

6.2 Storage of ROTAVAC®

Store at -20°C. It can be stored up to 6 months at 5°C ± 3°C at any time during shelf-life.

6.3 Transport

ROTAVAC® can be transported at 5°C ± 3°C using -20°C frozen gel packs.

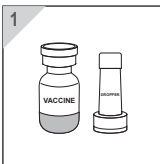
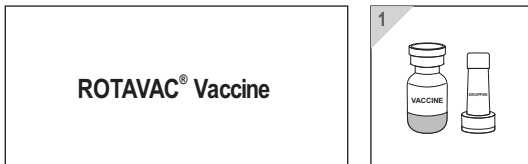
The expiry date of the vaccine is indicated on the label and packaging.

7.0 Presentation

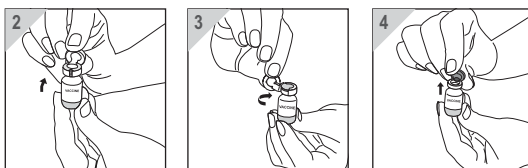
ROTAVAC® is presented in USP type 1 glass vials.

Single Dose : 0.5 mL vial

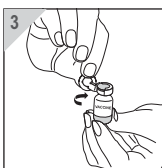
8.0 Administration of ROTAVAC® Vaccine



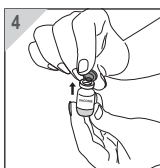
Vaccine vial & dropper (s)



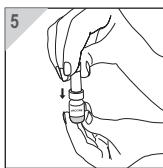
Pull out the aluminum seal along the indicated mark



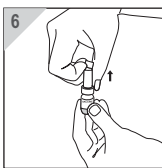
Tear off as shown to remove aluminum seal



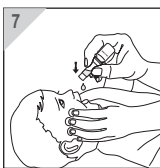
Pull out the rubber stopper



Connect the dropper firmly to the vial



Open the dropper tip



Keep dropper at 45° angle
Administer 5 drops into the
mouth of the baby

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only.

Manufactured & Marketed by:



Bharat Biotech International Ltd.
Genome Valley, Shameerpet Mandal,
Ranga Reddy District - 500 078
Telangana, India.
e-mail : feedback@bharatbiotech.com
www.bharatbiotech.com

रोटावायरस वैक्सिन (लाइव एट्युएटेड, ओरल) आई पी Rotavirus Vaccine (Live Attenuated, Oral) IP Vero cell-derived ROTAVAC® Single Dose

1. NAME AND DESCRIPTION OF THE ACTIVE IMMUNISING AGENT

Rotavirus Vaccine (Live Attenuated, Oral) is a monovalent vaccine containing suspension of live rotavirus 116E prepared in Vero cells. Rotaviruses are double-stranded RNA virus of the genus Reoviridae. Rotaviruses are classified in a dual classification system based on two proteins on the surface of the virus into G and P types. Based on this nomenclature, Rotavirus 116E is classified as G9P [11]. A single human dose of ROTAVAC® is 0.5 mL containing not less than [NLT] 10⁷ FFU [Focus Forming Unit] of live rotavirus 116E.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

List of ingredients and quantities

2.1 Composition of ROTAVAC®

Ingredients	Quantity / 0.5 mL
Rotavirus 116E Bulk, Live Attenuated	NLT 10 ⁷ FFU
Potassium Phosphate Monobasic IP	0.258 mg
Potassium Phosphate Dibasic IP	0.625 mg
Sucrose IP	37.31 mg
Potassium L-glutamate Monohydrate	1.0 mg
Neomycin Sulphate IP	15 µg
Kanamycin Sulphate IP	15 µg
Dulbecco's Modified Eagle's Medium	4.4 mg
Water for Injections IP	q.s

pH is in the range of 7.2 to 8.0

3. PHARMACEUTICAL FORM

ROTAVAC® is a liquid in frozen form.

In liquid form, the vaccine is generally pink in colour and may sometimes change to orange (or light yellow) in colour. This change in colour does not impact the quality of vaccine.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For prophylactic use only.

ROTAVAC® is indicated for active immunization of 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. Dosage and method of administration

Dosage

ROTAVAC® should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age. ROTAVAC® may be co-administered with other routine childhood immunizations (i.e., Diphtheria, Tetanus and Pertussis [DTwP], Hepatitis B vaccine and Oral Polio Vaccine [OPV]). Based on recommendations from the World Health Organization (Rotavirus vaccines WHO Position Paper, January 2013 in Weekly Epidemiological Report No.5, 2013, 88, 49-64), if the routine childhood immunizations are initiated later than 6 weeks of age and/or at a longer dose interval than 4-weeks, ROTAVAC® can still be co-administered with DTwP.

ROTAVAC® VIAL SHOULD BE FULLY THAWED (TILL LIQUID) PRIOR TO ADMINISTRATION.

It is recommended that infants who receive ROTAVAC® as the first dose should complete the 3 dose regimen with ROTAVAC®. There is no data on safety, immunogenicity or efficacy when ROTAVAC® is administered interchangeably with other rotavirus vaccines.

Paediatric Population

All doses of Rotavirus vaccine should be administered to children by the age of 8 months (34 weeks) (Centre for Disease Control and Prevention, <http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-faqs.htm>).

Method of administration

ROTAVAC® is for oral use only and SHOULD NOT BE INJECTED.

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. However, in clinical trials, the reported incidence of spitting or vomiting is <0.5%.

*Physician's discretion is advised

4.3 Contraindications

- Hypersensitivity to any component of the vaccine. Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of ROTAVAC® should not receive further doses of ROTAVAC®.
- Individuals with Severe Combined Immunodeficiency Disease (SCID). Cases of gastroenteritis associated with live rotavirus vaccines have been reported in infants with SCID.
- History of intussusception (IS).

4.4 Special warning/Precautions

No safety or efficacy data are available from clinical trials regarding the administration of ROTAVAC® to immunocompromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of ROTAVAC® may be considered with caution in immunocompromised infants and infants in close contact with immunodeficient persons, if in the opinion of the physician, withholding the vaccine entails a greater risk. Similarly, acute infection or febrile illness may be reason for delaying the administration of ROTAVAC®, unless in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever and mild upper respiratory tract infection are not contraindications to ROTAVAC®.

Available published data shows a small increased incidence of intussusception (IS) following the first dose of Rotavirus vaccines especially after the first dose (WHO position paper, January 2013, <http://www.who.int/wer/2013/wer8005.pdf?ua=1>). The safety data from the clinical trials of ROTAVAC® did not show an increased risk of IS for ROTAVAC® when compared to placebo. However, it is advised that health care providers follow-up on any symptoms suggestive of IS e.g., continuous vomiting, blood in stools and abdominal lump or distension of the abdomen. Parents/caregivers should be advised to promptly inform such symptoms to healthcare providers.

Rotavirus Gastroenteritis (RVGE) with Genotype of Vaccine strain, G9P [11]

Twenty-two G9P[11] rotavirus gastroenteritis cases occurred following 13,296 administrations of ROTAVAC® (approximately 1 event in 600 doses); 20 occurred after the first dose, 2 after the second dose, and none after the third dose throughout the duration of follow-up. No severe cases of rotavirus gastroenteritis were associated with G9P[11]. There can be two possible explanations for these findings: the vaccine causes rare, and mostly mild gastroenteritis; or shedding of ROTAVAC® was detected in cases of gastroenteritis caused by other non-identified pathogens. Similar to other vaccines, vaccination with ROTAVAC® may not result in complete protection against rotavirus induced gastroenteritis or gastroenteritis due to other pathogens.

There is no data to support use of ROTAVAC® for post exposure-prophylaxis.

4.5 Interaction with other medicinal products/active immunising agents and other forms of interaction

The analysis of the immune response for the 3 OPV serotypes was performed by analysing geometric mean titre (GMT) and the proportion of subjects meeting the accepted protective titre (neutralizing antibody ≥ 1:8) for recipients of OPV plus ROTAVAC® and OPV plus placebo. Post-vaccination GMTs were comparable between the two groups. Similarly, the proportion of subjects with titre ≥ 1:8 was comparable between ROTAVAC® and placebo groups. In summary, the analysis of post immunization revealed that subjects receiving OPV concurrently with ROTAVAC® generated comparable immune responses to all three polio serotypes compared to those receiving OPV without ROTAVAC®. The trial design did not permit an evaluation of the impact of OPV on the immune responses to ROTAVAC®.

In phase III clinical trial, subjects received 3 doses of ROTAVAC® or placebo concomitantly with childhood vaccines DTwP, Hepatitis B vaccine and OPV. Vaccines were administered at 6-7 weeks, ≥ 10 weeks and ≥ 14 weeks of age. There was no significant difference in immediate or follow-up adverse events in the ROTAVAC® or the placebo group.

No interaction studies have been performed in infants with other medicinal products. For use with other vaccines, see Section 4.2.

4.6. Pregnancy and lactation

ROTAVAC® is a paediatric vaccine and should not be administered to adults including pregnant women. Breast-feeding of infants was permitted in clinical studies. There was no evidence to suggest that breast-feeding reduced the protection against rotavirus gastroenteritis conferred by ROTAVAC®. There are no restrictions on the infant's liquid consumption including breast-milk, either before or after vaccination with ROTAVAC®.

4.7. Effect on ability to drive and use machines

Not applicable.

4.8 Adverse Reactions

Clinical Trial Experience

Safety data from phase I - III trials of ROTAVAC® is discussed below. Overall the events reported are similar to those reported in other rotavirus vaccine clinical trials.

In the phase Ib/IIa dose escalation study conducted on Oral Rotavirus Vaccine (ORV) 116E in India with 369 infants of 6-8 weeks age, no significant adverse events were demonstrated to be associated with the ORV 116E. Commonly reported adverse events included fever, vomiting, and diarrhoea. In the larger phase III efficacy study conducted in India with 6,799 infants of 6-7 weeks of age, prevalence of immediate, solicited and serious adverse events was similar in the vaccine and placebo groups. Analyses for solicited adverse events showed a similar prevalence of fever, vomiting, diarrhoea, cough, runny nose, irritability and rash. Commonly observed immediate adverse event within 30 minutes of administration are vomiting, and spitting up (<0.5%).

In the phase III trial, no differences were detected between ROTAVAC® and placebo groups in the post-vaccination reactivity observations. The modest and inconsistent imbalances in fever, diarrhoea and vomiting noted in the phase Ib/IIa trial were not confirmed in the much larger phase III trial. The overall lower incidence of reactivity noted in the phase Ib/IIa trial, is likely due to the separation of the childhood vaccines from the administration of ROTAVAC®/placebo. There were higher rates of fever reported in the phase III trial when subjects received routine childhood vaccines concomitantly with ROTAVAC®/placebo; however, the frequency of fever was similar between the ROTAVAC® and placebo groups.

No vaccine-related SAEs were reported in the phase Ib/IIa trial. In the phase III trial, 925 of the 4,531 subjects receiving ROTAVAC® (20.4%) and 499 of 2,265 subjects receiving placebo (22.0%) reported an SAE. All but 3 were considered not related to ROTAVAC®/placebo; the 3 possibly related SAEs were sepsis and gastroenteritis (GE) in two placebo recipients, and urticaria in one ROTAVAC® recipient.

No deaths were observed among the 369 subjects in the phase Ib/IIa trial, and 42 deaths occurred among the subjects in the phase III; 25 of them among the 4,531 subjects (0.55%) in the ROTAVAC® group and 17 among 2,265 subjects (0.75%) in the placebo group (p=0.3279). None of the deaths were deemed to be related to administration of ROTAVAC®/placebo.

No cases of IS were observed in the phase Ib/IIa trial. In the phase III trial, there were six confirmed cases of IS observed among the 4,532 ROTAVAC® recipients (0.13%), and two among the 2,267 placebo recipients (0.09%). The minor difference in number of subjects with IS was not statistically significant (p=0.7267). There were no reports of IS in the 14 day period following vaccination; the first case identified occurred in a placebo subject, 36 days after the third dose. The first case reported among ROTAVAC® recipients occurred 112 days after the third dose. G1P [8] was identified in the stool from this subject. All IS events were resolved after pneumatic reduction or barium enema; none required surgical intervention and none fatal.

As per WHO position paper January 2013, on Rotavirus vaccines, "..... the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception."

Preterm infants and infants with human immunodeficiency virus (HIV) infection

Clinical studies have not been conducted in these groups of population and data is not available

Post marketing surveillance data

A post marketing surveillance is planned to be undertaken with Drug Controller General (India) approval vide File No.12-31/BHARAT/13-BD

4.9. Overdose

In the phase III trial, one subject received a double dose of ROTAVAC®. This subject was followed daily with home visits for 14 days and no adverse events were identified or reported.

5. PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutic group: rotavirus diarrhoea vaccines.

5.1 Pharmacodynamic properties

Protective efficacy

Efficacy

Multicentre clinical study was conducted in India to evaluate the efficacy of ROTAVAC® to prevent severe rotavirus gastroenteritis. Data for vaccine efficacy has been presented for the first year and second year of life. The results of these two analyses were similar, suggesting that the vaccine efficacy persists into second year of life.

Vaccine efficacy (VE) for severe non-vaccine RVGE was 56.4% [95% CI 36.6, 70.1] and 34.6% [95% CI 19.7, 46.6] for non-vaccine RVGE of any severity, during the first year of life. In the same study, the VE against severe non-vaccine RVGE in the second year of life was 49% (95% CI 17.5, 68.4) and 35.0% [95% CI 19.1, 47.7] against non-vaccine RVGE of any severity.

Non-vaccine RVGE requiring hospitalisation and of any cause

ROTAVAC® prevented 47.7% (95% CI: 24.5, 63.8) of all hospitalizations ≥ 24hrs due to severe non-vaccine rotavirus gastroenteritis. ROTAVAC® was also efficacious against severe GE of any aetiology (VE=18.6% [95% CI 1.9, 32.3]).

Immune response

The immunogenicity of ROTAVAC® was assessed by serum anti-rotavirus IgA ELISA. In the phase Ib/IIa trial a serological response (≥ 4-fold increase) was seen in 89.7% of ROTAVAC® recipients (compared to 28.1% of placebo recipients). In the phase III trial, the observed serological response rate after the third dose of ROTAVAC® was 40.3% in comparison to 18.4% in the placebo group.

Summary: In the phase III Efficacy clinical trial in infants, ROTAVAC®

- Is efficacious in the prevention of severe non-vaccine RVGE (primary endpoint)
- Is efficacious in the prevention of severe non-vaccine RVGE during the first year and second year of life.
- Is efficacious in the prevention of non-vaccine RVGE of any severity during the first and second year of life.
- Offers broad protection against the most commonly circulating RV genotypes in India.
- Reduced hospitalisations and supervised rehydration therapy due to severe GE of any aetiology.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Pre-clinical safety data

A 28 day repeated dose non-clinical toxicity study on oral rotavirus candidate vaccine 116E live attenuated strain was carried out in rats and rabbits. The non-clinical toxicity studies with formulations containing virus titre higher than that in single human dose proved that the Rotavirus 116E Live Attenuated candidate vaccine is safe and induced no toxicity in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

This product should not be mixed with any other medicinal products/active immunizing agents.