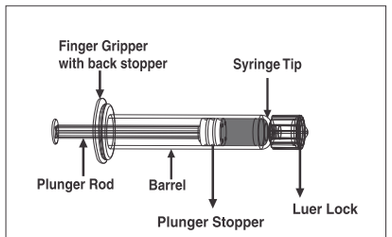
6.3 Shelf life
The expiry date of the vaccine is indicated on the label and carton of the product.

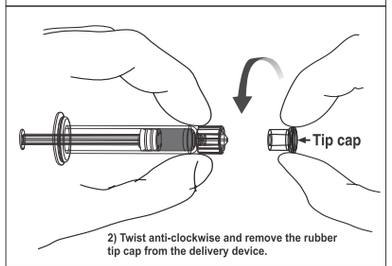
6.4 Special precautions for storage
The Vaccine should be stored at + 2°C to + 8°C. Do not freeze.
Keep out of reach of children. Do not use the vaccine after the expiration date shown on the label.

7. PRESENTATION
ROTAVAC 5D® is presented in USP type I glass PFS.
Single Dose PFS : 0.5mL

8. ADMINISTRATION OF ROTAVAC 5D® VACCINE
Fig: PFS Handling Diagram



1) Single dose ROTAVAC 5D® vaccine delivery device for Oral use.



2) Twist anti-clockwise and remove the rubber tip cap from the delivery device.

3) Open the mouth of the infant and push the plunger rod gently to administer ROTAVAC 5D® vaccine drop by drop. Do not deliver entire contents in one shot.

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Manufactured & Marketed by:

BHARAT BIOTECH
Lead Innovation

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For complaints and suggestions about the product, and any adverse event,
please email feedback@bharatbiotech.com or call on Toll free number 1800 102 2245
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For the use of a Registered Medical Practitioner or Hospital or a Laboratory only.

Rotavirus Vaccine (Live Attenuated, Oral) IP

VERO CELL DERIVED

ROTAVAC 5D®

1. NAME AND DESCRIPTION OF THE ACTIVE IMMUNIZING AGENT
Rotavirus Vaccine (Live Attenuated, Oral) is a monovalent vaccine containing suspension of live attenuated 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 5D®** is 0.5 mL containing not less than [NLT] $10^{5.5}$FFU [Focus Forming Unit] of live rotavirus 116E.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition :	
Each dose of 0.5 mL contains:	
Vero cell derived Rotavirus 116E bulk, Live attenuated	NLT $10^{5.5}$FFU
Neomycin Sulphate IP	15 µg
Kanamycin Acid Sulphate IP	15 µg
Sucrose IP	0.25 gms
Trehalose BP	2.5 mg
Lactalbumin Hydrolysate (LAH)	2.5 mg
Human Albumin IP	0.35 %
Potassium Dihydrogen Orthophosphate BP	1.65 mg
Dipotassium Hydrogen Orthophosphate BP	10 mg
Trisodium Citrate Dihydrate IP	7.75 mg
Water for Injections IP	q.s

pH range: 6.50 to 7.50

3. PHARMACEUTICAL FORM
ROTAVAC 5D® is pale yellow colored sterile liquid for oral use.

4. CLINICAL PARTICULARS

4.1Therapeutic indications
For prophylactic use only.
ROTAVAC 5D® 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 regimen.

4.2 Posology and method of administration
Posology
ROTAVAC 5D® should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age. **ROTAVAC 5D®** may be co-administered with other routine childhood immunizations (i.e., Diphtheria, Tetanus and Pertussis [DTwP], Haemophilus Influenzae type B, Hepatitis B vaccine and Oral/ injectable Polio Vaccine [OPV& IPV]). 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 5D®** can still be co-administered with DTwP.

It is recommended that infants who receive **ROTAVAC 5D®** as the first dose should complete the 3 dose regimen with **ROTAVAC 5D®**. There is no data on safety, immunogenicity or efficacy when **ROTAVAC 5D®** is administered interchangeably with other rotavirus vaccines.

Pediatric Population:
The upper age limit for the 3 dose primary schedule 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 5D® 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 less than 0.5 %.

*Physician's discretion is advised

4.3 Contraindications
- Hypersensitivity to any component of the vaccine. Babies who develop symptoms suggestive of hypersensitivity after receiving a dose of **ROTAVAC 5D®** should not receive further doses of **ROTAVAC 5D®**
- Babies 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)/intestinal malformations predisposing to intussusception.
- Ongoing Gastroenteritis

4.4 Special warning/ Precautions
No safety or efficacy data are available from clinical trials regarding the administration of **ROTAVAC 5D®** to immune-compromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of **ROTAVAC 5D®** may be considered with caution in immune-compromised infants and infants in close contact with immune-deficient 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 5D®**, 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 5D®**.

Available published data shows a small increased incidence of Intussusception (IS) following the first dose of Rotavirus vaccines (WHO position paper, January 2013, http://www.who.int/wer/2013/wer8805.pdf?ua=1). However, the safety data from the clinical trials of **ROTAVAC 5D®** did not show an increased risk or incidence of IS. Yet, it is advised to health care providers to look into 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 promptly to inform such symptoms to health care providers.

Similar to other vaccines, vaccination with **ROTAVAC 5D®** 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 5D®** for post exposure-prophylaxis.

***ROTAVAC 5D® SHOULD NOT BE INJECTED AT ANY CIRCUMSTANCES**

4.5 Interaction with other medicinal products/active immunizing agents and other forms of interaction
In this clinical trial, OPV, IPV and pentavalent (DTwP, HepB and Hib) vaccines were administered concurrently with **ROTAVAC 5D®**. Three doses of **ROTAVAC 5D®** can be safely administered with three doses of pentavalent vaccine and three doses of OPV as well as IPV without diminishing the antibody response to each component of these vaccines. It is well tolerated when administered concomitantly with routine childhood vaccines.

4.6 Pregnancy and lactation
ROTAVAC 5D® is a pediatric 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 5D®**. There are no restrictions on the infant's liquid consumption including breast-milk, either before or after vaccination with **ROTAVAC 5D®**.

4.7 Effect on ability to drive and use machines
Not applicable.

4.8 Adverse reactions
Clinical Trial Experience
The most commonly observed Adverse Events during the clinical trial were Fever, Diarrhea, Cough and others like running nose and irritability. No vaccine related SAEs were reported. There was no vaccine related case of intussusception observed/reported. Fever could be due the concomitant injectable vaccines.
List of adverse reactions

Adverse reactions reported are listed according to the following frequency
Frequency is defined as:
Very common: (≥1/10)
Common : (≥1/100, <1/10)
Uncommon : (≥1/1000,<1/100)
Rare : (≥1/10000,<1/1000)
Clinical Trial Data
Very common: Fever, Cough ,crying
Common : Diarrhea

4.9 Overdose
No case of overdose has been reported.

5.0 PHARMACOLOGICAL PROPERTIES
Pharmaco-therapeutic group: rotavirus diarrhea vaccines.

5.1 Pharmacodynamic properties
Protective efficacy

5.1.1 Efficacy
In total 12 clinical trials, approximately ~15000 subjects were vaccinated with different formulations of ROTAVAC® vaccines consisting ORV116E as the active ingredient with a virus titer of NLT $10^{5.5}$ FFU. These ORV116E strain containing ROTAVAC® formulations (ROTAVAC®, ROTAVAC 5C & **ROTAVAC 5D®**) were tested for their Safety, Immunogenicity and Non-inferiority. The adverse reaction profile and immunogenicity profile observed in subjects administered with these three formulations were similar. ROTAVAC® & ROTAVAC 5C formulations were tested for their Lot consistency and Non-interference with EPI vaccines and concluded that ROTAVAC® formulations do not interfere with EPI vaccines and their manufacturing consistency was established. Since **ROTAVAC 5D®** has also been evaluated for safety and immunogenicity in comparison to ROTAVAC® while being co-administered with EPI vaccines, It is concluded that **ROTAVAC 5D®** formulation is equally safe and immunogenic as ROTAVAC® and ROTAVAC 5C. Efficacy, non-interference with EPI vaccines and manufacturing consistency of ROTAVAC® and ROTAVAC 5C formulations can be extrapolated to **ROTAVAC 5D®** formulation.

ROTAVAC® (ORV 116E):
A Multi-center clinical study was conducted in India to evaluate the efficacy of ROTAVAC® to prevent severe rotaviral gastroenteritis. Data for vaccine efficacy has been presented for the first year and second year of life. The results of these two analysis 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 hospitalization and of any cause ROTAVAC® prevented 47.7% (95% CI: 24.5, 63.8) of all hospitalization ≥24hrs due to severe non-ROTAVAC® vaccine rotavirus gastroenteritis. ROTAVAC® was also efficacious against severe GE of any etiology (VE=18.6% [95% CI 1.9, 32.3]).

EPI - noninterference study & Lot to Lot consistency
Post-vaccination, seroprotective level of antibodies against poliovirus type 1,2, and 3 were 98.2%, 99.4% and 92.4%, respectively, in infants receiving OPV along with ROTAVAC® and 99%, 98.3% and 92.7%, respectively, in infants receiving OPV along with placebo. Difference in proportions between these groups was 0.8% (95%CI −1.1%, 2.2%) for type1 strain, −1.2% (95%CI −3.3%, 0.2%) for type2 strain and 0.3% (95%CI −3.5%, 3.6%) for type3 strains of polio virus. Almost all infants, irrespective of the treatment group, developed protective antibody titre against diphtheria toxoid, tetanus toxoid and Hib (anti-PRP antibodies). Over 93% developed protective titre against HepB (anti- HBs antibodies).

The difference in proportion of infants who developed protective antibody titres was 0.5% (95%CI −1.3, 2.3) for diphtheria toxoid, 0.9% (95% CI − 0.3, 2.4) for tetanus-toxoid, 2.2% (95%CI −1.7, 6.0)for anti-HBs antibodies and 0% (95% CI −1.3, 1.1) for anti-PRP antibodies. The ratio of GMCs between the placebo and ROTAVAC® groups for pertussis toxin was 1.0 (95% CI: 0.8, 1.1)

The baseline and post 3rd dose vaccination GMTs of IgA antibodies according to lot of ROTAVAC® ; Baseline GMT was similar across the three groups (2.7-2.8); post vaccination GMTs had a rise of 10.8 from 8.5.

ROTAVAC 5C (ORV 116E)
There were no statistically significant differences in the pre- and post-vaccination IgA titers between the ROTAVAC 5C and ROTAVAC® (mean baseline titer 22.3 and 24.2 U/mL respectively (p=0.84 comparing all arms); and post vaccination titer 59.1 and 76.0 U/mL, respectively (p=0.12).

Seroconversion occurred by day 84 in 37.6% (95% CI: 31.1%, 44.2%) of the ROTAVAC 5C arm, and 41.3% (95% CI: 34.7%, 47.8%) of the ROTAVAC®. There was no significant difference in seroconversion rates between the ROTAVAC®and ROTAVAC 5C (p=0.489).

EPI - noninterference study & Lot to Lot Consistency
In the Immunogenicity Population, all three lots of ROTAVAC 5C were non-inferior to the ROTAVAC® with the lower bound of the 95% confidence interval for the GMT ratio (ROTAVAC 5C / ROTAVAC®) being greater than 0.5: Lot 1 GMT ratio 1.069 (95% CI 0.827 to 1.382; p<0.0001); Lot 2 GMT ratio 1.096 (95% CI 0.840 to 1.429; p<0.0001) and Lot 3 GMT ratio 1.129 (95% CI 0.867 to 1.471; p<0.0001). When all lots were combined, the GMT ratio was 1.097 (95% CI 0.888 to 1.357; p<0.0001).

There were no statistically significant differences in the pre- and post-vaccination IgA titers between the ROTAVAC 5C and ROTAVAC® arms (mean baseline titer 24.0, 23.6, 21.5 and 28.5 for ROTAVAC 5C Lot 1, 2 and 3; and ROTAVAC®, respectively; p=0.7275 ANOVA comparing the four arms).

There was no difference in the GMT titers between ROTAVAC 5C (all lots) and ROTAVAC® -20°C for *Bordetella pertussis,* Diphtheria*, Haemophilus influenza* type B, Hepatitis B or Tetanus (the lower limit for all was > 0.50). There was no difference between lots for any of the vaccines. Thus ROTAVAC 5C can be successfully co-administered with other childhood vaccines.

ROTAVAC 5D®(ORV 116E)
There were no statistically significant differences in the pre and post vaccination IgA titers between the **ROTAVAC 5D®** and ROTAVAC®(mean baseline titer10.31 and 11.57 U/mL respectively (p=0.29 comparing all arms); and post vaccination titer18.70 and 19.55 U/mL, respectively (p=0.77).

Four-fold Seroconversion occurred by day 84 in 22.18% (95% CI: 17.01%, 27.35%) of the **ROTAVAC 5D®** arm, and 21.25% (95% CI: 12.29%, 30.21%) of the ROTAVAC®. There was no significant difference in seroconversion rates between the ROTAVAC®and **ROTAVAC 5D®** (p=0.86).

Post -marketing surveillance data
Post-marketing surveillance is carried out for the Rotavirus 116E strain based vaccine ROTAVAC® and no SAEs were observed thus far.

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

5.3 Pre-clinical safety data
Repeated dose non-clinical toxicity study on oral rotavirus candidate vaccine 116E live strain was carried out in mice, rats and rabbits. These studies were initiated with 0.5 mL formulations and later on in continuation of developing formulations with buffer wherein the dose volume is 1.5 mL and 2.0 mL (ROTAVAC 5C) were subjected for pre-clinical toxicology studies. In both the cases, the excipients used were same except for concentration used. **ROTAVAC 5D®** is having similar excipients as in ROTAVAC 5C but only difference is the concentration. Dose volume, concentration of buffer system and excipients were tested in animal model for toxicity and found to be safe. The pre-clinical safety data establish the safety of the vaccine for **ROTAVAC 5D®** formulation.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Neomycin Sulphate
Kanamycin Acid Sulphate
Sucrose
Trehalose
Lactalbumin Hydrolysate (LAH)
Human Albumin
Potassium Dihydrogen Orthophosphate
Dipotassium Hydrogen Orthophosphate
Trisodium Citrate Dihydrate

6.2 Incompatibilities
This product should not be mixed in same syringe with any other medicinal products/active immunizing agents.

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