SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Measles/rubella (live) (attenuated, freeze-dried) 5-dose vaccine

Measles/rubella (live) (attenuated, freeze-dried) 10-dose vaccine

2. Qualitative and quantitative composition

Each reconstituted dose of 0.5 mL contains ≥ 1000 $CCID_{50}$ of measles virus and ≥ 1000 $CCID_{50}$ of rubella virus.

Excipient with known effect
Each 0.5 mL dose also contains 25mg of sorbitol. See section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Lyophilized powder for solution for injection (vaccine).

White to yellow, compact cake supplied with a clear, colourless sodium chloride 0.9% w/v solution for injection diluent.

4. Clinical particulars

4.1 Therapeutic indications

For active immunization against measles and rubella in 9-12 months healthy infants are 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 are 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 of unvaccinated children and 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 the administration of each of the single antigen products. The safety and immunogenicity of this combination vaccine appear to be similar to that of its 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 the thigh (fatty tissue over anterolateral 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.

Instructions for Use
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 the 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 the 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 a few contraindications to the administration of the MR vaccine. It is particularly important to immunize children with malnutrition. Low-grade fever, mild respiratory infections or diarrhoea, and other minor illnesses should not be considered contraindications. On theoretical grounds, the 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 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 of abortion.

Immune Deficiency
Children with known or suspected HIV infection are at increased risk of severe measles and should be offered a measles vaccine as early as possible. The standard WHO recommendation for children at high risk of contracting measles is to immunize with the 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 leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or antimetabolites, or in persons who are receiving immunosuppressive therapeutic radiation.

4.3 Special warnings and precautions for use

Warnings
Persons with a history of an anaphylactic reaction to any components of the vaccine should not be vaccinated.

Precautions
On theoretical grounds, the 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) months should be observed after rubella immunization.

The occurrence, severity and protraction of toxicity are likely to be greater in patients who have received extensive prior treatment with the drug for their disease or with cisplatin, have poor performance status and are advanced in years. Renal function parameters should be assessed prior to, during and after carboplatin therapy. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.

Excipients
This medicine contains **sorbitol**. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

4.5 Interaction with other medicinal products and other forms of interaction
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 Fertility, pregnancy and lactation
On theoretical grounds, the 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) months should be observed after rubella immunization.

4.7 Effects on the 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 two (2) cases 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 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 emergencies in subjects with a 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 the hospital, even though they may appear to have made a full recovery. An airway will only be used by properly trained and competent health professionals, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
Not applicable.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 18.2 Vaccines.

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

5.2 Pharmacokinetic properties
An evaluation of pharmacokinetics in vaccines is not necessary.

5.3 Preclinical safety data
During the course of a 14-day acute toxicity study in Sprague Dawley rats injected with a 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 signs 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 a 14-day toxicity study in Swiss Albino Mice injected with a combination vaccine containing Measles and Rubella, no abnormalities were observed in the treatment as well as the control group. None of the animals died during the study period and there were no observations of signs of toxicity related to general behaviour, nervous system and respiratory systems in both 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 a combination vaccine containing Measles and Rubella was 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 a 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
Polyethylene glycol
Sodium chloride
Benzethonium chloride
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store between 2° and 8°C.

6.5 Nature and contents of the container
An amber-coloured, USP-type I glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium flip-off seal.

Measles/rubella (live) (attenuated, freeze-dried) 5-dose vaccine
Diluent fill volume: 2.5 mL.
Pack size: 1 vial per carton.

Measles/rubella (live) (attenuated, freeze-dried) 10-dose vaccine
Diluent fill volume: 5 mL.
Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling
Discard if the vaccine has been frozen as per the approved procedures.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
Biological E. Limited
18 / 1 & 3, Azamabad
Hyderabad - 500020
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India

8. MANUFACTURER
Biological E. Limited
Plot No. 1, Phase II, Biotech Park, Kolthur Village
Shameerpet Mandal, Medchal – Malkajgiri (District)
Telangana - 500078
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9. REGISTRATION DETAILS
Measles/rubella (live) (attenuated, freeze-dried) 5-dose vaccine
Zimbabwe registration number: 2023/18.2/6507
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Measles/rubella (live) (attenuated, freeze-dried) 10-dose vaccine
Zimbabwe registration number: 2023/18.2/6508
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT
February 2024