

Summary of Product Characteristics

Name and description of the Active Immunization Agent

Rotavirus Vaccine (Live, Oral) is a monovalent vaccine containing suspension of live attenuated rotavirus 116E prepared in Vero cells. Rotaviruses are doublestranded 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] $10^{5.0}$ FFU [Focus Forming Unit] of live rotavirus 116E.

Brand Name:

ROTAVAC 5D®

Generic Name:

Rotavirus Vaccine (Live, Oral) BP

Qualitative and Quantitative Composition:

Each 0.5 mL (5 drops) contains:

Vero cell derived Rotavirus 116E Bulk, Live attenuated.....NLT $10^{5.0}$ FFU

Neomycin sulphate BP.....15µg

Kanamycin Acid sulphate BP.....15µg

Pharmaceutical Form

ROTAVAC 5D® is pale yellow coloured sterile liquid for oral use.

Clinical Particulars

Therapeutic 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 series.

Posology and Method of administration:

Dosage

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 Influenza Type b, 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 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/vpdvac/rotavirus/vac-faqs.htm>).

Method of administration:

ROTAVAC 5D® 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 +2°C to +8°C and used in the same immunization session (within maximum 6 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 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.

Contraindications:

- Hypersensitivity to any components of the vaccine. Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of ROTAVAC 5D® should not receive further doses of ROTAVAC 5D®.
- 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) intestinal malformation predisposing to intussusception.
- Ongoing gastroenteritis.

Special warnings and precautions for use:

No safety or efficacy data is available from clinical trials regarding the administration of ROTAVAC 5D® to immunocompromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of ROTAVAC 5D® may be considered with caution in immunocompromised 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 the 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 vaccine 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 5D[®] did not show an increased risk of IS for ROTAVAC 5D[®] 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.

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.

Interaction with other medicinal products and other forms of interaction: In this Clinical trial, OPV, IPV and Pentavalent (DTwP, HepB, Hib) vaccines are administered concurrently with ROTAVAC 5D[®]. Three doses of ROTAVAC 5D[®] can be safely administered with 3 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.

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[®].

Effect on ability to drive and use machine:

Not applicable.

Adverse Reactions:

Clinical Trial Experience:

The most commonly observed adverse events during the clinical trial are fever, diarrhea, cough and others like running and irritability. No vaccine related SAE's were reported. There was no vaccine related case of Intussusception observed/ reported. Fever could be due to concomitant injectable vaccines.

List of adverse Reactions:

Adverse reactions reported are listed according to the following frequency.

Frequency is defined as:

Very common : ($\geq 1/10$)

Common : ($\geq 1/100$, $< 1/10$)

Uncommon : ($\geq 1/1000$, $< 1/100$)

Rare : ($\geq 1/10000$, $< 1/1000$).
Clinical trial data
Very common : Fever, Cough and Crying
Common : Diarrhoea

Overdose:
No case of overdose is reported.

Pharmacological Properties:
Pharmaco-therapeutic group: rotavirus diarrhoea vaccines.

Reporting of suspected adverse reactions:

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

Pharmacodynamic Properties Protective Efficacy

Efficacy: In total 12 clinical trials, approximately ~15000 subjects were vaccinated with different formulations of ROTAVAC Vaccine consisting ORV 116E as the active ingredient with a virus titre of NLT 10 FFU. These ORV116E strain containing ROTAVAC formulation (ROTAVAC, ROTAVAC 5C & ROTAVAC 5D) were tested for their safety, immunogenicity and Non-inferority. The adverse reaction profile and immunogenicity profile observed in subjects administered with these three formulations were similar. ROTAVAC & ROTAVAC 5C formulations do not interfere with EPI vaccine 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 formulation can be extrapolated to ROTAVAC 5D[®] formulation.

ROTAVAC[®] (ORV116E):

A 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 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= 16.6% [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%, 99% and 92% 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 type 1 strain, -1.2% (95%CI-3.3%, 0.2%) for type 2 strain and 0.3% (95%CI- 3.5%, 3.6%) for type 3 strains of polio virus. Almost all infants, irrespective of the treatment 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-HIBs 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-HIBs 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 (ORV116E)

There were no statistically significant differences in the pre- and post-vaccination IgA titers between the ROTAVAC 5C and ROTAVAC® (mean baseline titre 22.3 and 24.2U/mL respectively (p=0.84 comparing all arms); post vaccination titre 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- non-interference study & Lot to Lot Consistency

In the immunogenicity population, all three lots of ROTAVAC 5C were noninferior 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: 0.927 to 1.382; p<0.0001) ratio 1.096 (95% CI: 0.840 to 1.429;

p<0.0001) and Lot 3 GMT ratio 1.129 (95% CI: 0.857 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 titres between the ROTAVAC 5C and ROTAVAC® arms (mean baseline titre 24.0, 23.6, 21.5 and 28.5 for ROTAVAC 5C Lot 1, 2 and 3; and ROTVAC, respectively; p=0.7275 ANOVA comparing the four arms).

There was no difference in the GMT titres between ROTAVAC 5C (all lots) and ROTAVAC® -20C for Bordetella pertussis, Diphtheria, Haemophilus influenza type, 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® (ORV116E)

There were no statistically significant difference in the pre and post vaccination IgA titres between the ROTAVAC 5D® and ROTAVAC® (mean baseline titre 10.31 and 11.57 U/mL respectively (p=0.29 comparing all arms); and post vaccination titre 18.70 and 19055 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.

Pharmacokinetic properties

Evaluation of Pharmacokinetic properties is not required for vaccines.

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 0.5mL 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.

Pharmaceutical Particulars:

Incompatibilities:

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

Shelf life:

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

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.

Presentation

ROTAVAC 5D® is presented in USP type I glass vials

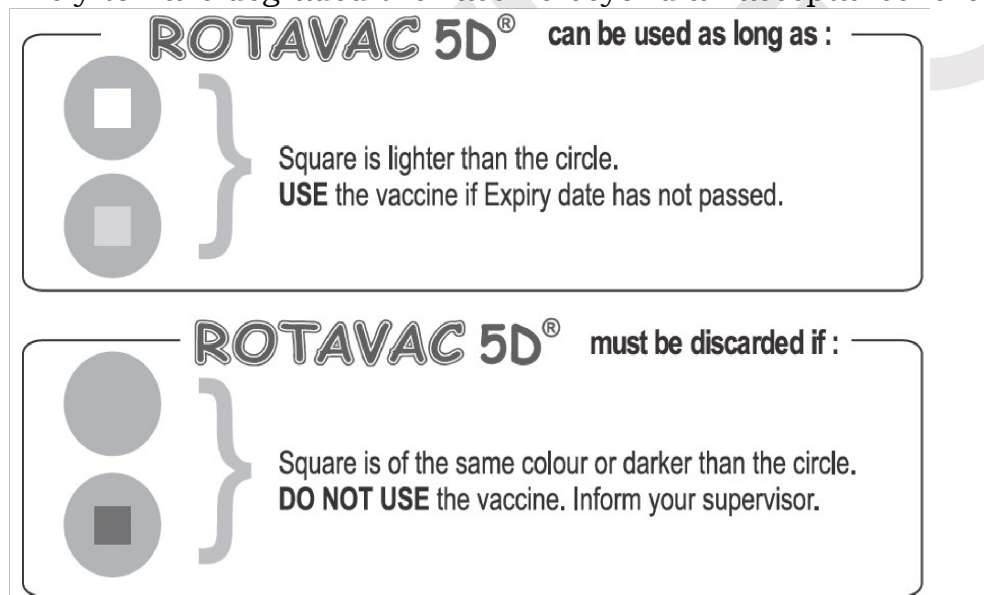
Single Dose: 0.5 mL Vial

Single Dose: 0.5 mL Pre-filled Syringe

Multi Dose: 2.5 mL Vial

The Vaccine Vial Monitor7 (VVM7)

Vaccine Vial Monitor7 (VVM7) dot is on the seal ROTAVAC 5D®. This is a time-temperature sensitive dot that provides an indication of the cumulative heat which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptance level.



The interpretation of VVM7 is simple. Focus on the central square. Its color will change progressively. As long as the color of this square is lighter than the color of the ring, the vaccine can be used. As soon as the color of the central square is the same color as the ring or of a darker color than the ring, the vial should be discarded.

Administration of ROTAVAC 5D® vaccine.



Marketing Authorisation Holder:

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Address of the Site &
Corporate Office

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Marketing Authorisation Number (s):
CTD10815

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