Summary of Product Characteristics

- **Name of the medicinal product:**
  
  **Brand Name:**
  ROTAVAC®

  **Generic name:**
  Rotavirus Vaccine, (Live Oral)

- **Pharmaceutical form:**
  
  A liquid in frozen form.

  In liquid form, the vaccine is generally pink in colour and may sometimes change to orange (or light yellow) in colour. This change in colour does not impact the quality of vaccine.

- **Qualitative and Quantitative Composition:**

  *Each 0.5 mL of dose contains:*

  - Rotavirus 116E Bulk, Live Attenuated................NLT 10⁵.⁰ FFU
  - Potassium Phosphate monobasic USP/BP............0.258 mg
  - Potassium Phosphate dibasic USP/BP...............0.625 mg
  - Sucrose USP/BP........................................37.31 mg
  - Potassium L-glutamate monohydrate USP/BP........1.0 mg
  - Neomycin sulphate USP/BP.........................15 µg
  - Kanamycin sulphate USP/BP.........................15 µg
  - Dulbecco’s Modified Eagle’s Medium (DMEM)...4.4 mg
  - Water for Injection USP/BP........................q.s
  - *pH is in the range of 7.2 to 8.0

- **Clinical Particulars**

  **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.

  **Dosage and Method of Administration:**

  **Dosage & Schedule:**

  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 (DTP), 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 DTP.

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:
All doses 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/yp-vac/rotavirus/vac-faqs.htm).

Mode and Route of Administration:
ROTAVAC® is for oral use only and should not be injected.
For multi-dose presentations, 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 5°C ±3°C and used in the same immunization session (within maximum 8 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 <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® should not receive further doses of ROTAVAC®.
- 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).

Special Warnings and Precautions for use:
No safety or efficacy data is available from clinical trials regarding the administration of ROTAVAC® to immune compromised infants, infants infected with HIV or infants with chronic gastroenteritis. Administration of ROTAVAC® 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 the 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®.

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® did not show an increased risk of IS for ROTAVAC® 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.
Rotavirus Gastroenteritis (RVGE) with Genotype of Vaccine strain G9P [11] Twenty-two G9P[11] rotavirus gastroenteritis cases occurred following 13,296 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 ROTAVAC® 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.

**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®.

**Effect on ability to drive and use machines:**
Net applicable.

**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 6-8 weeks 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 6-7 weeks 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.

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 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.

No cases of IS were observed in the phase Ib/Ila 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.

As per WHO position paper January 2013, on Rotavirus vaccines, "...... the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceed 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:*
A post marketing surveillance is planned to be undertaken with Drug Controller General (India) approval vide File No.12-31/BHARAT/13-BD.

*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.
Pharmacological properties:

Pharmacodynamics:
Protective efficacy

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 hospitalization 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/Ila 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 endpoint)
- 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 hospitalizations and supervised rehydration therapy due to severe GE of any etiology.

**Pharmacokinetics:**
Evaluation of pharmacokinetic properties is not required for vaccines.

**Pre-clinical safety data:**
A 28 day repeated dose non-clinical toxicity study on oral rotavirus candidate vaccine 116 E 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.

- **Pharmaceutical particulars:**
  **List of excipients:**
  - Potassium dihydrogen phosphate
  - Potassium phosphate dibasic
  - Sucrose
  - L-Glutamic acid potassium salt monohydrate
  - Kaaamycin sulphate
  - Neomycin sulphate
  - DMEM
  - Sodium bicarbonate
Incompatibilities:
This product should not be mixed with any other medicinal products / active immunising agents.

Shelf life:
5 years from the date of manufacture.

Special precautions for Storage:
Store at -20°C. It can be stored up to 6 months at 5°C ± 3°C at any time during shelf life.

Nature and contents of container:
ROTAVAC® is presented in USP type 1 glass vials, as:

Single Dose vial : 0.5 mL
5 Doses vial : 2.5 mL
10 Doses vial : 5.0 mL

Vaccine Vial Monitor2 (Multi-Dose Presentations):

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 the 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, then 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, then the vial should be discarded.

- **Marketing authorization holder:**
  BioNet – Asia Co., Ltd. Bangkok, THAILAND

- **Marketing Authorization number:**
  1C 23/61 (NBC)

- **Date of First Authorization/Renewal of the Authorization:**
  Date of first authorization: 17/04/2018
  Date of Last renewal

- **Date of revision of text**
  May 15, 2018