

## Onco-BCG Injection (BCG for Immunotherapy I.P - Freeze-dried)

### Composition

Each vial contains:

Bacillus Calmette-Guerin strain... 40 mg/ml

(between  $1-19.2 \times 10^8$  CFU)

Reconstitute with 50 ml of Sodium Chloride Injection

### Dosage Form

Available as freeze-dried BCG powder for reconstitution. Appearance is white to off-white pellet with powder in an amber color vial.

FOR INTRAVESICAL INSTILLATION ONLY

### Pharmacology

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

#### ► Pharmacodynamics

##### *Mechanism of action*

BCG acts as a non specific 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  $\alpha$ -TNF which are responsible for Tumor cell lysis.

#### ► Pharmacokinetics

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.

### 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 And Administration

Treatment should be started 2-3 weeks after performing TURBT. The treatment schedule is weekly repeated instillation with Onco-BCG (80mg or 120 mg) during first 6 weeks, followed by 3 consecutive weekly instillations at 3 months, at 6 months and thereafter every 6 months up to 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.

#### ► Method of Preparation

##### 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 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 at least 1 week. Use immediately after reconstitution and discard unused portion.

## Contraindications

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.

Gross haematuria: In these cases, Onco-BCG therapy should be stopped or postponed until the haematuria has been successfully treated or has resolved.

A patient with fever needs careful evaluation before therapy is instituted.

Ongoing treatment with antitubercular agents.

## Warnings And Precautions

## ► General

### *Handling Precautions*

Because Onco-BCG contains live mycobacteria, Reconstitution, preparation and administration should be performed under aseptic conditions.

Onco-BCG and all equipment, supplies and receptacles in contact with Onco-BCG, should be disposed as biohazardous waste (or material). Use aseptic techniques, wear gloves and eye protection, and take precautions to avoid contact of Onco-BCG with broken skin. Avoid needle stick injuries during the handling and mixing of Onco-BCG. Urine voided for 6 hours after instillation also needs to be properly disinfected.

BCG infections have been reported in health care workers preparing BCG for administration. Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs that were prepared in areas in which BCG was prepared.

Onco-BCG should not be administered intravenously, subcutaneously or intramuscularly.

The product is not intended for immunization.

Do not expose the contents to light before and after reconstitution.

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.

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.

## ► Drug Interactions

BCG for Immunotherapy 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 BCG for Immunotherapy or whether the interactions result in clinically relevant reduction of multiplication activity of BCG for Immunotherapy. Hence, it is not clear whether activity of BCG for Immunotherapy 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.

Immunosuppressants and/or bone marrow depressants and/or radiation may interfere with the development of the immune response and thus with the anti-tumour efficacy and should therefore not be used in combination with Onco-BCG.

### Systemic BCG Reaction

A systemic BCG reaction is a systemic granulomatous illness, which may occur subsequent to exposure to BCG for Immunotherapy. Because it is usually difficult to isolate BCG organisms from affected organs, the extent such a reaction is caused by an infectious process versus an inflammatory hypersensitivity reaction often is unclear. "Systemic BCG reaction" may be defined as the presence of any of the following signs, if no other etiologies for such signs are detectable: fever  $\geq 39.5^{\circ}\text{C}$  ( $\geq 103.1^{\circ}\text{F}$ ) for  $\geq 12$  hours; fever  $\geq 38.5^{\circ}\text{C}$  ( $\geq 101.3^{\circ}\text{F}$ ) for  $\geq 48$  hours; pneumonitis; hepatitis; other organ dysfunction outside of the genitourinary tract with granulomatous inflammation on biopsy; or the classical signs of sepsis, including circulatory collapse, acute respiratory distress, and disseminated intravascular coagulation. If BCG for Immunotherapy is administered within two weeks of either biopsy, TUR or traumatic bladder catheterization (associated with hematuria), a systemic BCG reaction is much more likely to occur.

### BCG infection

To help prevent serious infections, avoid trauma and/or introduction of contaminants to the urinary tract. Delay treatment in patients who experience traumatic catheterization till mucosal damage has healed.

BCG infections of aneurysms and prosthetic devices (including arterial grafts, cardiac devices, and artificial joints) have

been reported following intravesical administration of BCG. The risk of these ectopic BCG infections has not been determined. The benefits of BCG for Immunotherapy therapy must be carefully weighed against the possibility of an ectopic BCG infection in patients with pre-existing arterial aneurysms or prosthetic devices of any kind.

Some male genitourinary tract infections (orchitis/epididymitis) have been refractory to multiple drug antituberculous therapy and required orchiectomy.

Monitor patients for the presence of symptoms and signs of toxicity after each intravesical treatment. If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, permanently discontinue BCG instillations, evaluate and treat the patient immediately for BCG infection, and seek an infectious diseases consultation. As standard therapy for BCG infection, promptly initiate treatment with 2 or more antimycobacterial agents while conducting diagnostic evaluation, including cultures. Do not use single antibiotic therapy. Negative cultures do not rule out infection.

#### Bacterial Urinary Tract Infection (UTI)

If a bacterial urinary tract infection (UTI) occurs during the course of Onco-BCG treatment, withhold Onco-BCG instillation until complete resolution of the bacterial UTI.

#### Antimicrobial Therapy

Do not use antimycobacterial drugs (e.g., isoniazid) prophylactically to prevent the local, irritative side effects of BCG for Immunotherapy. They may affect the effectiveness of BCG for Immunotherapy and there are no data to suggest that the acute, local urinary tract symptoms common with intravesical BCG are due to mycobacterial infection.

#### ► Pregnancy

Onco-BCG instillation for carcinoma of the bladder is contraindicated during pregnancy.

#### ► Lactation

Onco-BCG instillation for carcinoma of the bladder is contraindicated during lactation.

#### ► Paediatric Use

Safety and effectiveness of BCG for Immunotherapy for the treatment of superficial bladder cancer in pediatric patients have not been established.

#### ► Small Bladder Capacity

In patients with small bladder capacity, consider increased risk of bladder contracture when making the decision to treat with BCG for Immunotherapy.

## 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 2<sup>nd</sup> or 3<sup>rd</sup> 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.

Post-marketing surveillance study was conducted on 105 patients attending Urology clinics/ out-patient departments of different hospitals in India. A total of 549 doses of Onco-BCG (each 40 mg vial containing  $1-19.2 \times 10^8$  CFU) was instilled intravesically in a dose of 80 mg or 120 mg of Onco-BCG at each instillation. 37 Patients (35.24%) received 80 mg and 68 patients (64.76%) received 120 mg of Onco-BCG at each instillation. Following table shows the frequency of adverse events observed in this PMS study.

Table: Adverse Events observed after administration of Onco-BCG in Post-marketing Surveillance (PMS) Study

Adverse reactions	After 1 <sup>st</sup> instillation	After 2 <sup>nd</sup> instillation	After 3 <sup>rd</sup> instillation	After 4 <sup>th</sup> instillation	After 5 <sup>th</sup> instillation	After 6 <sup>th</sup> instillation
Number of patients	105	98	94	87	84	81
Dysuria	20(19.05%)	6 (6.12%)	3 (3.19%)	1(1.15%)	1(1.19%)	0
Urgency/ frequency	7 (6.67 %)	2 (2.04%)	1 (1.06%)	0	0	0
Haematuria	22(20.95%)	4(4.08%)	0	1(1.15%)	0	0
Flu like Syndrome	2 (1.90%)	1 (1.02 %)	0	0	0	0
Fever	8 (7.62%)	1 (1.02 %)	0	0	0	0
Pain	3 (2.86%)	1 (1.02 %)	0	0	0	0
Cystitis	2 (1.90 %)	1 (1.02 %)	0	0	0	0
Bladder cramps	4 (3.81%)	1 (1.02 %)	1 (1.06 %)	0	0	0
Nausea/ Vomiting	0	0	0	0	0	0
Incontinence	0	0	0	0	0	0

Arthritis/ Myalgia	0	0	0	1 (1.15 %)	0	0
Urinary tract Infection	3 (2.86%)	1 (1.02 %)	0	0	0	0
Any other	1 (0.95 %) Tremor	0	0	0	0	0

Data on file

## Overdosage

In case of overdosage, the patient should be closely monitored for signs of systemic BCG infection and if necessary treated with anti-tuberculosis drugs.

## Storage And Handling Instructions

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. Discard the unused portion.

## Packaging Information

Onco-BCG: Each carton containing 1 vial of freeze-dried BCG powder for reconstitution

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# Onco-BCG Injection

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