



GreenSignal Bio Pharma Private Limited
Gummidipoondi, Chennai

SUMMARY OF PRODUCT CHARACTERISTICS-BCG FOR IMMUNOTHERAPY

1. Name of the Medicinal Product (Generic Name):

- 1.1 Product Name : BCG for immunotherapy (Freeze Dried) Live attenuated
- 1.2 Generic name : Bacillus Calmette - Guerin (Mycobacterium bovis- Danish 1331 strain)
- 1.3 Strength : 40 mg/ Vial 1- 8×10^8 CFU / Vial
- 1.4 Pharmaceutical & Dosage Form : White Lyophilized Pellet for intravesical instillation

2. Qualitative and Quantitative Composition:

- 2.1 BCG for immunotherapy is a live freeze-dried preparation made from attenuated strain of *Mycobacterium Bovis*.
- 2.2 Each vial contains 40 mg of Bacillus Calmette - Guerin (Danish - 1331 strain) having $1- 8 \times 10^8$ CFU / Vial.
- 2.3 **Stabilizer:** 5% Monosodium glutamate is used as a stabilizer.
- 2.4 The BCG for immunotherapy has to be reconstituted with 50 ml of sodium chloride injection (0.9% W/V).
- 2.5 The BCG for Immunotherapy has to be administered Intravesically and it contains BCG of Danish 1331 of attenuated strain of *Mycobacterium Bovis*.

S. No.	Components	Concentration
1.	Bacillus Calmette - Guerin (Danish - 1331 strain)	$1-8 \times 10^8$ CFU per Vial

3. Pharmaceutical Form (Dosage Form and Strength):

- 3.1 Pharmaceutical form - White Lyophilized pellet.
- 3.2 Strength - $1-8 \times 10^8$ CFU per Vial

4. Clinical Particulars:

4.1 Therapeutic Indications:

- Carcinoma in situ of urinary bladder, (prophylaxis and treatment) BCG is used intravesically for prophylaxis and treatment of primary multifocal, high grade and relapsed superficial transitional bladder carcinoma.



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- It is used to reduce the frequency of tumor recurrence after transurethral resection and to eliminate the existing tumors, including (T_a and T₁ tumors) and carcinoma in situ (CIS tumors) with or without associated papillary tumors.
- It is not indicated for treatment of papillary tumors occurring alone or for prevention of papillary tumors after transurethral resection.

4.2 Posology and method of administration:

Per instillation the contents of 2 or 3 vials (80mg – 120mg) are required.

Reconstitute each vial with 50mL of sodium chloride (0.9% w/v) injection for instillation into the urinary bladder.

Method of Administration:

Intravesical treatment with BCG for immunotherapy should begin between 7 to 14 days after biopsy or Trans Urethral Resection (TUR). After use, all equipment should be sterilized or disposed properly, as with any other bio hazardous waste. BCG for immunotherapy should not be injected subcutaneously or intravenously.

Draw 1 mL of sterile diluent (Preservative free 0.9% w/v sodium chloride injection) into a sterile syringe and add to one vial of BCG for immunotherapy to resuspend. Leave them in contact for 1 min. Then mix the suspension by withdrawing it into the syringe and expelling it gently back into the vial 2 to 3 times.

Avoid the formation of foam and should not expose the reconstituted product to sunlight, directly or indirectly. Exposure to artificial light should be kept to minimum period of time.

Dilute the reconstituted product in an additional 49 mL of diluent, bringing the total volume to 50 mL. Below mentioned information's should be followed strictly before start administering the product.

4.3 Contraindications

BCG for immunotherapy should not be used in following situations

- When the patient has an injury / infection in urinary tract.
- HIV positive patients.
- Known tuberculosis patients and those who are on treatment with anti-tuberculosis drugs.
- It is advisable to abstain from intercourse till 10 days after the last installation of treatment.



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4.4 Special Warnings and Precautions for Use:

BCG for immunotherapy contains live attenuated *Mycobacterium Bovis*. It should be prepared, handled and disposed off as a biohazardous material as it can cause serious Infections in susceptible individuals. BCG infections have been reported in health care workers and immunosuppressed patients. BCG is capable of dissemination when given intravesically and fatal infections have been reported in scientific literature. The product labeled as for immunotherapy is for use only in the treatment of bladder cancer. It is not intended to be used as an immunizing agent for the prevention of tuberculosis. BCG for immunotherapy is not a vaccine for the prevention of cancer and is not to be used as a vaccine against tuberculosis.

Possible Side effects of BCG for Immunotherapy are Urinary frequency, dysuria, flu – like symptoms, fatigue and malaise.

Use BCG as per the prescription of an Oncologist only and should be stored in Dark between 2 to 8°C. Protect from direct sunlight.

Use the reconstituted preparation immediately after reconstitution and discard the unused portion. Reconstitution, preparation and administration should be performed under aseptic conditions.

4.5 Interaction with other Medicinal Products and other forms of interactions (Drug Interactions):

Antimicrobial therapy (potential negative effect on actions of BCG), bone marrow depressants or immunosuppressant or radiation (may impair immune response to BCG). The interval between discontinuation of medications that cause Immunosuppression and restoration of the patient's ability to respond BCG depends on the intensity and type of Immunosuppression causing therapy used, the underlying disease and other factors; estimates vary from 3 months to 1 year. Also, may increase the risk of osteomyelitis or disseminated BCG infections.

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.) (Pregnancy and Lactation)

Studies have not been done in humans and / or animals.

4.7 Effects on ability to drive and machine:

Not Applicable.



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4.8 Undesirable Effects:

The Undesirable Effects with BCG for Immunotherapy is as follows urinary frequency, dysuria, Flu like symptoms, fatigue and malaise.

4.9 Overdose:

Not Applicable.

5. Pharmacological Properties:

5.1 Mechanism of Action:

BCG for immunotherapy is intended to be administered intravesically. BCG attaches to the cell surface after instillation into bladder, due to its access to the bladder cancer cells and the normal urothelial cells. The Fibronectin (FN) on the surface of tumor cells and normal urothelial cells link cells through the $\alpha 5\beta 1$ receptor. The combination of Fibronectin attachment protein (FAP) existing on BCG cell wall surface and FN enables BCG to attach to the cell surface. The surface of normal bladder cells contains a hydrophilic, highly sulfated glycosaminoglycan (GAGs), which bears negative charges. The surface of the BCG cell wall is also negatively charged. Therefore, BCG attaches much less to normal bladder epithelial cells, which will reduce the damage of BCG to the normal bladder epithelial cells and the adverse reaction BCG therapy. However, the certainty is that residual tumor cells in the bladder and normal epithelial cells repaired after damage can internalize the intravesical BCG several weeks after transurethral resection of bladder tumor (TURBT), which is an important mechanism that triggers the subsequent immune response.

5.2 Pharmacodynamics Properties:

BCG acts as a non-specific immunostimulant and attacks to the tumor cell through fibronectin protein and induces innate immunity by producing cytokines like interleukin (IL2, IL12), Interferon gamma and α -TNF which are responsible for tumor cell lysis.

5.3 Pharmacokinetic Properties:

The attachment of BCG to the bladder wall after voiding is found significant for the treatment and to prevent the prophylaxis of bladder cancer. This approach enables a targeted pharmacological effect at the site of application by triggering a localized inflammatory response and cellular infiltration, while simultaneously stimulating the systemic reticuloendothelial system. After two hours of instillation, BCG is excreted with the first urine void.



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6. Preclinical safety data (Non-Clinical Properties):

6.1 Animal Toxicology or Pharmacology

The non-clinical data reveals no hazard for humans based on the safety assessment conducted. During the follow-up there were no deaths or serious adverse events or adverse events observed and no safety issues emerged during observation period.

7. Description

White Lyophilized Pellet

BCG for immunotherapy is freeze dried live attenuated *Bacillus Calmette - Guerin* derived from strain of *Mycobacterium Bovis*, Danish 1331 strain. It is used to prevent the reoccurrence of tumors in urinary bladder (Urinary bladder carcinoma).

8. Pharmaceutical Particulars:

8.1 List of Excipients:

S. No.	Name of the excipient	Concentration
1.	Monosodium Glutamate	5 % (W/V)

8.2 Incompatibilities:

Not Applicable.

8.3 Shelf life:

BCG for immunotherapy has a shelf life of 24 months, provided it is stored in dark between 2 - 8 °C and protected from light.

9. Nature and content of Container (Packaging Information):

The BCG for Immunotherapy is filled in USP Type I Amber colour glass vials with Bromo butyl rubber stoppers and aluminum flip off seal.

9.1 Storage and Handling Instruction

9.1.1 Special Precaution for Storage:

BCG for immunotherapy should be stored in Dark between 2 to 8°C. Protect from direct sunlight.

Use immediately after reconstitution.



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9.1.2 Special precaution for disposal:

If the preparation of BCG for Immunotherapy suspension cannot be performed in a biocontainment hood, the pharmacist or individual responsible personnel for mixing the agent should wear the gloves mask and gown to avoid inadvertent exposure to broken skin or inhalation of BCG organisms particularly in common area, to avoid the cross contamination of parental products with BCG and dispose the product directly.

10. Patient Counselling Information

Patients receiving intravesical BCG should be under the supervision of a Physician experienced in immunotherapy.

11. Marketing Authorization Holder (Details of Manufacturer):

GreenSignal Bio Pharma Private Ltd,
No. 49, Pappankuppam Village,
Gummidipoondi Taluk,
Chennai 601201, India.

12. Details of Marketing Authorization numbers(s) (Details of permission or License number with date))

The Market Authorization number is TN00002462 dated 29.12.2017.

13. Date of Revision

23/03/26