SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Name of the product: Rotavirus Vaccine (Live Attenuated, Oral)
Strength: Each dose of 0.5 mL (5 Drops) contains:
Rotavirus 116E Bulk, Live Attenuated: NLT $10^{5.0}$ FFU

Pharmaceutical Form: Vaccine (Liquid)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 mL (5 Drops) contains:	
Vero cell derived Rotavirus 116E bulk, Live attenuated	NLT $10^{5.0}$ 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 Di-Hydrogen Orthophosphate IP	1.65 mg
Di-Potassium Hydrogen Orthophosphate IP	10 mg
Tri-Sodium Citrate Di-hydrate IP	7.75 mg
Water for Injections IP	q.s.

3. PHARMACEUTICAL FORM

Vaccine (Liquid)

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.

Care should be taken not to contaminate the multi-dose dropper of the vaccine with saliva of the babies.

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

Multi-dose vials of **ROTAVAC 5D®** from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 28 days after opening, provided that all of the following conditions are met (as described in the WHO Policy Statement: Multi-Dose Vial Policy (MDVP) Revision 2014 WHO/IVB/14.07).

Once opened, multi-dose vials should be kept between +2°C and +8°C.

- The vaccine is currently pre-qualified by WHO.
- The vaccine is approved for use for up to 28 days after opening of the vial, as determined by WHO (http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/).
- The expiry date of the vaccine has not passed.
- The vaccine vial has been, and will continue to be, stored at the recommended temperature; furthermore, the vaccine vial monitor is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

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 AND Precautions for use

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 immunising 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 Undesirable effects

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 diarrhoea 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 105.0 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 formulation 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, Water for Injections.

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

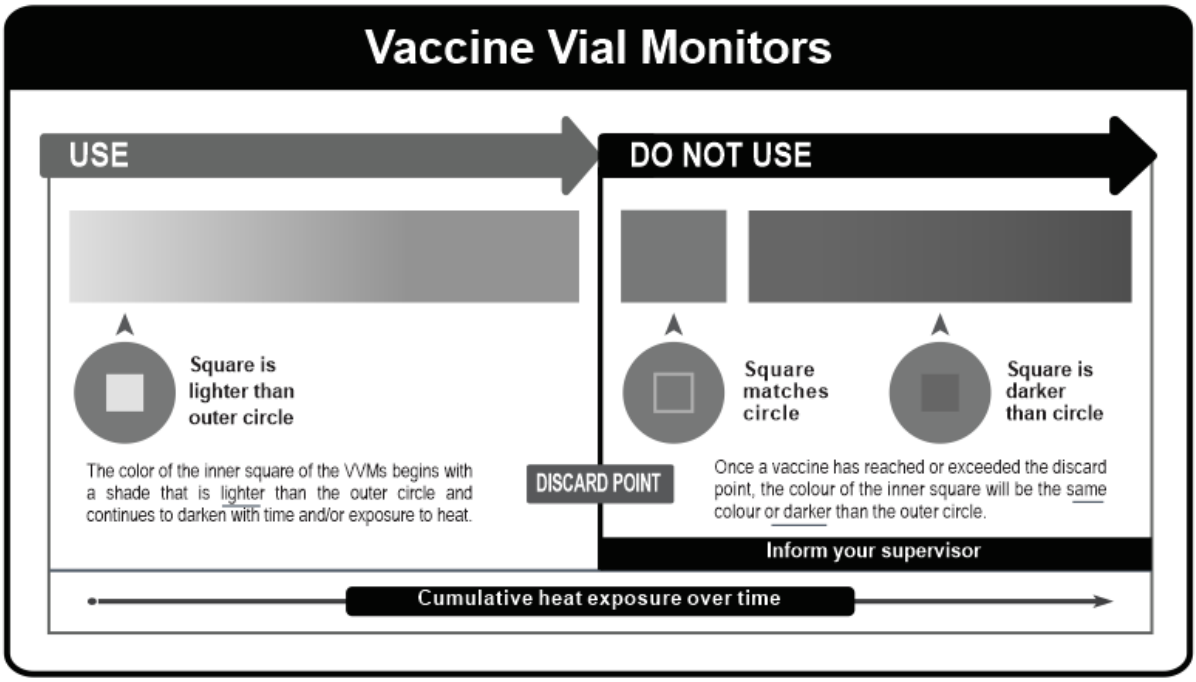
6.3 Shelf life
The expiry date of the vaccine is indicated on the label and packaging.

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.

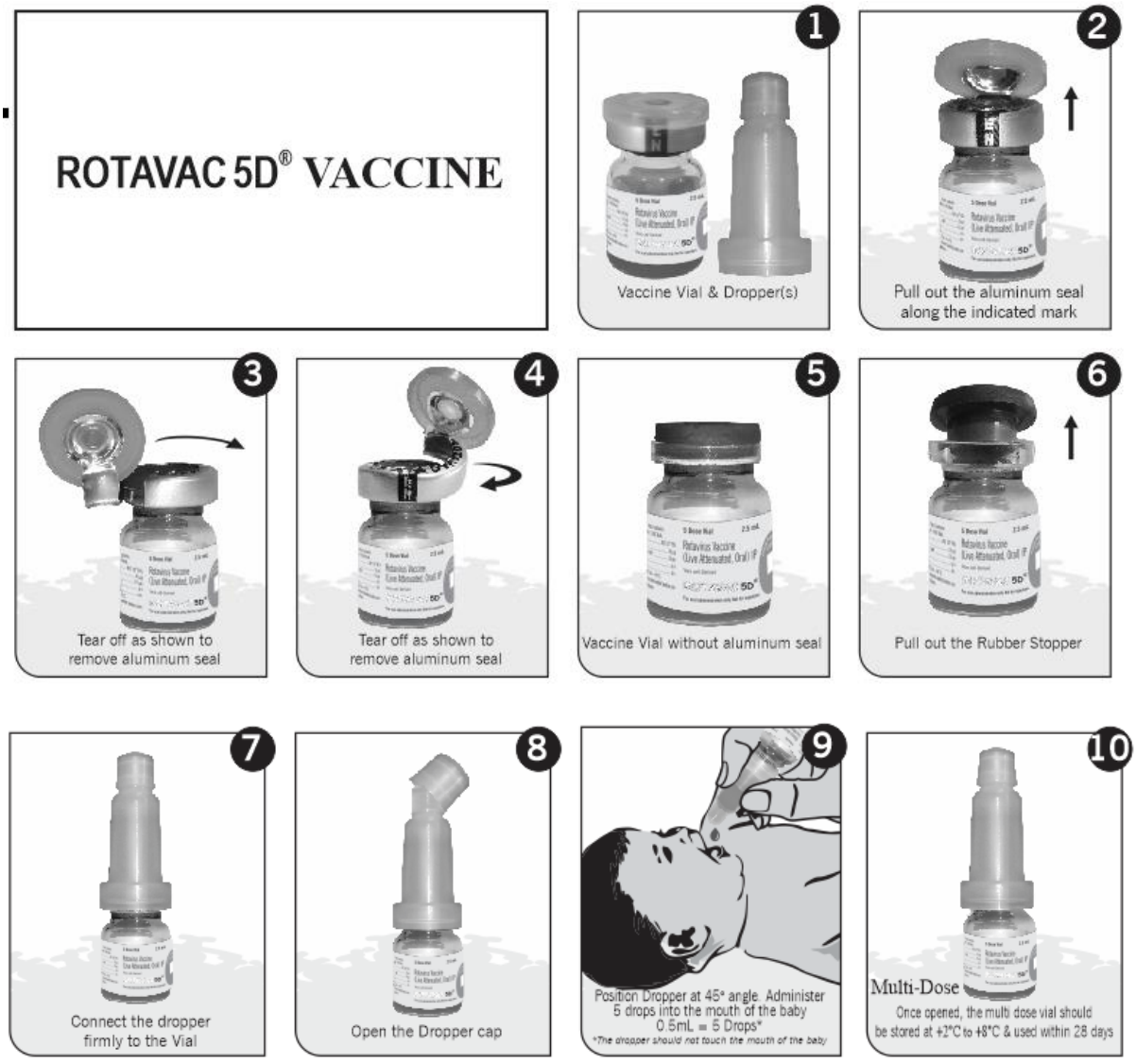
THE VACCINE VIAL MONITOR7 (VVM7)

Vaccine Vial Monitor7 (VVM7) dot is a part of the label on **ROTAVAC 5D®**. 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.



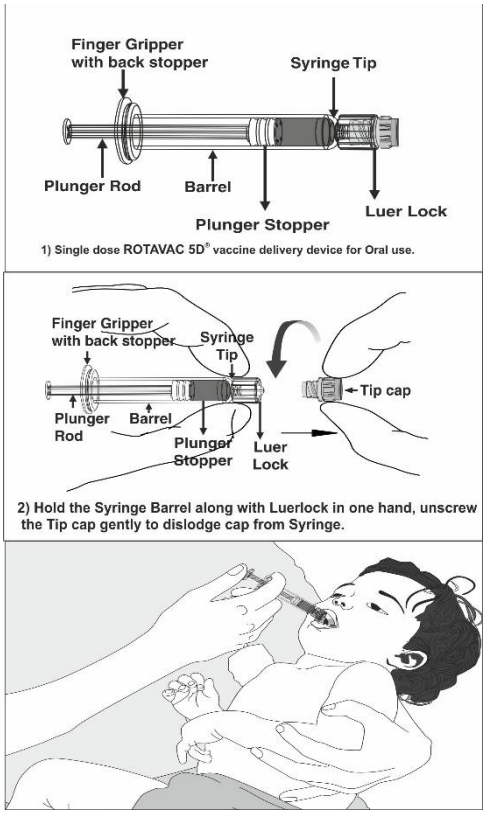
The interpretation of VVM7 is simple. Focus on the central square. Its color will change progressively. As long as the color of this square is lighter than the color of the ring, the vaccine can be used. As soon as the color of the central square is the same colour as the ring or of a darker color than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

ADMINISTRATION OF ROTAVAC 5D® VACCINE



ADMINISTRATION OF ROTAVAC 5D® VACCINE

Fig: PFS Handling Diagram



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.

6.5 Nature and contents of container

ROTAVAC 5D® is presented in USP type l glass vials and PFS.
Single Dose : 0.5 mL
Multi Dose : 2.5 mL
Single Dose PFS : 0.5 mL

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BHARAT BIOTECH Lead Innovation

Bharat Biotech International Limited situated
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal, Malkajgiri District, Telangana State, India, Pin: 500078.

8. MARKETING AUTHORISATION NUMBER

MF/BIO/18/000022

9. DATE OF FIRST MARKETING AUTHORISATION

31 Aug 2018

10. DATE OF REVISION

May 2022