For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

BCG for Immunotherapy B.P.

SII-ONCO-BCG

(Freeze-Dried)

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

DESCRIPTION
SII-ONCO-BCG (BCG for Immunotherapy B.P.) for intravesical instillation is a live freeze-dried preparation derived from attenuated strain of *Mycobacterium bovis* (Bacillus Calmette Guerin).

COMPOSITION
Each vial contains:
Bacillus Calmette-Guerin strain: 40 mg/ml
(between 1-19.2 x 10^8 CFU)

INDICATIONS
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.

DOSAGE
Treatment should be started 2-3 weeks after performing 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
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 of 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 the 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.

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 atleast 1 week.

ADVERSE 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 tumour 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 a 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, Haematuria, Orchitis, Transient urethral obstruction, Epididymitis or bladder contraction may occur.

CONTRAINDICATIONS

SII-ONCO-BCG for intravesical instillation in 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 infections : 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.
- On going treatment with antitubercular agents.

PRECAUTIONS

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.

INTERACTIONS

SII-ONCO-BCG is sensitive to most antibiotics specially to anti-tubercular drugs like Streptomycin, Isoniazid, Ethambutol, Rifampicin and PAS (Para-amino 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 (also see the "Contraindications"). Studies on interaction with other drugs are not performed.

STORAGE

SII-ONCO-BCG should be stored in dark between +2° and +8°C. Do not expose the contents to light before and after reconstitution. Use immediately after reconstitution.

Although it is recommended to use SII-ONCO-BCG immediately after reconstitution, the reconstituted solution can be stored for up to 4 hours when refrigerated at +2° and +8°C and protected from light. Any unused portion should be discarded as a biohazardous waste. If the reconstituted product exhibits clumping, then it should be gently shaken before use.

SHELF LIFE

Do not exceed the expiry date stated on the external packing.

PRESENTATION

One carton containing 1 vial of SII-ONCO-BCG (Freeze-Dried).

Pack of three cartons each containing 1 vial of SII-ONCO-BCG (Freeze-Dried).

Manufactured by:

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