1. NAME OF THE MEDICINAL PRODUCT

Rotavirus Vaccine (Live Attenuated, Oral) I.P. (Freeze-Dried) – ROTASIIL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rotavirus Vaccine (Live Attenuated, Oral) I.P. (Freeze-Dried) constitutes five viruses (Human and Bovine reassortant strains) of serotype G1, G2, G3, G4, and G9. All these strains constitute VP7 gene of respective serotype from human strains reassorted with bovine (UK) rotavirus.
Each dose of 2.5 ml contains:
Live Attenuated Bovine - Human Rotavirus Reassortant [G1, G2, G3, G4 and G9] $\geq 10^{5.6}$ FFU / Serotype. Reconstitute with Diluent for Rotavirus Vaccine. Diluent is a sterile solution (Citrate Bicarbonate Buffer) prepared using 9.6 mg/ml citric acid monohydrate and 25.6 mg/ml sodium bicarbonate.

Excipients:
Eagle's MEM (Minimum Essential Medium) with Hank's Salts, Glutamine and Sodium bicarbonate, Sucrose and Glycine.

3. PHARMACEUTICAL FORM

Rotavirus vaccine is available as a vial of freeze-dried vaccine to be reconstituted with a liquid diluent in a vial containing antacid (Citrate Bicarbonate Buffer). Vaccine is to be reconstituted with the help of adapter and syringe just prior to oral administration.
The vaccine or diluents contains no preservatives. The vaccine is for oral administration and not for injection.
The vaccine conforms to I.P. and the World Health Organization (W.H.O.) requirements.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROTASIIL is indicated for active immunization of healthy infants from the age of 6 weeks for the prevention of gastroenteritis due to rotavirus infection when administered as a 3-dose series.

4.2 Posology and method of administration

ROTASIIL is for ORAL USE ONLY and MUST NOT BE ADMINISTERED PARENTERALLY.

Dosage:
ROTASIIL should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age. Based on recommendations from the World Health Organization, if the routine childhood immunizations are initiated later than 6 weeks of age and/or at a longer dose interval than 4-weeks, ROTASIIL can still be administered, by itself or concomitantly with DTP, inactivated poliovirus vaccine (IPV), oral poliovirus vaccine (OPV), H. influenzae type b conjugate (Hib)

vaccine, and hepatitis B vaccine. Because of the typical age distribution of rotavirus gastroenteritis, rotavirus vaccination of children > 24 months of age is not recommended. There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with ROTASIIL.
It is recommended that infants who receive ROTASIIL as the first dose should complete the three-dose series with ROTASIIL. There is no data on safety, immunogenicity or efficacy of ROTASIIL when administered interchangeably with other available rotavirus vaccines.
In case that an incomplete dose is administered (the baby spits up or regurgitates most of the vaccine), a single replacement dose may be administered at the same vaccination visit*. The baby may continue to receive the remaining doses as per schedule.

*Physician's discretion is advised

Dosage administration
Each single oral dose of ROTASIIL is approximately 2.5 mL in volume. The vaccine package constitutes one vial of freeze-dried vaccine, one vial of citrate bicarbonate buffer, one adapter and syringe(s) for vaccine reconstitution and administration. Only the specific buffer diluent provided must be used for reconstitution. If the integrity of either the vaccine or buffer diluent vial has been compromised, that particular vial must be discarded. The content of vial containing buffered diluent should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to reconstitution. Reconstituted vaccine must be used immediately.

If not used immediately, it can be held for a period of maximum 6 hours, provided, a syringe* is used to cap the opening of the vial adapter and the entire assembly is stored at 2 to 8°C.
* Fresh syringe if it is the second dose, else use the syringe used for reconstitution.

Reconstituted vaccine may contain inherent product aggregates. The vaccine must not be mixed with other medicinal products.

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

4.3 Contraindications
Hypersensitivity to any component of the vaccine is a contraindication to vaccine. Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of ROTASIIL should not receive further doses. Infants with a history of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant for intussusception should not receive vaccine. Individuals with Severe Combined Immunodeficiency Disease (SCID) should not receive vaccine as cases of gastroenteritis associated with other live rotavirus vaccines have

been reported in infants with SCID. History of intussusception (IS) is a contraindication to vaccine administration.

4.4 Special warnings and precautions for use

No safety or efficacy data of ROTASIIL is available in immunocompromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of ROTASIIL may be considered with caution in immunocompromised infants and infants in close contact with immunodeficient persons, if in the opinion of the physician the benefit far outweigh the risks of vaccine. Similarly, acute infection or febrile illness may be a reason for delaying the administration of ROTASIIL. Low-grade fever and mild upper respiratory tract infection are not contraindications to ROTASIIL.

Available published data shows a small increased incidence of intussusception (IS) following other live oral rotavirus vaccines especially after the first dose. The safety data from the clinical trials of ROTASIIL did not show any increased risk of IS. However, health care providers should carefully evaluate cases with symptoms suggestive of IS.

Similar to other rotavirus vaccines, vaccination with ROTASIIL may not protect all vaccine recipients against rotavirus infection. Also, ROTASIIL will not provide protection against gastroenteritis caused by the other pathogens.

4.5 Interaction with other medicinal products and other forms of Interaction

Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than minimal doses), may reduce the immune response to vaccines.

ROTASIIL can be administered concomitantly with other vaccines of the infant immunization programme, including combined diphtheria, tetanus toxoid and pertussis vaccine (DTP), inactivated poliovirus vaccine (IPV), oral polio vaccine (OPV), H. influenzae type b conjugate (Hib) vaccine, and hepatitis B vaccine.

No interaction studies have been performed with ROTASIIL in infants with other medicinal products.

4.6 Pregnancy

Animal reproduction studies have not been conducted with ROTASIIL. It is also not known whether ROTASIIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ROTASIIL is not indicated for adults including women of child-bearing age and should not be administered to pregnant females.

4.7 Effects on ability to drive and use machines

Effect of ROTASIIL on ability to drive and use machines is not known. However, ROTASIIL is indicated for use in infant population and hence, this is not applicable.

4.8 Undesirable effects

Following solicited adverse reactions have been reported during the phase 3 efficacy clinical trial of ROTASIIL within 7 days of each dose of vaccine.

Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

General disorders and administration site conditions:

Very common (≥1/10): Fever, irritability, decreased activity level.

Gastrointestinal disorders:

Very common (≥1/10): Decreased appetite, vomiting
Common (≥1/100 and < 1/10): Diarrhea

In the phase III trial of ROTASIIL, no differences were detected between ROTASIIL and placebo groups in the post-vaccination rates of solicited adverse events within 7 days of each dose of vaccine. These events in decreasing order of frequency were : Fever (68.2% in the ROTASIIL group, 69.7% in the placebo group), irritability (42.6% in the ROTASIIL group, 36.1% in the placebo group), decreased appetite (20.4% in the ROTASIIL group, 20.0% in the placebo group), decreased activity level (18.8% in the ROTASIIL group, 17.1% in the placebo group), vomiting (17.0% in the ROTASIIL group, 16.9% in the placebo group) and diarrhea (8.4% in the ROTASIIL group, 10% in the placebo group). Except for irritability, the incidence of all solicited events was similar in ROTASIIL and placebo groups. Most of these events were of short duration and predominately mild (98% of episodes) in severity. It should be noted that in the phase 3 efficacy study, ROTASIIL and placebo were administered to all children concomitantly with DTwP vaccine, which is known to cause a level of reactogenicity similar to that observed in this study.

The occurrence of unsolicited adverse events was monitored throughout the phase 3 efficacy trial. The most frequent serious adverse events observed included gastroenteritis, lower respiratory tract infection, bronchiolitis, bronchopneumonia, pyrexia and pneumonia. Except for 11 cases of gastroenteritis that occurred within 7 days post-vaccination, none of the SAEs observed were considered to be related to study products. Of the 11 gastroenteritis cases, 6 participants had received ROTASIIL and 5 had received Placebo. However, out of these 11, only one tested positive for rotavirus antigen in stool by ELISA.

A total of seven cases of intussusception occurred until time of primary analysis of which four were in the ROTASIIL group and three in the Placebo group. None of the cases occurred within

28 days of receiving a dose of ROTASIIL or Placebo. All cases of intussusception were causally unrelated to study vaccination.

4.9 Overdose

No case of overdose has been reported

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines,

Rota virus, pentavalent, live, reassorted, ATC code J07BH02.

The immune response to natural rotavirus infection is not completely understood. It is known that prior exposure to rotavirus provides incomplete protection from the virus and therefore, infants and children can be reinfected from year to year. Natural infection, however, may provide some protection from severe diarrhea during subsequent infections. This may result from a virus-specific immune response generated at the intestinal mucosal surface. ROTASIIL has been developed to mimic the immunologic responses stimulated by natural infection. It is assumed that vaccine virus replicates in the small intestine and induces immunity. The immunologic mechanism by which ROTASIIL protects against rotavirus gastro-enteritis is not entirely understood. It is thought that IgA antibodies generated against ROTASIIL reflect a local immune response. Though there is no serological correlate of protection, a Phase II randomized, double-blind, placebo-controlled study assessed the serum IgA response to ROTASIIL in 60 healthy infants. Three doses of the $10^{5.6}$ FFU/serotype formulation induced a significant immune response. The seroconversion rate at 28 days post dose 3 was 60% among vaccine recipients and 7.69% among placebo recipients ($p < 0.05$). The seroconversion rates indicated that the vaccine is immunogenic in infants. These results are similar to those reported in India for other licensed rotavirus vaccines.

In a Phase III multicentre, open-label, randomized, controlled study in India, 1500 infants were randomized to receive either ROTASIIL or Rotarix at 6, 10 and 14 weeks of age, in addition to the other vaccines in the Universal Immunization Programme (UIP). At 4 weeks after the 3rd dose, the anti-Rotavirus IgA seropositivity rate were 46.98% (95%CI 43.86-50.11) in ROTASIIL group which significantly higher than that in the Rotarix group [31.12% (95%CI 26.17-36.41)]. The Geometric Mean Concentrations were significantly higher in the ROTASIIL group [19.16 IU/ml (95% CI 17.37–21.14)] which was significantly higher than that in Rotarix group [10.92 IU/ml (95% CI 9.36–12.74)]. ROTASIIL did not interfere with the immunogenicity of the concomitantly administered routine infant vaccines.

5.2 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not applicable for vaccines.

5.3 Preclinical safety data
SIIPL conducted single- and repeated-dose toxicity studies of rotavirus vaccine in rodents (Wistar rats) and non-rodents (New Zealand white rabbits) by oral gavage administrations. These studies were conducted with a hexavalent vaccine which included G1, G2, G3, G4, G8 and G9 reassortants. Single dose studies included 60 rats and 18 rabbits in three groups while repeated dose studies included 70 rats in four groups and 18 rabbits in three groups. The vaccine in single- and repeated-dose toxicity studies in both the species had no effects on their general health. There were no changes in body temperature, cumulative net body weight gains and hematological, clinical chemistry and urinalysis parameters in animals of either sex. Fecal samples were negative for the presence of rotavirus antigen in all the animals. No gross or microscopic histopathological changes were detected.

The results of these studies showed that ROTASIIL is well tolerated in Wistar rats and New Zealand white rabbits even at more than the ten times of human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sucrose and Glycine, 50mg each per dose and MEM quantity sufficient are the excipients used in formulation as stabilizer.

6.2 Incompatibilities
Under no circumstances should ROTASIIL be mixed with any other medicinal products.

6.3 Shelf life
30 months. Do not use after expiry date.

6.4 Special precautions for storage
Rotavirus Vaccine, Live Attenuated (Oral) (Freeze-Dried) should be stored at or below + 25°C.
In case the product is supplied with optional Vaccine Vial Monitor (VVM 30) the recommended storage is 2 to 8°C to maintain the integrity of VVM.

<u>The vaccine vial monitor (VVM 30) (optional):</u>
Vaccine Vial Monitor (VVM 30) is applied on the top of seal of freeze-dried vaccine container of ROTASIIL. This is a time temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded. Indicative usage guide is as follows:

• Inner Square lighter than outer circle. If the expiry date has not passed, USE the vaccine.
• At a later time, inner square still lighter than outer circle. If the expiry date has not passed, USE the vaccine.
• Discard point: Inner Square matches colour of outer circle. DO NOT use the vaccine.
• Beyond the discard point: Inner square darker than outer ring. DO NOT use the vaccine.

6.5 Nature and contents of container

- 1 dose (2.5 ml) : 1 vial of freeze dried vaccine + 1 vial containing liquid diluent
- 2 dose (5 ml) : 1 vial of freeze dried vaccine + 1 vial containing liquid diluent

6.6 Special precautions for disposal

Once vaccine has been administered, the injection equipment and vaccine containers should be disposed of according to the standard procedures for medical waste.

7. MARKETING AUTHORIZATION

Serum Institute of India Pvt Ltd,
212/2, Hadapsar, Off Soli Poonawalla Road,
Pune – 411028, Maharashtra, INDIA.
Telephone: + 91-20- 26993900, + 91-20-26602379
Fax: ++ 91- 20-26993921 / 26993945
Website: www.seruminstitute.com

8. MARKETING AUTHORISATION NUMBER (S)

Manufacturing permission number: MF-222/2016
Manufacturing License number: 10.

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first Authorization: 23.12.2016.

Date: 31 December 2022