. It is believed that the drug stimulates emergence of inflammatory condition in the bladder wall which defends the organism against development of the disease, and stimulates the patient's immune system.

5.3. Preclinical safety data

Non-clinical data from conventional pharmacological safety and toxicity studies do not indicate any particular hazard.

No mutagenicity, carcinogenicity or reproductive toxicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder:
Monosodium glutamate

Solvent:
Isotonic solution of sodium chloride

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years
Use the product immediately after reconstitution.

6.4. Special precautions for storage

Store in a refrigerator (2°C-8°C)
Keep the ampoules or vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

100 mg of the powder in an ampoule or vial made of glass type I and 1.0 mL of the solvent in an ampoule made of glass type I in a cardboard box –packaging of 1 or 5.
Vial stopper is made of chlorobutyl or bromobutyl rubber with silicone layer.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any opening of ampoules or puncturing of vials, introduction of solvent and preparation of a homogeneous suspension should be carried out in such a way as to avoid contamination.

Only sterile, single-use needles and syringes should be used for infusion preparation.

No incompatibility was observed between the medicinal product and the medical device used for reconstitution and administration of drugs in a closed system, consisting of polypropylene (PP), polycarbonate (PC), and polyisoprene.

Any unused drug residues or waste should be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

No. 4317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 July 1999
Date of latest renewal: 09 July 2013

10. DATE OF REVISION OF THE TEXT
03/2026