

Applicant name: The Biovac Institute (Pty) Ltd  
Product name: ROTAVAC 5D  
Dosage form and strength: Liquid for oral administration  
Each 0,5 ml of vaccine contains:  
10<sup>5,0</sup> Focus Forming Units (FFU) of  
live attenuated Rotavirus 116E

1.3.1.1  
08 October 2024

**PROFESSIONAL INFORMATION  
FOR  
ROTAVAC 5D (Rotavirus) VACCINE**

**SCHEDULING STATUS**

S2

**1. NAME OF THE MEDICINE**

**ROTAVAC 5D.** Oral liquid. Rotavirus vaccine, live attenuated.

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One dose 0,5 ml or 5 drops contains:

Rotavirus 116E strain\* (live attenuated) not less than 10<sup>5,0</sup> FFU \* produced in Vero cells.

This vaccine may contain traces of human albumin.

This vaccine contains a trace amount of neomycin and kanamycin. **See section 4.3.**

Excipient(s) with known effect:

This vaccine contains sucrose 0,25 g and trehalose 2,5 mg per dose. **See section 4.4.**

For full list of excipients, **see section 6.1.**

**3. PHARMACEUTICAL FORM**

Oral liquid. ROTAVAC 5D is a clear pinkish to pale yellow coloured liquid, free from particles.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications:**

ROTAVAC 5D is indicated for active immunisation of infants from the age of 6 weeks for the prevention of gastroenteritis caused by Rotavirus infection when administered as a 3-dose series.

**4.2 Posology and method of administration**

**Posology**

A single oral dose (0,5 ml / 5 drops) of ROTAVAC 5D should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age.

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ROTAVAC 5D may be co-administered with other routine childhood immunisations (i.e., pentavalent vaccine containing Diphtheria, Tetanus and Pertussis (DTwP), *Haemophilus Influenza* type B, Hepatitis B vaccine), trivalent Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV) and Pneumococcal conjugate vaccine. (PCV). **See sections 4.4, 4.5, 4.8**

Based on recommendations from the World Health Organisation if the routine childhood immunisations 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.

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

The 3-dose primary schedule of Rotavirus vaccine should be administered to children by the age of 8 months (34 weeks). **See sections 4.5, 4.8.**

In clinical trials, spitting or regurgitating of the vaccine was not commonly observed, and under such circumstances a replacement dose was not given. However, in the unlikely event that an infant spit out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit. The infant may continue to receive the remaining doses as per schedule.

### **Special populations**

No safety or efficacy data are available from the clinical trials regarding the use of ROTAVAC 5D in immune-compromised infants and infants infected with HIV. Few studies have assessed the efficacy, immunogenicity, or safety of rotavirus vaccine in HIV-1-infected children. Limited data suggest rotavirus infection is not more frequent or more severe in HIV-1-infected children. **see section 4.4 and 4.8.**

### **Method of administration**

**ROTAVAC 5D is for oral use only and should not be injected.**

The vaccine is ready to use (no reconstitution or dilution is required). There are no restrictions on the infant's liquid consumption including breast milk, either before or after vaccination with

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ROTAVAC 5D. Seat the child leaning slightly backwards. Keep the vaccine at 45 degrees and administer the dose in the mouth of the infant toward the inner cheek. Refer to the pictorials in Figure 1 and Figure 2.

**Note:** ROTAVAC 5D single dose vial has a volume of 0,5 ml. The full contents should be administered to one child. For the multi-dose vial, 5 drops (0,5 ml), should be administered.

Care should be taken not to contaminate the multi-dose dropper of the vaccine with saliva of the babies. An opened vial must be discarded immediately if the sterile procedures have not been fully observed, if there is visible evidence of contamination such as a change in appearance or floating particles, or if there is a suspicion that the opened vial has been contaminated.

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Figure 1: Administration of ROTAVAC 5D vials.



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### 4.3. Contraindications

- ROTAVAC 5D should not be administered to infants with known hypersensitivity to any component of the vaccine. For the full list of excipients **see section 6.1**.
- Individuals who experienced a severe allergic reaction (e.g. anaphylaxis) after a previous dose.
- Individuals with Severe Combined Immunodeficiency Disease (SCID). Cases of gastroenteritis associated with live rotavirus vaccines have been reported in infants with SCID.
- Infants with a history of intussusception (IS) or intestinal malformations predisposing to intussusception and infants with a history of congenital abdominal disorders.
- Infants with ongoing gastroenteritis.
- Individuals allergic to neomycin or kanamycin as ROTAVAC 5D contains these antibiotics in its formulation.
- As with other vaccines, ROTAVAC 5D should be postponed in infants suffering from an acute severe febrile illness.

### 4.4 Special warnings and precautions for use

Available published data shows a small increased incidence of intussusception (IS) following the first dose of Rotavirus vaccine.

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 healthcare providers immediately follow-up on any symptoms suggestive of IS e.g. continuous vomiting, blood in stools, an abdominal lump or distension of the abdomen. Parents or caregivers should immediately inform their healthcare provider or go to the emergency department should these symptoms appear.

No safety or efficacy data is available from clinical trials regarding the administration of ROTAVAC 5D to immunocompromised infants, infants infected with HIV, infants with chronic gastroenteritis or infants with growth retardation.

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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.

If given, precautions should be taken to avoid transmission of any excreted vaccine virus. Contacts of recent vaccinees should be advised to observe careful hygiene (including washing their hands after changing child's nappies). 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. As with 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 contains sucrose and trehalose as excipients. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take ROTAVAC 5D.

#### **ROTAVAC 5D Should under no circumstances be injected.**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### **4.5 Interactions with other medicines and other forms of interaction**

Clinical data show that-ROTAVAC 5D can be administered concomitantly with oral polio vaccine (OPV), inactivated polio vaccine (IPV) and combination (DTwP), hepatitis B vaccine (HBV) and *Haemophilus influenzae* type B vaccine (Hib)]. Three doses of ROTAVAC 5D can be safely administered with 3 doses of pentavalent vaccine (DTwP, HBV, Hib) and three doses of OPV as well as IPV without diminishing the antibody response to each component of these vaccines.

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In other clinical trials, ROTAVAC 5D was co-administered with OPV/inactivated polio vaccine (IPV), pentavalent (DTwP, HBV, Hib) and pneumococcal conjugate vaccine (PCV).

BCG vaccine was also offered to infants who had not received this vaccine before. The clinical studies concluded that ROTAVAC 5D is safe and well tolerated when administered concomitantly with routine EPI childhood vaccines. There are no restrictions on the infant's liquid consumption including breast milk, either before or after vaccination with ROTAVAC 5D.

#### **4.6 Fertility, pregnancy and lactation**

ROTAVAC 5D 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 breastfeeding reduced the protection against rotavirus gastroenteritis conferred by ROTAVAC 5D.

#### **4.7 Effects on ability to drive and use machines**

ROTAVAC 5D is not intended for use in adults.

#### **4.8 Undesirable effects**

##### **a. Summary of the safety profile**

The safety profile is based on clinical trial data obtained from studies conducted with ROTAVAC 5D. The most commonly observed adverse events during the clinical trials were fever, diarrhoea, cough and others such as running nose and irritability. No vaccine related serious adverse effects were reported.

There was no vaccine related case of intussusception observed or reported. Fever was commonly observed; however, this could be due to concomitant injectable vaccines.

##### **a. Tabulated list of adverse reactions**

Adverse reactions reported are listed according to the following frequency definition:

- Very common: ( $\geq 1/10$ )
- Common: ( $\geq 1/100$ ,  $< 1/10$ )
- Uncommon: ( $\geq 1/1000$ ,  $< 1/100$ )
- Rare: ( $\geq 1/10000$ ,  $< 1/1000$ )
- Very rare: ( $< 1/10\ 000$ )

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**Table 1: Tabulated summary of adverse reactions from clinical trials**

System Organ Class	Frequency	Adverse reaction
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Common	Diarrhoea
General disorders and administration site conditions	Very common	Fever and irritability (crying)

Intussusception (IS) is a safety concern for all rotavirus vaccines.

The Phase III Clinical studies revealed that six of 4532 (0,13 %) subjects in the Rotavirus Vaccine (Live, Oral) group and two of the 2267 (0,09 %) subjects receiving placebo had confirmed intussusception. The timing of the confirmed cases of IS with respect to the vaccination ranged from 36 to 291 days after the third dose; the lack of temporal association argues strongly against a causative relationship between Rotavirus Vaccine (live, oral) and IS.

**Table 2: Adverse events (solicited) reported with post-marketing clinical studies (phase IV studies)**

System Organ Class	Frequency	Adverse reaction
Nervous system disorders	Common	Crying
Gastrointestinal disorders	Common	Diarrhoea, vomiting
General disorders and administration site conditions	Very common	Fever

**For data from sources other than clinical trials data:**

There are literature reports of other frequent adverse events in subjects receiving rotavirus vaccines which include fatigue, irritability, otitis media, nasopharyngitis and bronchospasm.

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### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

Alternatively, adverse reactions can be reported directly to the Holder of the Certificate of Registration via an e-mail to the following email address:

[DrugSafety@biovac.co.za](mailto:DrugSafety@biovac.co.za)

### 4.9 Overdose

No cases of overdose with ROTAVAC 5D have been reported.

Overdose is unlikely for the single dose vial presentation.

In overdose (multi-dose vial), side effects can be precipitated and/or be of increased severity, **see section 4.8.**

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: rotavirus diarrhoea vaccines ATC code: J07BH01

Protection against rotavirus infection is associated with the presence of virus-specific immunoglobulin IgA at the intestinal mucosal surface and therefore serum IgA responses are often measured to evaluate immune responses to vaccines. Each structural protein bears type-specific antigenic determinants, elicits serotype-specific neutralising antibodies, and induces serotype-specific protective immune responses *in vivo*.

Immunogenicity and vaccine protective efficacy were evaluated in various clinical trials with approximately 15500 subjects in total. Subjects were vaccinated with different final product formulations of oral rotavirus vaccine consisting of Rotavirus 116E (RV116E) as the active ingredient with a virus titre of not less than (NLT) 10<sup>5.0</sup> focus forming units (FFU).

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#### Immunogenicity:

Immunogenicity of RV116E vaccine at a dosage of NLT 10<sup>5,0</sup> FFU was determined clinically by an evaluation of the seroconversion rate of participants. Seroconversion was defined as a fourfold, or higher, rise in serum rotavirus specific IgA titre.

#### Protective Efficacy:

A multi-centre clinical study was conducted to evaluate the protective efficacy of the RV116E vaccine against severe rotavirus gastroenteritis ( $\geq 11$  on the 20-point Vesikari scoring scale). The Vesikari scoring system is a commonly used method to evaluate the clinical case based on the severity and duration of diarrhoea and vomiting, intensity of fever, and dehydration and treatment given or hospitalisation. Vaccine efficacy data for the study is presented for the first year and second year of life. The efficacy results over the two years were similar suggesting that the vaccine efficacy persists into the second year of life.

Vaccine efficacy (VE) for severe non-vaccine rotavirus gastro- enteritis (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. On-vaccine RVGE requiring hospitalisation and for any cause ROTAVAC 5D prevented 47,7 % [95 % CI: 24,5, 63,8] of all hospitalisations  $\geq 24$  hours due to severe non-ROTAVAC 5D vaccine rotavirus gastroenteritis. ROTAVAC 5D was also efficacious against severe GE of any aetiology (VE = 16,6 % [95 % CI: 1,9, 32, 31]).

#### Viral Shedding:

Stools were collected from a subset of subjects (at each site) on days 3 and 7 post administration of each dose of ROTAVAC 5D. Shedding of the vaccine strain was observed at a low rate. G9P [11] was shed in 12,2 % of ROTAVAC 5D recipients after dose 1; 2,0 % after dose 2 and 1,3 % after dose 3. Among placebo recipients, one subject shed this strain after the first dose, one subject shed after the second dose, and no placebo recipients shed this strain after the third dose. The assay could not distinguish between wild type and vaccine G9P[11]. RV of genotypes

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other than G9P[11] were rarely detected during the post vaccination period (11 subjects in the ROTAVAC 5D group and 5 in the placebo group).

### 5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines

### 5.3 Preclinical safety data

Repeated dose non-clinical toxicity studies on oral rotavirus candidate vaccine 116E live strain were conducted in mice, rats and rabbits. The pre-clinical safety data established 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
- Human albumin
- Potassium di-hydrogen orthophosphate
- Di-potassium hydrogen orthophosphate
- Tri-sodium citrate di-hydrate
- Water for injection

### 6.2 Incompatibilities

This vaccine should not be mixed with any other medicinal product or active immunising agent.

### 6.3 Shelf life

The shelf-life of the vaccine is 24 months from the date of manufacture when stored at the recommended storage temperature of 2 °C to 8 °C.

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The multi-dose vial must be used in the same immunisation session (within maximum 6 hours),  
**see section 6.4 and 6.6.**

#### **6.4 Special precautions for storage**

The vaccine should be stored at 2 °C to 8 °C.

#### **DO NOT FREEZE.**

Once opened, the multi-dose vial should be kept between 2 °C to 8 °C. For storage conditions  
**see section 6.3.**

#### **6.5 Nature and contents of container**

Not all presentations may be marketed.

ROTAVAC 5D is presented in:

- Single dose (0,5 ml) USP Type I glass vial with a grey bromo butyl rubber stopper and sealed with a Tear Lift Flip-down pink seal with a low-density polyethylene (LDPE) plastic dropper packed in a carton. 36 vials are packed into an outer carton.
- Multi-dose, 5 doses, (2,5 ml) USP Type I glass vial with a grey bromo butyl rubber stopper and sealed with a Tear Lift Flip-down pink seal with a LDPE plastic dropper packed in a carton. 26 vials are packed into an outer carton.

#### **6.6 Special precautions for disposal and other handling**

Check the appearance of the vaccine before administration. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Unused portions of the multi-dose vial may be refrigerated between 2 °C to 8 °C for up to 6 hours. Remaining opened vials (partially or fully used), expired, damaged and with VVM reaching discard point (unusable stage) must be taken out of the cold chain and destroyed together with other medical waste at a regional/national level according to National Guidelines.

Safely dispose of the empty vial, cap, and oral applicator in an approved biological waste container according to local regulations.

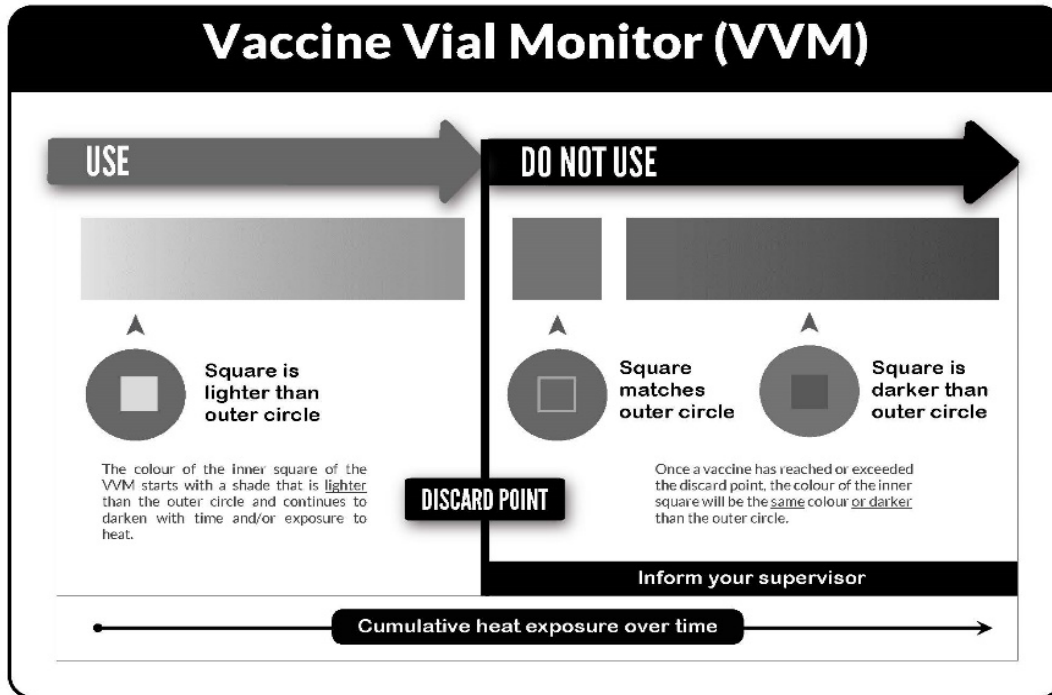
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#### The Vaccine Vial Monitor (VVM)

Figure 1: The Vaccine Vial Monitor (VVM)



Vaccine Vial Monitor (VVM) is part of the label. The coloured dot which appears on the label of the vial is a VVM. 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 the VVM 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 circle, the vaccine can be used. As soon as the colour of the central square becomes the same colour as the circle or a darker colour than the circle, then the vial should be discarded.

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### **7. HOLDER OF CERTIFICATE OF REGISTRATION**

**The Biovac Institute (Pty) Ltd.**

15 Alexandra Road, Pinelands,

7405, Cape Town

Tel: +27 21 514 5000

### **8. REGISTRATION NUMBER(S)**

56/30.2/0481

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**08 October 2024**

### **10. DATE OF REVISION OF THE TEXT**

Not Applicable.