WHO PUBLIC ASSESSMENT REPORT (WHOPAR)			
BCG Vaccine (Bacillus Calmette-Guérin)			
GreenSignal Bio Pharma Pvt Limited, India			
Ref. no. PQ-FVP-2024-0008-WHOPAR-04			
Effective date: 3 Dec 2024	**Published: 31 Jan 2025**	**Last Update: 31 Jan 2025**	**Version: 1**

What is BCG Vaccine?

BCG Vaccine is a live, freeze-dried vaccine made from a live attenuated strain of *Mycobacterium bovis*, Danish 1331 strain. It is used for the prevention of tuberculosis. The bulk vaccine is filled in amber colour type I glass vials, and it is subjected to the process of lyophilization (freeze-drying). Because the vaccine is presented in a lyophilized form, it has to be reconstituted with the diluent provided with the vaccine, to form a homogeneous and slightly opaque suspension for injection.

BCG suspension for injection is administered through intradermal route.

Each vaccine vial contains:

Active components and quantity per dose	
Bacterial suspension (Danish 1331 strain)	2.0 to 8.0 × 10^6 Colony Forming Units
Monosodium glutamate USP (vaccine stabilizer)	1.5%

The vaccine has to be reconstituted with 1.0 mL ampoule of Sodium Chloride Injection (0.9% w/v). After reconstitution, a dose of 0.05 mL is equivalent to 1 to 4 × 10^5 CFU and a dose of 0.1 mL is equivalent to 2 to 8 × 10^5 CFU shall be used for each administration. Before administration, national recommendations should be consulted regarding the dosage.

Each 1mL of reconstituted vaccine is equal to 20 doses (0.1 to 0.4 million CFU/dose) and equal to 10 doses (0.2 to 0.8 million CFU/dose). The standard dose of reconstituted BCG vaccine is 0.05 mL of the reconstituted vaccine for children up to 1 year, equivalent to 0.1 to 0.4 million CFU and a dose of 0.1 mL for children over 1 year and adults, equivalent to 0.2 to 0.8 million CFU.

BCG should be given routinely to all infants at birth. For maximum protection, this vaccine should be given as soon as possible after birth. If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed, to protect the child before exposure to infection occurs.

BCG Vaccine manufactured by GreenSignal Bio Pharma comes in a pack of 50 vaccine amber colour vials in a carton box plus a pack of 50 ampoules of vaccine diluent in a carton box. The vials closure system is complemented with a stopper made of bromobutyl and sealed with aluminum seal with polypropylene flip-off plastic cap.

The stability data submitted by the prequalification holder supports a shelf life of 24 months when the vaccine is stored between 2°C to 8°C and protected from direct light exposure. The data provided support the use of a Vaccine Vial Monitor (VVM) Type 14 and, it will be part of the packing configuration and placed on the top of polypropylene flip-off plastic cap.

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BCG Vaccine manufactured by GreenSignal Bio Pharma PVT. LTD., at No.49, Pappankuppam Village, Gurnrnidipoondi, Tamilnadu - 601201. India.

What is BCG Vaccine is used for?

BCG Vaccine manufactured by GreenSignal Bio Pharma PVT. LTD., is indicated for an active immunization against tuberculosis.

Vaccination with BCG Vaccine elicits a cell-mediated immune response that confers a variable degree of protection to infection with *M. tuberculosis*. The duration of immunity after BCG vaccination is not known, but there are some indications of a waning immunity after 10 years. Vaccinated persons normally become tuberculin positive after 6 weeks. A positive tuberculin test indicates a response of the immune system to prior BCG vaccination or to a Mycobacterial infection.

How is BCG Vaccine used?

BCG should be given routinely to all infants at birth. For maximum protection, this vaccine should be given as soon as possible after birth.

After reconstitution, a dose of 0.05 mL for children up to 1 year, equivalent to 0.1 to 0.4 million CFU and a dose of 0.1 mL for children over 1 year and adults, equivalent to 0.2 to 0.8 million CFU.

The reconstituted vaccine is injected strictly by the intradermal route.

Although anaphylaxis is rare, facilities for its management should always be available during vaccination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Injections made too deeply, increase the risk of lymphadenitis and abscess formation.

What are the vaccine characteristics?

BCG Vaccine manufactured by GreenSignal Bio Pharma PVT. LTD., must be stored as recommended by manufacturer, between 2°C to 8°C. Under these recommended storage conditions, the vaccine is stable for 24 months from the date of manufacture.

The vaccine should not be exposed to direct source of light.

It is a lyophilized vaccine that does not contain preservative therefore it should be used immediately after reconstitution. If not used immediately after reconstitution, the vaccine should be kept under cold chain management to maintain its temperature between 2 °C to 8 °C.

Any opened vials remaining at the end of an immunization session (within six hours of reconstitution) should be discarded as per WHO's "Open Vial Policy".

The vaccine does not contain preservative.

Cold chain volume per dose on secondary packaging is 1.43 cm^3/dose of 0.1 mL or 0.71 cm^3/dose of 0.05 mL, in the carton boxes for 50 amber glass vials.

Who is the regulatory authority responsible for its oversight vis a vis WHO?

The Tamil Nadu Foods Safety and Drugs Administration Department and Central Drugs Standard Control Organization (CDSCO) governed by the Drug Controller General of India (DCGI) are the regulatory bodies responsible for the oversight of the BCG Vaccine manufactured by GreenSignal Bio Pharma. These bodies are the Regulatory Authority of record for the WHO prequalification procedure.

The Marketing Authorization (MA) for BCG Vaccine manufactured by GreenSignal Bio Pharma was issued by the CDSCO/DCGI on 29 December 2017, on perpetuity.

How has BCG Vaccine been studied from the clinical point of view?

This vaccine was prequalified in 2015; however, a reassessment was performed due to Chemistry, Manufacturing and Control (CMC) issues. For the reassessment, GreenSignal Bio Pharma PVT LTD., provided additional clinical data from an "Open Label, Prospective, Multicenter, Single Arm, Single Treatment, Single Dose Post Marketing Surveillance Study to Evaluate the Safety And Tolerability of BCG Vaccine (Freeze- Dried)." This was a post marketing study that enrolled 3500 subjects who were followed up till 1 year post vaccination.

As per this report, Injection Site Abscess and Injection Site Papule were noted in 99.80% of the vaccinees within 30 minutes of vaccination and on day 3 post vaccination. Nearly all vaccinees had a local abscess which is unusually high particularly on Day 0. In addition, these local AEs such a papule had in this study an earlier onset compared to published data.

At day 45 post vaccination, injection site papule, mild ulceration, suppurative lymphadenitis, skin lesions were reported in 195/3461 (5.6%), 168/3461 (4.9%), 2/3461 and 1/3461 study participants. An injection site scar was noted in 3350 (96.8%) vaccinees.

At month 6 post vaccination, suppurative lymphadenitis, skin lesions and osteitis/osteomyelitis were reported in 2/3261 (0.06%), 4/3261 (0.12%) and 1/3461(0.03%) study participants. An injection site scar was noted in only 28/3261 (0.85%) vaccinees.

At month 12 post vaccination, skin lesions were reported in 1 vaccinee, BCG lymphadenitis in 1 vaccinee, disseminated BCG disease in 1 vaccinee and osteitis/osteomyelitis in 1 vaccinee out of 3370 study participants were followed up at this timepoint.

Based on the clinical trial data reassessment outcome, it is apparent that the vaccine safety profile remains satisfactory.

Other information about evaluation of BCG Vaccine®

Evaluation of BCG Vaccine prequalification application was based on the review of the information submitted by GreenSignal Bio Pharma PVT LTD., the WHO outcome of the site inspection to the facilities where the vaccine is manufactured and the satisfactory results of the test of vaccine samples in WHO contracted laboratories.

The vaccine prequalification dossier was submitted in a CTD format. The vaccine meets WHO Technical Report Series (e.g., Replacement of Annex 2 of WHO Technical Report Series, No. 745, and Amendment to Annex 12 of WHO Technical Report Series, No. 771). In addition, the vaccine was found in compliance with WHO programmatic suitability criteria and labelling requirement.