1. NAME OF THE MEDICINAL PRODUCT

Measles and Rubella Vaccine (Live) (Attenuated, Freeze dried) I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each reconstituted dose of 0.5 mL contains:

Measles virus (CAM-70 strain), propagated in Chicken Embryo fibroblast cells ≥ 1000 $CCID_{50}$

Rubella virus (Wistar RA 27/3 strain), propagated in MRC 5 cells ≥ 1000 $CCID_{50}$

Reconstitute the vaccine vial with the diluent (0.9% w/v Sodium Chloride Injection I.P.) supplied.

For full list of excipients, refer section 6.1

3. PHARMACEUTICAL FORM

Lyophilized powder for Subcutaneous Injection upon reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

For active immunization against Measles and Rubella in 9-12 months healthy infants at risk. The vaccine can be safely and effectively given simultaneously with DTP, DT, TT, Td, BCG, Polio vaccine (OPV and IPV), *Haemophilus Influenzae* type b, Hepatitis B, Yellow fever vaccine and vitamin A supplementation.

4.2 Posology and method of administration:

Posology: In countries where the incidence and mortality from measles is high in the first year of life, the recommended age for vaccination against measles is at 9 months of age (270 days) or shortly after. In countries where infection occurs later in life (due to sustained high vaccination coverage), the age of vaccination can be moved to 12-15 months. It is recommended that all children have two (2) opportunities for immunization with a measles-containing vaccine to reduce the number both of unvaccinated children and of those who are vaccinated but fail to respond to the vaccine (primary vaccination failures). The second dose of measles-containing vaccine may be provided as early as one (1) month following the first dose through routine or supplemental immunization activities.

The combination vaccine produces an immunological response to each antigen equivalent to that following administration of each of the single antigen products. The safety and immunogenicity of this combination vaccine appears to be similar to that of its individual components.

Method of Administration: Inject a single dose of 0.5 mL MR vaccine subcutaneously. The preferred site of injection is the upper arm (fatty tissue over triceps) or in front of thigh (fatty tissue over antero-lateral thigh muscle).

The lyophilized vial must be reconstituted by adding the entire contents of the supplied diluent to the vaccine vial. The vaccine pellet should be completely dissolved in the diluent. Following reconstitution, the vaccine should be inspected visually for any foreign particulate matter prior to administration. If observed, the vaccine must be discarded.

The reconstituted vaccine should be used within six (6) hours. Any opened vials remaining at the end of an immunization session or six hours after reconstitution should be discarded.

The vaccine is supplied along with the diluent. Only the diluent supplied along with the vaccine should be used to reconstitute the vaccine. Using an incorrect diluent will result in damage to the vaccine and/or serious reactions to those receiving the vaccine. Diluent must not be frozen but must be cooled between +2°C and +8°C before reconstitution.

A sterile needle and sterile syringe must be used for the reconstitution of the vaccine and aseptic techniques should be followed.

Draw the diluent into Syringe, pierce the bung of the vial with the needle and gently inject the diluent into the vial. Detach the syringe, leaving the needle in vial bung, after 15 seconds remove the needle. Rotate the vial gently between your palms till the material dissolves. Avoid shaking the vial as this would cause frothing. Withdraw the reconstituted solution into the syringe, now ready for administration.

4.3 Contraindications

A previous allergic reaction to measles or MR vaccine is a contraindication. Persons with a history of an anaphylactic reaction to any components of the vaccine should not be vaccinated. Apart from these, there are few contraindications to the administration of MR vaccine. It is

particularly important to immunize children with malnutrition. Low-grade fever, mild respiratory infections or diarrhea, and other minor illnesses should not be considered as contraindications. On theoretical grounds measles vaccine should also be avoided in pregnancy. The vaccine must not be given to a pregnant woman and that woman should not become pregnant with in two months after having the vaccine. No serious cases have been reported in more than 1000 susceptible pregnant women who inadvertently received a Rubella vaccine in early pregnancy. Rubella vaccination during pregnancy is not an indication for abortion.

Immune Deficiency:

Children with known or suspected HIV infection are at increased risk of severe measles and should be offered measles vaccine as early as possible. The standard WHO recommendation for children at high risk of contracting measles is to immunize with measles vaccine at six (6) months of age, followed by an extra dose at nine (9) months. The vaccine is contraindicated in persons who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or antimetabolites, or in persons who are receiving immunosuppressive therapeutic radiation.

4.4 Special Warnings and Precautions for use:

Persons with a history of an anaphylactic reaction to any components of the vaccine should not be vaccinated. On theoretical grounds measles vaccine should also be avoided in pregnancy. Rubella vaccination should be avoided in pregnancy because of the theoretical (but never demonstrated) teratogenic risk. If pregnancy is being planned, then an interval of Two (2) month should be observed after rubella immunization.

4.5 Drug interactions

The vaccine can be safely and effectively given simultaneously with DTP, DT, TT, Td, BCG, Polio vaccine (OPV and IPV), *Haemophilus Influenzae* type b, Hepatitis B, Yellow fever vaccine and vitamin A supplementation.

4.6 Use in Special Populations (such as pregnant women, lactating women)

The vaccine must not be given to a pregnant woman and that woman should not become pregnant within two months after having the vaccine. No serious cases have been reported in more than 1000 susceptible pregnant women who inadvertently received a rubella vaccine in early pregnancy. Rubella vaccination during pregnancy is not an indication for abortion.

4.7 Effects on Ability to Drive and Use Machines

Not Applicable. MR vaccine is indicated for primary immunization in 9-12 months healthy infants at risk.

4.8 Undesirable Effects:

Side effects following MR vaccination are mostly mild and transient and are similar in frequency and severity to those following administration of each of the single antigen products.

The most frequently reported local adverse events were Injection site pain (5.00%), Erythema (3.33%) and Swelling (3.33%). The most frequently reported systemic adverse events were Pyrexia (6.33%), Irritability (3.67%), Crying (3.00%), Rash (1.0%) and Urticaria (0.33%).

Most of the local and systemic AEs reported were either mild or moderate in their intensity. The most commonly observed AEs were in line with the expected AE profile as seen with other available Measles and Rubella containing combination vaccines.

Side effects following measles vaccination are generally mild and transient. Slight pain and tenderness at the site of injection may occur within 24 hours of vaccination, sometimes followed by mild fever and local lymphadenopathy. About 7 - 12 days after vaccination up to 5% of measles vaccine recipients may experience fever > 39.4 °C for 1 - 2 days.

A transient rash may occur in approximately 2% of vaccinees, usually starting 7- 10 days following vaccination and lasting 2 days. Side effects, with the exception of anaphylactic reactions, are less likely to occur after receipt of a second dose of measles containing vaccine. Encephalitis has been reported following measles vaccination at a frequency of approximately one (1) case per one (1) million doses administered although a causal link is not proven.

Side effects following vaccination with rubella vaccine are also mild, particularly in children. Common side effects include pain, redness and induration at the site of injection. Low-grade

fever and rash, lymphadenopathy, myalgia and paraesthesia are commonly reported. Joint symptoms tend to be rare in children (0% -3%) and in men, but are common among vaccinated adolescents and adult females; they include arthralgias (25%) and arthritis (10%) that usually last from a few days to two (2) weeks. These transient reactions seem to occur in non-immune individuals only, for whom the vaccine is important. Thrombocytopenia is rare and has been reported in less than 1 case per 30,000 doses administered.

Anaphylactic reactions are also rare but have the potential to be fatal. The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving. It should be used at the first suspicion of anaphylaxis. For treatment of severe anaphylaxis, the initial dose of adrenaline is 0.1-0.5 mg (0.1-0.5 mL of 1:1000 injection) given s/c or i/m. Single dose should not exceed 1 mg (1 mL). For infants and children, the recommended dose of adrenaline is 0.01 mg/kg (0.01 mL/kg of 1:1000 injection). Single paediatric dose should not exceed 0.5 mg (0.5 mL). This will help in tackling the anaphylactic shock/reaction effectively.

The use of intravenous (IV) adrenaline (epinephrine) is hazardous and should only be considered in extreme emergency in subjects with profound shock that is immediately life-threatening. Only dilute adrenaline (at least 1:10,000) will be used, and the injection given slowly. Because of the possibility of delayed reactions, subjects who have had an anaphylactic reaction will be retained in hospital, even though they may appear to have made a full recovery. An airway will only be used by properly trained and competent health professional, and only in unconscious subjects.

Hydrocortisone and antihistaminics should also be available in addition to supportive measures such as oxygen inhalation. These should be considered, however, in the further management of anaphylaxis by appropriately trained staff.

Clinical experience has exceptionally recorded isolated reactions involving the CNS. These more serious reactions have however, not been directly linked to vaccination.

4.9 Overdose

Not applicable as this vaccine is given by a registered medical practitioner.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

The MR combination vaccine produces an immunological response to each antigen equivalent to that following administration of each of the single antigen products.

5.2. Pharmacodynamic properties

This section is not applicable for this product.

5.3 Pharmacokinetic Properties

This section is not applicable for this product

5.3 Preclinical Safety Data

During the course of 14-day acute toxicity study in Sprague Dawley rats injected with combination vaccine containing Measles and Rubella, no abnormalities were observed in the treatment as well as control group. None of the animals died during the study period and there was no observation of sign of toxicity related to general behaviour, nervous system and respiratory systems in both the groups.

The organ weights also show no changes. Histopathological examination of the prime organs also revealed any notable changes.

During the course of 14 day toxicity study in Swiss Albino Mice injected with combination vaccine containing Measles and Rubella, no abnormalities were observed in the treatment as well as control group. None of the animals died during the study period and there were no observation of sign of toxicity related to general behaviour, nervous system and respiratory systems in both the groups.

The organ weights also show no changes. Histopathological examination of the prime organs also revealed any notable changes.

The 90 day repeat dose toxicity study in Sprague dawley rats injected with multiple doses of combination vaccine containing Measles and Rubella were also carried out. The general behaviour pattern showed no sign of toxicity in all six different treatment groups. Statistically insignificant differences were observed between the control and treatment groups in Sprague

dawley rats in respective body weight changes which can be inferred as uniform growth during the long study period.

For immunogenic assessment, rat plasma IgG was measured and the observation of the study shows that the level of released/secreted plasma IgG was elicited post immunization (Day 29) when compared to the pre dose plasma. The average percentage fold increase in IgG level post dose when compared to pre dose was approximately 10% in the test group which was higher as compared to the controls thereby indicating that the freeze dried measles and rubella vaccine was immunogenic.

The 90-day repeat dose toxicity study in New Zealand White Rabbits injected with multiple doses of combination vaccine containing Measles and Rubella were also carried out. The general behaviour pattern showed no sign of toxicity in all three different treatment groups. Statistically insignificant differences were observed between the control and treatment groups in Sprague dawley rats in respective body weight changes which can be inferred as uniform growth during the long study period.

For immunogenic assessment, rabbit plasma IgG was measured and the observation of the study shows that the level of released/secreted plasma IgG was elicited post immunization (Day 29) when compared to the pre dose plasma. The average percentage fold increase in IgG level post dose when compared to pre dose was approximately 61% in the test group which was higher as compared to the controls thereby indicating that the freeze dried measles and rubella vaccine was immunogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

- Hydrolyzed Gelatin
- D-Sorbitol
- Sucrose
- Sodium Bicarbonate
- Dextrose anhydrous (Glucose)
- HSA (Human Serum Albumin)
- Citric acid Anhydrous
- Disodium hydrogen orthophosphate anhydrous

6.2 Incompatibilities

In the absence of compatibility studies, MR must not be mixed with other medicinal products. However, the vaccine can be safely and effectively given simultaneously with DTP, DT, TT, Td, BCG, Measles, Polio vaccine (IPV and OPV), Hepatitis B, *Haemophilus influenzae* type b, Yellow fever vaccine and Vitamin A supplementation.

6.3 Shelf Life

24 months from the date of manufacture. The expiry date of the vaccine is indicated on the label and packing.

6.4 Special precautions for storage: It is important to protect both the lyophilized and reconstituted vaccine from the light. The vaccine should be stored in the dark at a temperature between +2°C to +8°C. The diluent should not be frozen, but should be kept cool.

6.5 Nature and contents of the container

The vaccine is filled in USP Type I amber colored glass vials closed with bromobutyl rubber stoppers and sealed with aluminium flip-off seals.

The vaccine is offered in following presentations.

- 1 dose vial along with diluent (0.5 mL)
- 5 dose vial along with diluent (2.5 mL)
- 10 dose vial along with diluent (5 mL)

Handling of multi dose vial:

The reconstituted vaccine should be stored between 2°C to 8°C and should be used within six (6) hours. Any opened vials remaining at the end of an immunization session or six hours after reconstitution should be discarded. Protect the reconstituted vaccine from the light.

6.6 Special Precautions for Disposal

The reconstituted vaccine should be used within six (6) hours. Any opened vials remaining at the end of an immunization session or six hours after reconstitution should be discarded.. The vaccine is supplied along with the diluent (0.9% w/v Sodium Chloride Injection I.P.). Only the diluent supplied along with the vaccine should be used to reconstitute the vaccine.

7. MARKETING AUTHORISATION HOLDER

Biological E. Limited

Regd. office: 18/1 & 3, Azamabad, Hyderabad, Telangana - 500 020, INDIA.

Manufacturing Site Address:

Shameerpet site.	**SEZ Site:**
M/s. Biological E. Limited Plot No. 1, Biotech Park, Phase II, Kolthur Village - 500 078, Shameerpet, Medchal-Malkajgiri District, Telangana, INDIA. Web site: www.biologicale.com	M/s. Biological E. Limited (SEZ Unit) Sy. No. 549, 550, 552 to 556 Kolthur Village - 500 078, Shameerpet, Medchal-Malkajgiri District, Telangana, INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

MF-190/2017

9. DATE OF FIRST AUTHORISATION

16.08.2017