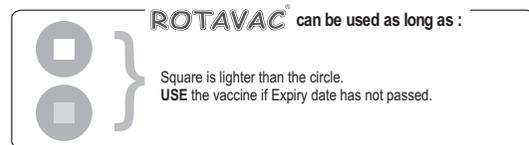


It is absolutely critical to ensure that the storage conditions specified above are complied with. Bharat Biotech assumes no liability in the event that **ROTAVAC**® has not been stored in compliance with the storage instructions. Furthermore, Bharat Biotech assumes no responsibility in case the VVM2 is defective for any reason.

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

7.0 Presentation
ROTAVAC® is presented in USP type I glass vials.
5 Doses : 2.5 mL vial
10 Doses : 5mL vial

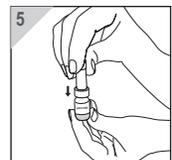
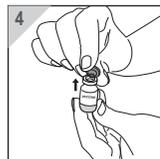
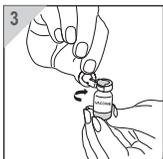
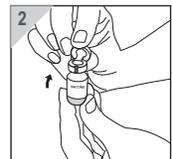
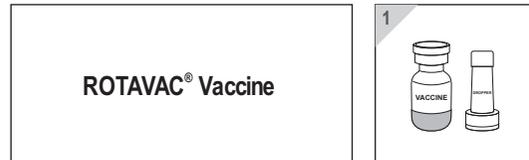
8.0 The Vaccine Vial Monitor²



Vaccine Vial Monitor² (VVM2) dot is a part of the label on **ROTAVAC**® vials. 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 VVM2 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, 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, the vial should be discarded.

9.0 Administration of ROTAVAC® Vaccine



Last Revision date: January 2017

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

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

रोटावायरस वैक्सिन (लाइव एट्यूएटेड, ओरल) आई पी
Rotavirus Vaccine (Live Attenuated, Oral) IP
Vero cell-derived
ROTAVAC®
Multi 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] 10⁸ FFU (Focus Forming Unit) of live rotavirus 116E.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
List of ingredients and quantities

2.1 Composition of ROTAVAC®
Each dose of 0.5 mL (5 Drops) contains

Ingredients	Quantity / 0.5 mL
Rotavirus 116E Bulk Live Attenuated	NLT 10 ⁸ 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 (DMEM)	4.4 mg
Water for Injections IP	q.s

pH range: 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 Epidemiol Record 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 (TIL 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.html>).

Method of administration

ROTAVAC® is for oral use only and SHOULD NOT BE INJECTED. Care should be taken not to contaminate the multi-dose dropper of the vaccine with saliva of the babies. Once opened, multi-dose vials should be kept at 5°C ± 3°C and used in the same immunisation session (within maximum 8 hours).

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 visit¹. 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%.

¹Physician'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/wer8805.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.

In phase IV trial subjects received 3 doses of **ROTAVAC**® with buffer administered 5 minutes before, without buffer and **ROTAVAC**® and buffer administered simultaneously. All childhood vaccines DTwP, Hepatitis B and OPV were administered concomitantly. There was no significant difference in immediate or follow up adverse events between the groups.

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 IIb/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 IIb/IIa trial were not confirmed in the much larger phase III trial. The overall lower incidence of reactivity noted in the phase IIb/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.

In the phase IV trial in India 900 infants of 6-7 weeks of age showed a similar prevalence of adverse events in all three groups. Fever, diarrhoea, vomiting, cough, cold and irritability were the most commonly reported adverse events. The distribution of adverse events was equal amongst all three treatment groups.

No vaccine-related SAEs were reported in the phase IIb/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 vaccine related SAEs were observed/reported.

No deaths were observed among the 369 subjects in the phase IIb/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.

There was one death reported in the phase IV trial unrelated to vaccine administration. No cases of IS were observed in the phase IIb/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. GIP (B) 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.

No cases of intussusception were reported in the phase IV trial. 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

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

5.1.1 Efficacy

Multi-centre 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 hospitalization ≥ 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 IIb/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 end point)
- 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. Seroinconversion was comparable in all 3 groups in the phase IV trial.

5.1.2 Phase III - EPI Noninterference trial

In a phase III placebo controlled trial, lot to lot consistency was determined in 3 production lots as well non interference with EPI antigens in 1356 infants aged 6-7 weeks at enrollment. In this clinical trial trivalent OPV (types 1, 2 & 3) as well as Pentavalent (DTwP, Hep B and Hib) vaccine were administered concurrently with **ROTAVAC** with buffer.

Fever, vomiting, diarrhoea, cough, listlessness, runny nose, irritability and rash were the most commonly reported AEs. No vaccine related SAEs were reported. There was no case of intussusception was observed/reported in this trial.

Statistical clinical equivalence was established across all three production lots. Three doses of **ROTAVAC**® can be safely administered with three doses of pentavalent vaccine and three doses of OPV without diminishing the antibody response of each component of these vaccines. It is well tolerated when administered with routine childhood vaccines. There was no statistical difference in rotavirus serum IgA seroconversion and GMTs amongst the three lots

5.1.3 Phase IV clinical trial

In a separate clinical trial, role of buffer was assessed in 900 subjects across three groups : **ROTAVAC**® with buffer administered 5 minutes before (300), **ROTAVAC**® without buffer (300) and **ROTAVAC**® mixed with buffer before administration (300).

In this clinical trial OPV and Pentavalent vaccines were administered concomitantly. There was no significant difference in immediate or follow up adverse events between the groups. Fever, diarrhoea, vomiting, cough, cold and irritability were the most commonly reported adverse events. The distribution of adverse events was equal amongst all three treatment groups.

No vaccine related SAEs were observed/reported. There was one death reported in the phase IV trial unrelated to vaccine administration.

No cases of intussusception were reported in the phase IV trial. Serum samples were analysed on day 0 and 84 pre and post vaccination to check for number of subjects who had titres less than 20 and ≥ 20. As per seroconversion definition, for rotavirus specific IgA, titres of ≥ 20 are considered to be seroconverted. In this clinical trial there is no statistically significant difference among the three groups for the following parameters:

- seroconversion
- geometric mean titres
- 4 fold seroconversion

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Pre-clinical safety data

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.

6.2 Storage of ROTAVAC®

The expiry date of the vaccine is indicated on the label and packaging. The Vaccine should be stored at -20°C. It can be stored at 2 - 8°C at any time during its shelf-life until the expiry of VVM2. (Refer section 8.0). **ROTAVAC**® can be subjected to freeze-thaw cycles. The Vaccine should be used within 8 hours after opening.