1. NAME OF THE MEDICINAL PRODUCT
BCG for Immunotherapy I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
After reconstitution, each vial contains:
Bacillus Calmette-Guerin strain: 40mg/mL
Between 1-19.2 X 10^8 Colony Forming Units (CFU)
Stabilizer: Sodium glutamate 5%
Reconstitute each vial with 50 ml of sodium chloride injection.

3. PHARMACEUTICAL FORM
BCG for Immunotherapy I.P for intravesical instillation is a live freeze-dried preparation derived from attenuated strain of *Mycobacterium bovis*.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
For treatment of flat Urothelial Cell Carcinoma in Situ of urinary bladder and as adjunctive therapy following transurethral resection of primary or relapsing superficial noninvasive papillary tumors that are limited to the bladder mucosa (stage Ta or T1).
Intravesical BCG Immunotherapy has been shown to reduce tumor recurrence and prevent progression.

4.2 Posology and method of administration
4.2.1 Posology

Dosage:
Treatment should be started 2-3 weeks after performing Trans Urethral Resection of Bladder Tumour (TURBT). The treatment schedule is weekly repeated instillation with SII-ONCO- BCG (120 mg) during first 6 weeks, followed by 3 consecutive weekly instillations at 3 months, at 6 months and thereafter every 6 months upto 36 months. This means that a patient who stays tumor free after the initial resection will receive a total of 27 instillations in a period of three years.

The duration and frequency of maintenance treatment should be evaluated on the basis of tumor classification and clinical diagnosis.

Reconstitution procedure:
Add 1 mL of sterile isotonic preservative free saline (0.9% NaCl) by means of a sterile syringe to the contents of 1 vial of SII-ONCO-BCG and allow to stand for few minutes.
Then gently swirl the vial until a homogenous suspension is obtained (Caution: Avoid forceful agitation). The above procedure may be repeated to reconstitute each subsequent vial/s used.

Preparation of Solution for instillation:
Transfer the reconstituted suspension from the vial into a 50 mL syringe. Rinse the empty vial with 1 mL sterile isotonic saline. Add the rinse fluid to the reconstituted suspension in the 50 mL syringe. The above procedure may be repeated for each subsequent vial/s used. Finally, dilute the content of 50 mL syringe (by adding sterile physiological saline solution) upto a total volume of 50 mL. Mix the suspension carefully. The suspension is now ready to use.

4.2.2 Method of administration

Insert a catheter by aseptic technique through urethra into bladder and drain completely. Attach 50 ml syringe containing the prepared solution to the catheter and instill into bladder slowly by gravity where it should be retained for 2 hours. Patient should not ingest any fluid 4 hours before and 2 hours after instillation and should lie on their stomach for first 15 mins after instillation. Patient may have frequent position changes on either sides every 15 mins in order to distribute the medication properly throughout the bladder. Thereafter, the patient should be made to void the instilled contents in sitting position. If there is any bleeding or any other signs of traumatic injury, treatment should be postponed for at least 1 week.

4.3 Contraindications

BCG for Immunotherapy I.P (SII ONCO BCG) for intravesical instillation carcinoma in situ of bladder should not be used in:

- Impaired immune response irrespective of whether this impairment is congenital or caused by disease, drugs or other therapy.
- Positive HIV serology.
- Pregnancy and lactation: Safety of the mode of therapy in pregnant women, nursing mothers and Children has not been evaluated.
- Positive tuberculin reaction in conjunction with clinical evidence of existing active tuberculosis.
- Urinary tract infection: Treatment should be withheld till urine culture is negative and antibiotic therapy is stopped.
- Trauma to urinary bladder.
- A patient with fever needs careful evaluation before therapy is instituted.
- Ongoing treatment with antitubercular agents.

4.4 Special warnings and special precautions for use

Special Warning

This preparation is not to be used as a vaccine against tuberculosis.

Precautions

BCG for Immunotherapy I.P (SII ONCO BCG) should not be administered intravenously, subcutaneously or intramuscularly. The product is not intended for immunization. The preparation contains live attenuated mycobacterium (BCG) and should be used with aseptic technique. All equipment, supplies and receptacles in contact with BCG should be handled and disposed off as biohazardous. Urine voided for 6 hours after instillation also needs to be properly disinfected.

Special precautions for use:

- Do not expose the contents to light before and after reconstitution.
- Use immediately after reconstitution and discard unused portion.
- Reconstitution, preparation and administration should be performed under aseptic conditions.
- Before the first instillation, Tuberculin test should be performed, in case positive, the drug is contraindicated only if there is an evidence of active tuberculosis infection.
- Delay treatment in patients who experience traumatic catheterization till mucosal damage has healed.
- Adequate HIV assay are recommended in patients who are at risk of HIV infection.
- It is recommended to refrain from sexual intercourse for one week after instillation or use a condom.

4.5 Interactions with other medicinal products and other forms of interaction

BCG for Immunotherapy I.P. (SII ONCO BCG) is sensitive to most antibiotics especially to anti-tubercular drugs like Streptomycin, Isoniazid, Ethambutol, Rifampicin and PAS (Paraamino Salicylic Acid). It is not known whether interactions occur during intravesical instillation of SII-ONCO-BCG or whether the interactions result in clinically relevant reduction of multiplication activity of SII-ONCO-BCG. Hence, it is not clear whether activity of SII-ONCO-BCG is influenced by concomitant therapy with antibiotics. If a patient is receiving antibiotics treatment then intravesical instillation should be postponed till completion of antibiotics treatment. Studies on interaction with other drugs are not performed.

4.6 Pregnancy and lactation

Not evaluated.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse effects are generally mild and transient. They appear to be directly related to cumulative CFU count of BCG administered in various instillations. Common side effects are:

- Frequency, urgency of micturition and dysuria – these symptoms usually occur from 2nd or 3rd instillation onwards.
- Cystitis and typical granulomatous inflammatory reactions which occur in the mucosa of Urinary bladder may be an essential component of anti-tumor activity of the drug. The symptoms usually disappear within 2 days and do not require treatment. Cystitis may be more prolonged during maintenance treatment and if severe, isoniazid 300 mg daily can be given with analgesics until symptoms disappear.
- Malaise and low-medium grade fever and /or flu like syndrome. These symptoms usually occur in 4 hours after instillation and disappear within 24 - 48 hours.

Rare adverse effects:

- Fever more than 39°C. The fever resolves within 24-48 hours with antipyretics and fluids.
- Systemic BCG infections due to traumatic catheterization, perforation of bladder or early BCG instillation after extensive TURBT which may be manifested by Pneumonitis, Hepatitis or Cytopenia. Patients with such symptoms should be treated with Tuberculostatic drugs as per treatment schedules used, triple drug therapy with or without cycloserine for some weeks should be used.
- Granulomatous prostatitis
- Arthritis, Arthralgia, Haemturia, Orchitis, Transient urethral obstruction, Epididymitis or bladder Contraction may occur.

4.9 Overdose

Cases of overdose have not been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

BCG acts as a nonspecific immunostimulant and attacks to the tumor cell through fibronectin protein which causes internalisation of BCG in tumor cells, systemic RES stimulation and induces local inflammatory reaction & cell infiltration. This further activates macrophages, T
& B Lymphocytes and NK cells and produces Cytokines like Interleukin (IL2, IL12), Interferon gamma and α-TNF which are responsible for Tumor cell lysis.
Pharmacotherapeutic Group: L 03-AX03.

5.2 Pharmacokinetic properties

For the treatment and recurrence prophylaxis of bladder cancer, the attachment of BCG to the bladder wall after voiding has been shown to be important. This allows a targeted pharmacological effect at the site of application by inducing local inflammatory reaction and cell infiltration and also systemic reticulo endothelial system stimulation. BCG is excreted with the first urine void, two hours after the instillation.

5.3 Pre-clinical safety data

The product was tested for toxicity and efficacy in animal models and was found to be safe for potential clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium glutamate, USP-NF is the excipient used in the formulation as a stabilizer.

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other products.

6.3 Shelf life

SII-ONCO-BCG has a shelf life of 24 months provided it is stored in dark at 2° to 8°C and protected from light.

6.4 Special precautions for storage

BCG for Immunotherapy I.P (SII ONCO BCG) should be stored in dark between +2 °C and +8°C. Do not expose the contents to light before and after reconstitution. If not use immediately then it should be stored in the dark at 2-8°C for no longer than 4 hours. Discard unused portion.

6.5 Nature and contents of container

BCG for Immunotherapy I.P. (SII ONCO BCG) is filled in an amber color, tubular vial of 4 mL capacity, 40 mm height and 16.5 mm body diameter. Vials are closed with a grey, silicon slotted rubber stopper and green aluminum flip-off caps. These materials are standard primary packaging materials at Serum Institute of India Pvt. Ltd. (SIIPL).

Presentation: One carton containing 1 vial of BCG for Immunotherapy I.P.

6.6 Special precautions for disposal

All used materials should be disposed off in special disposal containers for infectious material. The patient´s urine containing BCG can simply be voided and then flushed in the toilet. From the hygiene point of view, the use of disinfectants or special detergents is not necessary, though this recommendation might differ from country to country.

7. MARKETING AUTHORIZATION HOLDER

Serum Institute of India Pvt. Ltd.
S. No 105-110, Manjari Bk.
Pune 412 307, India
Website: www.seruminstitute.com

8. MARKETING AUTHORISATION NUMBER (S)

Manufacturing permission number: MF/BIO/21/000128
Manufacturing License number: MH/103248

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of First Authorization: 16.12.2021.

Date: 31 December 2022