## Summary of Product Characteristics

### 1 Name of the medicinal product
Rotavirus Vaccine, Live Attenuated, (Oral) (Freeze-Dried)

### 2 Qualitative and quantitative composition
Each dose of 2.5 mL contains:
Live Attenuated Bovine-Human Rotavirus Reassortant
[G1, G2, G3, G4 and G9]* ≥ $10^{5.6}$ FFU / serotype.
Reconstitute with Diluent for Rotavirus Vaccine.
Diluent is a sterile solution (Citrate Bicarbonate Buffer) prepared using
9.6 mg/mL citric acid and 25.6 mg/mL sodium bicarbonate.
* Grown on vero cells.
Excipient(s) with known effect
Eagle's MEM (Minimum Essential Medium with Hank's Salts,Glutamine
and Sodium bicarbonate). Sucrose and Glycine.

The vaccine is supplied along with a 2.5 mL vial for one dose and 5 mL vial for two doses of buffered diluent. This vaccine contains no preservatives.

For the full list of excipients, see section 6.1.

### 3 Pharmaceutical form
Lyophilized powder to be reconstituted with buffered diluent for oral administration.

Description: Pinkish to yellowish white mass.
Appearance: Pinkish to yellowish liquid when reconstituted with diluent and maycontain inherent product aggregates.

### 4 Clinical particulars

#### 4.1 Therapeutic indications
Rotavirus Vaccine, Live Attenuated, (Oral) 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
***Rotavirus Vaccine, Live Attenuated (Oral) is for oral administration only and must not be injected.***
***Dosage:*** Rotavirus Vaccine, Live Attenuated (Oral) 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, Rotavirus Vaccine, Live Attenuated (Oral) 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. There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with Rotavirus Vaccine, Live Attenuated (Oral).

It is recommended that infants who receive Rotavirus Vaccine, Live Attenuated (Oral) as the first dose should complete the three dose series with Rotavirus Vaccine, Live Attenuated (Oral). There is no data on safety, immunogenicity or efficacy of Rotavirus Vaccine, Live Attenuated (Oral) when administered interchangeably with other available rotavirus vaccines.

In case, 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 Rotavirus Vaccine, Live Attenuated (Oral) 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. 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 administration. Reconstituted vaccine must be used within 6 hours of reconstitution or before the end of the immunization session, whichever is earlier when stored between 2 to 8°C. Any unused vaccine or waste material should be disposed of in accordance with local requirements. The reconstituted vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. The vaccine must not be mixed with other medicinal products.

Reconstitution instructions for Rotavirus Vaccine, Live Attenuated (Oral):

- Remove plastic caps from the vials containing diluent and freeze-dried powder.
- Fit the vial adapter on the diluent vial. Connect the syringe to the vial adapter.Withdraw the entire diluent into the syringe.
- Disconnect the vial adapter and the attached syringe from the diluent vial.
- Fit the vial adapter with the syringe on to the vaccine vial. Inject the entire contents of the syringe into the vial containing the freeze-dried powder.
- While holding the syringe, gently swirl until the solution is clear. Do not shake. The reconstituted vaccine will appear as pinkish to yellowish solution.
- While holding the plunger down, turn syringe with vial upside down. Pull back the plunger to withdraw single dose (2.5 ml) mixture back into the syringe.
- Remove the syringe from the vial adapter. The vaccine is ready for administration.
- Administer the entire content of the syringe orally (on the inside of the cheek). The child should be seated in a reclining position. Do not inject.

## 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 Rotavirus Vaccine, Live Attenuated (Oral) should not receive further doses of vaccine. 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 Rotavirus Vaccine, Live Attenuated (Oral) is available in immunocompromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral). Low-grade fever and mild upper respiratory tract infection are not contraindications to Rotavirus Vaccine, Live Attenuated (Oral).

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 Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) may not protect all vaccine recipients against rotavirus infection. Also, Rotavirus Vaccine, Live Attenuated (Oral) 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. Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) in infants with other medicinal products.

**4.6 Pregnancy**

Animal reproduction studies have not been conducted with Rotavirus Vaccine, Live Attenuated (Oral). It is also not known whether Rotavirus Vaccine, Live Attenuated (Oral) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) on ability to drive and use machines is not known. However, Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral), no differences were detected between Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) group, 69.7% in the placebo group), irritability (42.6% in the Rotavirus Vaccine, Live Attenuated (Oral) group, 36.1% in the placebo group), decreased appetite (20.4% in the Rotavirus Vaccine, Live Attenuated (Oral) group, 20.0% in the placebo group), decreased activity level (18.8% in the Rotavirus Vaccine, Live Attenuated (Oral) group, 17.1% in the placebo group), vomiting (17.0% in the Rotavirus Vaccine, Live Attenuated (Oral) group, 16.9% in the placebo group) and diarrhoea (8.4% in the Rotavirus Vaccine, Live Attenuated (Oral) group, 10% in the placebo group). Except for irritability, the incidence of all solicited events was similar in Rotavirus Vaccine, Live Attenuated (Oral) 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, Rotavirus Vaccine, Live Attenuated (Oral) 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.

Over the entire course of the phase 3 efficacy trial severe (grade 3) adverse events as well as serious adverse events (SAEs) were closely monitored. 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 these 11 gastroenteritis cases, 6 participants had received Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) group and three in the Placebo group. None of the cases occurred within 28 days of receiving a dose of Rotavirus Vaccine, Live Attenuated (Oral) 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
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 diarrhoea during subsequent infections. This may result from a virus-specific immune response generated at the intestinal mucosal surface. Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) protects against rotavirus gastro-enteritis is not entirely understood.

It is thought that IgA antibodies generated against Rotavirus Vaccine, Live Attenuated (Oral) 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 Rotavirus Vaccine, Live Attenuated (Oral) 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 placeborecipients ($p < 0.05$). 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

Serum Institute of India Pvt. Ltd. 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 allthe animals. No gross or microscopic histopathological changes were detected.

The results of these studies showed that Rotavirus Vaccine, Live Attenuated (Oral) 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, Glycine and MEM are the excipients used in formulation.

### 6.2 Incompatibilities

Under no circumstances should Rotavirus Vaccine, Live Attenuated (Oral) be mixed with any other medicinal products.

### 6.3 Shelf life

30 months

### 6.4 Special precautions for storage

Rotavirus Vaccine, Live Attenuated (Oral) should be stored at 2-8°C.

**6.5 Nature and contents of container**

- 1 dose vial plus 1 diluent vial (2.5 mL)
- 2 dose vial plus 1 diluent vial (5 mL)

THE VACCINE VIAL MONITOR (Optional)

- Inner square lighter than outer circle. If the expiry date has not passed, USE thevaccine.
- 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 thevaccine.
- Beyond the discard point: Inner square darker than outer ring. DO NOT use thevaccine.

Vaccine Vial Monitors (VVMs) are on the cap of Rotavirus Vaccine, Live Attenuated (Oral) supplied through Serum Institute of India Pvt. Ltd. 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.

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

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 authorisation holder**

Serum Institute of India Pvt. Ltd
212/2, Hadapsar, Pune 411028, INDIA

**8. Marketing authorisation number(s)**

TAN 21 HM 0456

**9. Date of first authorisation/renewal of the authorisation**

Date of first authorization: November 26, 2021
Date of latest renewal: N/A

**10. Date of revision of the text**

**April, 2022**

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