1. **Name of the medical product**
   Freeze-dried BCG Vaccine

2. **Qualitative and Quantitative composition**

<table>
<thead>
<tr>
<th>Composition</th>
<th>per vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG culture, strain of Tokyo 172</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Sauton medium (for supporting the culture)</td>
<td>trace</td>
</tr>
<tr>
<td>Sauton potato medium(for supporting the culture)</td>
<td>trace</td>
</tr>
<tr>
<td>Normal saline solution (for washing the culture)</td>
<td>trace</td>
</tr>
<tr>
<td>Sodium L-glutamate monohydrate</td>
<td>12.5 mg</td>
</tr>
<tr>
<td>Dextran</td>
<td>25.0 mg</td>
</tr>
<tr>
<td>Dextrose monohydrate (equivalent to dextrose anhydrous)</td>
<td>27.5 mg</td>
</tr>
<tr>
<td>Water for injection</td>
<td>0.5 ml</td>
</tr>
</tbody>
</table>

   The dose is 0.1 ml of reconstituted vaccine corresponding to 0.05 mg of BCG organisms. One dose contains a minimum of 200,000 culturable particles. The freeze-dried vaccine fulfils the requirements for dried BCG vaccine (Requirements for Biological substance No.11) formulated by WHO Expert Committee on Biological standardization.

3. **Pharmaceutical form**
   Lyophilization form. White lyophilized cake, when reconstituted with diluent, a whitish suspension is obtained.

4. **Clinical particulars**

   4.1 **Therapeutic indications**
   BCG Vaccine is recommended for immunization against tuberculosis

   4.2 **Posology and method of administration**
   Add aseptically 1 ml of the saline solution (0.9% Saline solution) into the vial containing the freeze-dried vaccine. Shake the vial well. The vaccinating dose is 0.1 ml of reconstituted vaccine. It should be used carefully by intradermal injection, avoiding penetration into the subcutaneous tissue.

   4.3 **Contraindication**
   1. Cell-mediated immune deficiency, immune deficiency due to drug and chronic diseases.
   2. Vaccination with live viral vaccine.
   3. Skin disease with open ulcerations at injection site.
   4. Any acute illness and viral infection.
   5. Pregnancy

   4.4 **Special warnings and precautions for use**
   The vaccine should be used immediately after reconstitution and any reconstituted vaccine not used within 2 hours must be discarded. Injections made too deeply increase the risk of lymphadenitis and abscess formation.
4.5 Interaction with other medical products and forms of interaction

Intradermal BCG vaccination may be given concurrently with inactivated or live vaccines, including combined MMR. Other vaccines if not given at the same time as BCG an interval of not less than four weeks should normally be allowed to lapse between the administrations of any two live vaccines. Other vaccines given at the same time as BCG vaccine should not be given into the same arm.

4.6 Pregnancy and lactation

Vaccination of pregnant women is usually delayed until after delivery, although no harmful effects on the fetus have been observed.

Animal reproduction studies have not been conducted with BCG Vaccine (Freeze-dried). It is also not known whether BCG Vaccine (Freeze-Dried) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. It is not known whether BCG Vaccine (Freeze-Dried) is excreted in human milk. Because live vaccines may be excreted in human milk, caution should be exercised when BCG Vaccine (Freeze-Dried) is administered to a nursing woman.

4.7 Effects on the ability to drive and use machines

No clinical data

4.8 Undesirable effects

A local reaction is normal after BCG injection. A small tender red swelling appears at the site of the injection which gradually changes to a small vesicle and then an ulcer in 2-4 weeks. The reaction usually subsides within two to five months and in practically all children, leaves a superficial scar 2-10 mm in diameter. Rarely, the nodule may persist and ulcerate. Occasionally, enlargement of auxiliary lymph nodes may appear in 2-4 months following immunization. Inadvertent subcutaneous injection produces abscess formation and may lead to ugly retracted scars.

4.9 Overdose

No clinical data. The recommended dosage for age should not be exceeded, as this may result in more extensive local reactions. Subcutaneous or intramuscular injection may result in an abscess at the injection site.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cell-mediated immune response against tuberculosis

5.2 Pharmacokinetic properties

Nine dried vaccine were prepared by using a nine day old culture of the nine strains showed the results on the growth, the harvest, pH of Sauton medium, viable counts in liquid and dried vaccines, and the heat resistance of dried vaccines are shown. The preliminary protection test, the guinea pigs were vaccinated with different amount of BCG and challenged with virulent bacilli infection. Macroscopic finding in tissue and the number of colonies recovered from tissue of guinea pigs infected were observed. To observe the fine difference in the protection with difference strains and amount of BCG were inoculate subcutaneously to guinea pigs then challenged infection at different weeks after vaccination and autopsied.

The tuberculin allergy induced immediately before challenge infection for showing the expression of tuberculous infection. To observe the multiplication of BCG in spleens of guinea pigs using different strains BCG were inoculated to guinea pigs by intravenous route.

5.3 Preclinical safety data

Prophylactic vaccines are one of the most useful and cost-effective tools for reducing the morbidity and mortality associated with infectious diseases. BCG is an
attenuated strain of *Mycobacterium bovis* which was originally virulent, however after 230 passages after stated to had been cultured in 13 years, it was found that this specific *M. bovis* had become completely avirulent. Non clinical drug development process is a risk based process that involves safety and efficacy evaluation of drugs in animal species that extrapolate to potential human outcome.

The non clinical pharmacologic and toxicological drug responses with respect to dose regimen and route of administration enable to initiate and continue research in human beings. In general, non clinical studies are performed to predict the safety and efficacy data from the animal models which support the conduct of research in human beings.

6. **Pharmaceutical particulars**

6.1 **List of excipients**

**Active Ingredient / Drug Substance**

*Mycobacterium bovis*, BCG (BCG seed strain of Tokyo 172)

**Excipients**

- Magnesium sulfate heptahydrate
- Citric acid monohydrate
- di-Potassium hydrogen phosphate
- L-Asparagine monohydrate
- Ferri-ammonium citrate
- Zinc sulfate heptahydrate
- Glycerol, 87%
- Ammonia solution, 25%
- Normal saline solution
- Sodium L-glutamate monohydrate
- Dextran
- Dextrose monohydrate
- Water for injection

6.2 **Incompatibilities**

The freeze-dried BCG vaccine must be reconstituted with the supplied saline solution (1 ml) prior to administration.

6.3 **Shelf-life**

4 years from the manufacturing date.

6.4 **Special precautions for storage**

The Freeze-dried BCG Vaccine should be kept in refrigerator (2 - 8°C) and protected from light. Expiration is 4 years after manufacturing date.

6.5 **Nature and contents of container**

As the product has to be freeze-dried, then the Type I glass vial with the fill volume of 2 ml was chosen as a primary packaging material. The following container and closure are used for the final product:

1. Transparent, amber borosilicate glass type I vial, tubing type, size 2 ml
2. Lyophilized halogenated butyl rubber stopper
3. Aluminum push-off cap with central opening and green plastic comp

6.6 **Special precautions for disposal and other handling**

Disposed as infectious waste

7. **Marketing authorization holder**
8. **Marketing authorization number(s)**
   None

9. **Date of first authorization/renewal of the authorization**
   None

10. **Date of revision of the text**
    30 June 2012