Rotavirus Vaccine (Live Attenuated, Oral) IP

Vero cell-derived

ROTAVAC®

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: liquid in frozen form

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each dose of 0.5 mL (5 Drops) contains:

Ingredients	**Quantity / 0.5 mL**
Rotavirus 116E Bulk, Live Attenuated	NLT $10^{5.0}$ FFU
Potassium Phosphate Monobasic BP	0.258 mg
Potassium Phosphate Dibasic BP	0.625 mg
Sucrose BP	39 mg
Potassium L-glutamate Monohydrate	1.0 mg
Neomycin Sulphate BP	15 µg
Kanamycin Acid Sulphate BP	15 µg
Dulbecco's Modified Eagle's Medium (DMEM)	4.4 mg
Water for Injections BP	q.s.

3. PHARMACEUTICAL FORM
Liquid in frozen form.

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 Posology 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], *Haemophilus Influenzae* 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®** 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
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® 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®** 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. 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 rotavirus vaccines have been reported in infants with SCID.

- History of intussulivesception (IS).

4.4 Special warnings and Precautions for use

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®**.

The safety data from the clinical trials of **ROTAVAC®** did not show an increased risk of IS for **ROTAVAC®** when compared to placebo.

Smart Safety Surveillance in India promoted by WHO has concluded that self-controlled case series analysis demonstrated no increased risk of intussusception associated with **ROTAVAC®** vaccination in two separateanalyses(https://www.worldsdg2030.org/images/White-paper-Book.pdf). Additionally, Global Advisory Committee on Vaccine Safety in its December 2019 report has concluded that "The data did not indicate a significantly higher risk of intussusception during the post-vaccination risk periods than in the reference period for **ROTAVAC®**. (http://www10.who.int/vaccine_safety/committee/reports/Dec_2019/en/).

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 following13,296 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 G9P[11] 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 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, *Haemophilus Influenzae* Type b, 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 Undesirable effects

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 6-8weeks 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 6-7weeks 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 reactogenicity 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 reactogenicity 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.

In the phase IV trial in India900 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 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 vaccine related SAEs were observed/reported.

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.

There was one death reported in the phase IV trial unrelated to vaccine administration.

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.

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 ongoing. The interim analysis of the data received for **ROTAVAC®** has shown fever, irritability and vomiting as common AEsfollowed by diarrhoea and rash. There were no SAEs and no cases of intussusception reported.

Integrated Safety profile
The safety profile presented below is based on the data from the clinical trials conducted with **ROTAVAC®.**

In a total of eight clinical trials approximately 30000 doses of **ROTAVAC®** were administered to approximately 10000 infants. In the pooled analysis from all the clinical trials in which **ROTAVAC®** was co-administered with routine paediatric vaccines, the following adverse reactions (collected 28 days post vaccination) like fever, diarrhoea, vomiting, loss of appetite, irritability and cough were observed and considered as possibly related to Rotavac or could be due to concomitantly administered 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, Diarrhoea and Cough
Common : Vomiting, irritability, Crying and Rash
Uncommon : Loss of appetite/Refusal to feed

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 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 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. Seroconversion was comparable in all 3 groups in the phase IV trial.

5.1.2 Phase III – EPIN on interference trial
In a phase III placebo controlled trial, lot to lot consistency was determined in 3 production lots as well noninterference 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 to 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 Preclinical safety data
A 28 day repeated dose non-clinical toxicity study on oral rotavirus candidate vaccine 116E live 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 candidate vaccine is safe and induced no toxicity in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium Phosphate Monobasic, Potassium Phosphate Dibasic,Sucrose, Potassium L-glutamate Monohydrate, Neomycin Sulphate, Kanamycin Acid Sulphate, Dulbecco's Modified Eagle's Medium (DMEM) , Water for Injections.

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of ROTAVAC® is indicated on the label and carton of the vaccine.

6.4 Special Precautions for Storage

The recommended storage temperature for **ROTAVAC®** is at -20°C or below until the expiry date indicated on the vial. It can be stored for up to six months between +2°C and +8°C.

ROTAVAC® can be subjected to 6 freeze- thaw cycles.

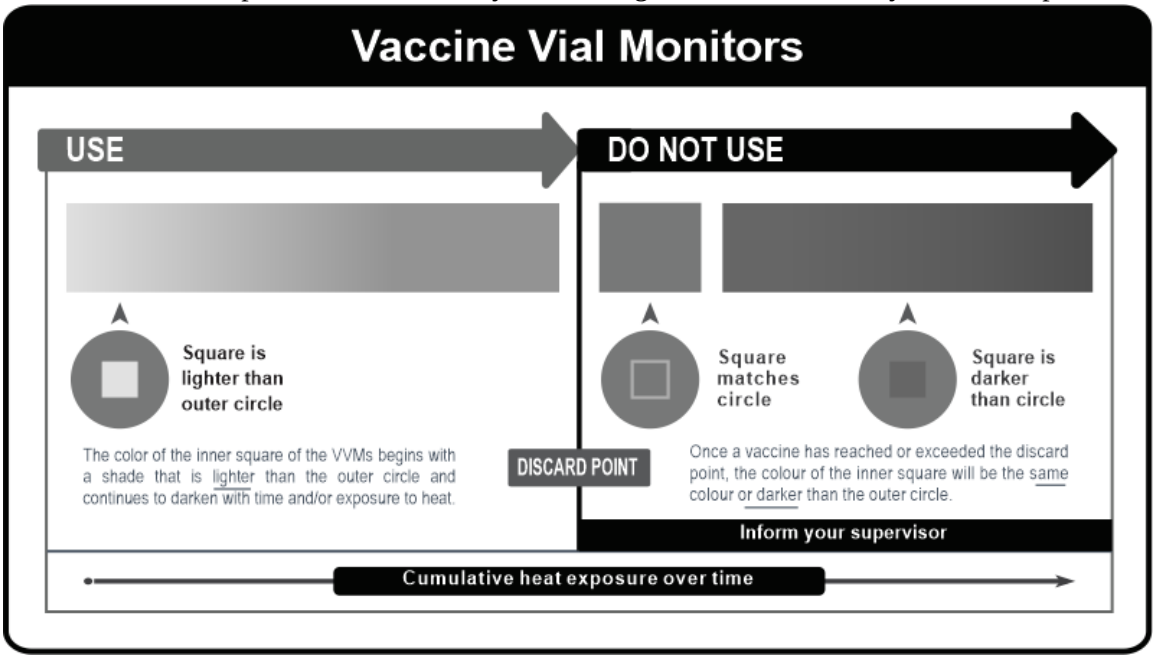
It is absolutely critical to ensure that the storage conditions specified above are complied with. Bharat Biotech assumes no liability in the event of **ROTAVAC®** has not been stored in compliance with the storage instructions.

Transport

ROTAVAC® can be transported at +2°C to +8°Cusing -20°C frozen gel packs.

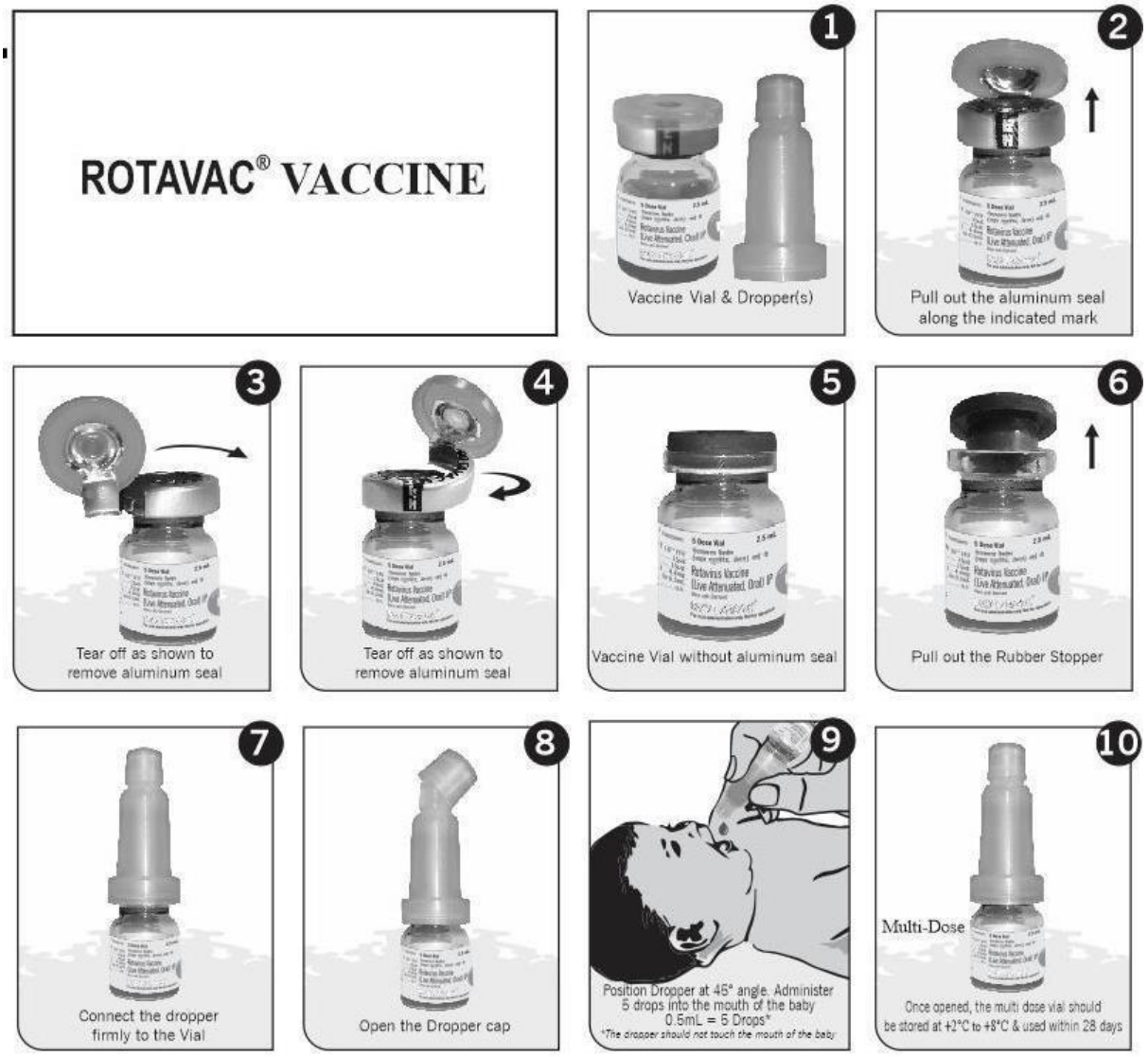
The Vaccine Vial Monitor2

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.

Administration of ROTAVAC® Vaccine



6.5 Nature and contents of container

ROTAVAC® is presented in USP type l glass vials.

Single dose : 0.5mL vial
5 Doses : 2.5 mL vial
10 Doses : 5mL vial

6.6 Special precautions for disposal

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

7. APPLICANT/MANUFACTURER

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