1. NAME OF THE MEDICINAL PRODUCT

Measles, Mumps and Rubella Vaccine (Live) I.P
Brand name: TRESIVAC®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRESIVAC® (Measles, Mumps, and Rubella Virus Vaccine (Live) I.P.) freeze dried is prepared from the live, attenuated strains of Edmonston-Zagreb Measles virus propagated on human diploid cell culture, L-Zagreb Mumps virus propagated on chick embryo fibroblast cells and Wistar RA 27/3 Rubella virus propagated on human diploid cell culture. The vaccine is freeze-dried and is provided with diluent. The product has the appearance of yellowish-white friable mass may or may not contains bubbles and /or indentations. The vaccine meets the requirement of I.P. and WHO when tested by the methods outlined in I.P. and WHO, TRS 840 (1994).

Each single human dose when reconstituted in a volume of 0.5 ml contains not less than:
1000 $CCID_{50}$ of measles virus
5000 $CCID_{50}$ of mumps virus
1000 $CCID_{50}$ of Rubella virus
Diluent: Sterile Water for Injections

3. PHARMACEUTICAL FORM

Injectable, Freeze-dried vaccine for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRESIVAC® is indicated for active vaccination of children from 9 months to 10 years of age against Measles, Mumps and Rubella infections simultaneously. For Immunisation of children above 10 years and susceptible non-pregnant adult individuals, we recommend to use MR-VAC (Measles and Rubella Vaccine) / R-VAC (Rubella vaccine) while observing certain precautions as indicated under the contraindications (4.3).
The IAP Committee of Immunisation recommends two doses of MMR vaccine to every child at 9 months and 15 to 18 months. The second dose of MMR vaccine can be given at any time 4 to 8 weeks after the first dose.

MMR vaccine can also be given to adults at any age in case they have missed the vaccination in childhood and or there is no vaccination record available, by giving 2 doses of MMR with an interval of minimum 4 weeks. However, it is important to note that vaccination in adults can cause higher percentage of adverse reactions as compared to childhood vaccination. Amongst these the commonly encountered adverse reactions are unilateral or bilateral parotitis and fever. To avoid such reactions, if the physician desires, MR vaccine can be recommended instead of MMR vaccine.

4.2 Posology and method of administration

Posology
0.5 ml of the reconstituted vaccine constitutes one dose.

Method of administration
FOR SUBCUTANEOUS USE ONLY.

The vaccine should be reconstituted with the entire contents of the diluent supplied (Sterile water for injections) using a sterile syringe and needle. With gentle shaking the dried cake is easily dissolved. After reconstitution the vaccine should be used immediately. A single dose of 0.5 ml should be administered by deep subcutaneous injection into the anterolateral aspect of upper thigh in toddlers and upper arm in older children.

If the vaccine is not used immediately then it should be stored in the dark at 2 - 8 º C for no longer than 6 hours.

The diluent supplied is specially designed for use with the vaccine. Only this diluent must be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or for MMR vaccine from other manufacturers. Water for injections must NOT be used for this purpose. Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine. Diluent must not be frozen but should be kept cool.

The diluent and reconstituted vaccine should be inspected visually for any foreign particulate matter and / or variation of physical aspects prior to administration. In the event of either being observed, discard the diluents or reconstituted vaccine.
FOR SUBCUTANEOUS USE ONLY

4.3 Contraindications

Individuals receiving corticosteroids, other immuno-suppressive drugs or undergoing radiotherapy may not develop an optimal immune response. The vaccine should not be given in febrile states, pregnancy, acute infectious diseases, leukaemia, severe anaemia and other severe diseases of the blood system, severe impairment of the renal function, decompensated heart diseases, following administration of gamma-globulin or blood transfusions or to subjects with potential allergies to vaccine components. The vaccine may contain traces of neomycin. Anaphylactic or anaphylactoid reactions to neomycin, history of anaphylactic or anaphylactoid reactions to eggs (Hypersensitivity to eggs), are absolute contraindications. There are extremely rare reports of hypersensitivity reactions with MMR vaccine in individuals who are allergic to cow’s milk. Such individuals should not receive the vaccine. Low-grade fever, mild respiratory infections or diarrhoea, and other minor illness should not be considered as contraindications. It is particularly important to immunize children with malnutrition.
MMR vaccine should not be administered in pregnant women because of the theoretical but never demonstrated teratogenic risk. Inadvertent receipt of MMR vaccine during pregnancy is not an indication for an abortion. Since MR vaccine is recommended in adults, if pregnancy is planned, then an interval of one month should be observed after

MR vaccination. No cases of CRS have been reported in any pregnant women who inadvertently received rubella-containing vaccine in early pregnancy.

4.4 Special warnings and special precautions for use

Individuals receiving corticosteroid, other immuno-suppressive drugs or undergoing radiotherapy may not develop an optimal immune response.
Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of MMR vaccine (or its component vaccines) may develop thrombocytopenia with repeat doses. In such patients, the risk-benefit of administering the MMR vaccine should be carefully evaluated and vaccine should be administered with caution.
Vaccinees should not conceive for 28 days period following vaccination.
Please ensure that the vaccine is administered by subcutaneous route only. As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the risk of inactivation, the MMR vaccine should not be given within the 6 weeks, and if it is possible within 3 months, after an injection of immunoglobulins or blood product containing immunoglobulins (blood, plasma). For the same reason, immunoglobulins should not be administered within the two weeks after the vaccination.
Tuberculin positive individuals may transitionally become tuberculin negative after vaccination.
MMR 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 Pregnancy and lactation

MMR vaccine should not be administered in pregnant women because of the theoretical but never demonstrated teratogenic risk. Inadvertent receipt of MMR vaccine during pregnancy is not an indication for an abortion. No cases of CRS have been reported in any pregnant women who inadvertently received rubella-containing vaccine in early pregnancy. Data on use of MMR vaccine during lactation is not available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The type and rate of severe adverse reactions do not differ significantly from the measles, mumps and rubella vaccine reactions described separately.
The measles vaccine may cause within 24 hours of vaccination mild pain and tenderness at the injection site. In most cases, they spontaneously resolve within two to three days

without further medical attention. A mild fever can occur in 5-15% of vaccinees 7 to 12 days after vaccination and last for 1-2 days. Rash occurs in approximately 2% of recipients, usually starting 7-10 days after vaccination and lasting 2 days. The mild side effects occur less frequently after the second dose of a measles-containing vaccine and tend to occur only in person not protected by the first dose. Encephalitis has been reported following measles vaccination at a frequency of approximately one case per million doses administered although a causal link is not proven.

The mumps component may result in parotitis and low grade fever. Febrile seizures and orchitis may also occur. However, moderate fever occurs rarely and aseptic meningitis has been reported very rarely. Vaccine-associated meningitis resolves spontaneously in less than 1 week without any sequelae. The onset of aseptic meningitis is delayed, which may limit the ability to detect these cases by passive surveillance. Vaccine associated aseptic meningitis is observed between 15-35 days post immunization.

The rubella component may commonly result in joint symptoms manifested as arthralgias (25%) and arthritis (10%) among adolescent and adult females that usually last from a few days to 2 weeks. However, such adverse reactions are very rare in children and in men receiving MMR vaccine (0%-3%). Symptoms typically begin 1-3 weeks after vaccination and last 1 day to 2 weeks. These transient reactions seem to occur in non-immunes only, for whom the vaccine is important. Low-grade fever and rash, lymphadenopathy, myalgia and paraesthesiae are commonly reported. Thrombocytopenia is rare and has been reported in less than 1 case per 30 000 doses administered.

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

Frequency of adverse events

The following adverse events, irrespective of causality, were observed in clinical trials with MMR vaccine of SIIPL.

Very Common ≥ 1/10
General disorders and administration site conditions: Pyrexia

Common (frequent) ≥ 1/100 and < 1/10
Infections and infestations: Nasopharyngitis, Conjunctivitis
General disorders and administration site conditions: Injection site pain, Injection site swelling, Injection site erythema
Skin and subcutaneous tissue disorders: Rash

Uncommon (infrequent) ≥ 1/1000 and < 1/100
Metabolism and nutrition disorders: Decreased appetite
Respiratory, thoracic and mediastinal disorders: Cough
Infections and infestations: Parotitis, Lower respiratory tract infection, Upper respiratory tract infection, Respiratory tract infection
Gastrointestinal disorders: Diarrhoea, Vomiting
Blood and lymphatic system disorders: Lymphadenopathy
General disorders and administration site conditions: Induration
Musculoskeletal and connective tissue disorders: Arthritis

Rare ≥ 1/10000 and < 1/1000
Respiratory, thoracic and mediastinal disorders: Catarrh, Rhinorrhoea, Nasal congestion
Gastrointestinal disorders: Abdominal pain, Constipation, Mouth ulceration, Perianal erythema
General disorders and administration site conditions: Injection site haemorrhage, Irritability, Febrile convulsion
Infections and infestations: Urinary tract infection, Varicella
Blood and lymphatic system disorders: Anaemia
Ear and labyrinth disorders: Cerumen impaction
Skin and subcutaneous tissue disorders: Seborrhoeic dermatitis
Injury, poisoning and procedural complications: Contusion
Renal and urinary disorders: Dysuria

Very Rare < 1/10000
General disorders and administration site conditions: Asthenia, Peripheral swelling
Infections and infestations: Abscess, Hand-foot-and-mouth disease, Helminthic infection, Herpangina, Otitis Media
Respiratory, thoracic and mediastinal disorders: Dyspnoea, Epistaxis
Skin and subcutaneous tissue disorders: Intertrigo, Dermatitis atopic, Dermatitis diaper, Polymorphic light eruption, Urticaria popular
Ear and labyrinth disorders: Otorrhoea
Gastrointestinal disorders: Abdominal discomfort
Eye disorders: Eye discharge, Ocular hyperaemia
Immune system disorders: Eyelid oedema
Nervous system disorders: Seizure
Injury, poisoning and procedural complications: Arthropod bite, Eye injury, Hand fracture, Limb injury, Wound
Musculoskeletal and connective tissue disorders: Neck pain
Psychiatric disorders: Pica
Metabolism and nutrition disorders: Vitamin D deficiency
Renal and urinary disorders: Haematuria

4.9 Overdose
No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Viral vaccines,
Measles, combinations with mumps and rubella, live attenuated, ATC code: J07BD52

MMR vaccine stimulates active immunity to measles, mumps and rubella by inducing production of measles-specific, mumps-specific and rubella-specific IgG antibodies.

Clinical studies have shown that the MMR vaccine is highly immunogenic and generally well tolerated. Following MMR vaccination in 9-24 months old children, the seropositivity was observed for measles in 68.3 - 100%, mumps in 82-100% and rubella in 84-100%. In children in age group of 6-12 years, the seropositivity post-vaccination with MMR vaccine was 100%, 99.5% and 92.6% for measles, mumps and rubella, respectively.

5.2 Pharmacokinetic properties

Pharmacokinetic studies are not applicable for vaccines.

5.3 Preclinical safety data

Single dose toxicity studies were conducted in mice and Beagle dogs with MMR vaccine live attenuated (Freeze-dried) by subcutaneous route. No toxicological effects were observed in mice and Beagle dogs after a single subcutaneous administration of MMR vaccine. The approximate lethal dose of MMR vaccine live attenuated (Freeze dried) was more than 80 times and 6.3 times the expected clinical dose, respectively.

In a repeated dose toxicity study in mice with MMR vaccine live attenuated (Freeze dried) by subcutaneous route no treatment related toxic effects were observed. There were no significant macroscopic and histopathological findings. The approximate lethal dose of MMR vaccine live attenuated (Freeze-dried) was more than 80 times the expected clinical dose in mice.

As part of the quality control every batch of the vaccine is tested in mice and guinea pigs for general safety and innocuity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin, Partially hydrolyzed, D-Sorbitol, L-Histidine, L- Alanine, Tricine, L-Arginine hydrochloride, Lactalbumin hydrolysate, Minimum Essential Medium (MEM)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store and transport refrigerated at 2°C – 8°C.
Protect both the lyophilised and reconstituted vaccine from light
The long-term storage (unlabelled containers), it is recommended to store the lyophilised vaccine in the freezer at -20°C
The diluent should not be frozen.

6.5 Nature and contents of container

<u>Packaging/ Container closure system of vaccine</u>

Lyophilised Measles, Mumps and Rubella (MMR) vaccine is a yellowish-white friable mass and is filled in 5ml amber coloured vials (Type I glass)

Sr. no.	Container Closure	Description
1	Glass Vials	5mL, USP Type-I, amber, tubular European blowback glass vials Height 50 mm, Body diameter 16.50 mm
2	Rubber Closures	13mm, Datwyler FM460, grey coloured rubber stopper and

		13mm, Aptar Stelmi *GS*6740, grey coloured rubber stopper Flange Diameter 12.45 mm, Flange thickness 1.98
3	Flip-off Aluminium Seals	Flip-off seal 13mm AF, Pantone 220C (Mauve)

Packaging/ Container closure system of Diluent (sWFI)

Based on the dose of the vaccine the Packaging/ Container closure of the diluent is classified as below. The OPC mechanism ampoules are tested as per SOP 130 0224.

Dose	Ampoule Type	Volume	Dimensions
1 Dose	Type 1, clear, tubular glass ampoule with One Point Cut (OPC) mechanism	1 ml	Height 65 mm Body Diameter 10.25 mm Base to Constriction height 28 mm
2 Dose	Type 1, clear, tubular glass ampoule with One Point Cut (OPC) mechanism	1 ml	Height 65 mm Body Diameter 10.25 mm Base to Constriction height 31 mm
5 Dose	Type 1, clear, tubular glass ampoule with One Point Cut (OPC) mechanism	3 ml	Height 75 mm Body Diameter 14.75 mm Constriction height 30 mm
10 Dose	Type 1, clear, tubular glass ampoule with One Point Cut (OPC) mechanism	5 ml	Height 87 mm Body Diameter 14.75 mm Constriction height 52 mm

6.6 Special precautions for disposal

The vaccine should be reconstituted only with the diluent (sterile water for injection) using a sterile syringe and needle. With gentle shaking the dried cake is easily dissolved. If the vaccine is not used immediately then it should be stored in the dark at 2°C – 8°C for no longer than 6 hours.

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

7. MARKETING AUTHORIZATION HOLDER

SERUM INSTITUTE OF INDIA PVT, LTD,

212/2, Hadapsar, Pune – 411028, Maharashtra, INDIA.
Telephone: ++ 91-20- 26993900
Fax: ++ 91- 20-26993924 / 26993921
Website: www.seruminstitute.com

8. MARKETING AUTHORISATION NUMBER(S)

Manufacturing License number: 10 (in form 28-D)

Measles, Mumps and Rubella Vaccine (Live) I.P Permission No MF/BIO/20/000082 in Form 46

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorization: 21st March, 1990
Date of Renewal of the Authorization: 12th October 2020

Date: 31 December 2022